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Pathogenesis and management of seasonal affective disorder

Seasonal affective disorder (SAD) has been recognised for many years and yet the validity of it as a specific syndrome continues to be questioned. Here, Dr Cotterell describes the principal characteristics of SAD, our current understanding of the pathogenesis of the syndrome and possible treatment options.

The mood of an individual, as well as diseases in general, have from the time of Hippocrates been linked with the changing of the seasons. Seasonal affective disorder (SAD) was first suggested as a specific syndrome by Rosenthal *et al*. in 1984[1] and was defined as the development of a depressive episode in the autumn or winter, resolving in the summer, in an individual not previously diagnosed with a major affective disorder. Since then it has been subclassified into a summer form, a winter form and a subsyndromal form.[2] A recurrent summer form in people living close to the equator has also been recognised, but this is very rare.

Despite being recognised as a syndrome, SAD does not currently exist as a specific diagnostic category in current frameworks. The ICD-10 Classification of Mental and Behavioural Disorders regards its presence as uncertain and has provided only provisional diagnostic criteria. In addition, in the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) it is classified under bipolar mood disorder or recurrent depressive disorder as a seasonal variant of a depressive episode. Initial scepticism regarding SAD concerned the fact that the normal population tends to experience variation in mood and that the initial population used to describe the phenomenon were enrolled through newspaper advertisements specifically designed to recruit people who thought they had a seasonal mood disorder. Patients diagnosed with an affective disorder have also been documented as having a seasonal variance in their symptoms.[3]

In addition, early trials looking at the influence of various pathogenetic factors and treatment modalities were plagued by inconsistencies in methodology and results of trials involving small numbers. Longitudinal studies of patients diagnosed with SAD have also shown remittance and conversion to a non-seasonal pattern of recurrent depression, suggesting a lack of sensitivity in the diagnosis. Sceptics have also focused on the use of the Seasonal Pattern Assessment Questionnaire (SPAQ), an instrument based heavily on self-reporting of retrospective symptoms. It was initially developed by Rosenthal *et al*. in 1984[1] and introduced as a diagnostic or screening instrument for SAD by Kasper *et al*. in 1989.[2] Although its use in the majority of studies enables accurate comparison of results, it appears to be more sensitive as a screening tool for seasonality than as a diagnostic instrument. A variety of studies testing the external validity of the SPAQ have revealed markedly contrasting results, with some suggesting it overestimates the prevalence of SAD and others suggesting the opposite.[4] Thus the validity of results based on studies using this tool must be questioned. However, despite these concerns, interest in this syndrome continues to be stimulated by developments in chronobiology, neuroscience, neuropsychology and novel antidepressants, particularly agomelatine.

Characteristics of SAD

SAD has been reported to affect between 0-7.9 per cent of the general population depending on which study and which geographical region is being focused on. Studies in the UK screening with the SPAQ and further interviewing using DSM-IV criteria have yielded rates between 2.4 and 3.5 per cent.[5,6] SAD is generally believed to affect women more than men and the age of onset is usually between 20-30 years, although most can recall symptoms from earlier in their life. The ratio discrepancy between the sexes tends to diminish in old age. The onset of symptoms characteristically commence in the autumn or winter, peak in December/January and then remit during the spring and summer during which up to a third of patients can develop hypomanic symptoms.[7] The symptoms of SAD tend to be in the 'atypical' neurovegetative cluster of the affective spectrum presenting more commonly than other affective disorders with carbohydrate craving, hyperphagia, hypersomnia, weight gain and psychomotor slowing as well as a lower incidence of suicidal ideation.[4] However, SAD shares symptoms of low mood, loss of interest, anhedonia, anxiety, low libido, low motivation and social

self-isolation with the affective disorders, with a similar impact on social functioning.

Pathogenesis

In the field of chronobiology, the possible influences of photoperiodic mechanisms, melatonin and circadian rhythms have all been the subject of intense interest. However, contributions from neuroscientific studies revealing neurotransmitter abnormalities as well as certain genetic vulnerabilities have also contributed greatly to our understanding of the syndrome.

The influence of the photoperiod

The seasons and their associated changes in the photoperiod are known to have profound effects on the physiology and behaviour of various species. They are known to affect breeding patterns and also initiate energy conservation strategies such as hibernation, with which the symptoms of winter SAD share some common features. Since extending the photoperiod underpinned some of the first successful treatments of winter SAD, it is understandable that initial interest focused on a lack of winter sunshine as a causal factor. Unfortunately, early prevalence data failed to support this theory, with inconsistent results. Low prevalence rates detected in 'migratory stable' northern populations, *eg* Iceland, have since been felt to reflect a reproductive advantage and a diminished risk of migrating southwards. In contrast, migrating further north or south from the equator is likely to result in an increased risk of SAD. This suggests a complex interaction between genetic vulnerability and migratory habits, creating heterogenous sample populations.

In other studies, warmer weather and more time outside have been reliably shown to have a positive effect on mood and cognition during the spring time but not at other times of the year.[8] However, additional factors such as climate, temperature and natural light exposure during the winter time vary between geographical areas as well as between the individuals being studied. Any study producing reliable results would thus have to allow for these highly intercorrelated variables. A more robust recent study by Young *et al*,[9] which allowed for these environmental factors suggested that the photoperiod may indeed affect the onset and clinical course of SAD. This has been supported by other studies in the literature[10] but the strength of this influence has not yet been clarified.

Melatonin and the phase shift hypothesis

An abnormality in nocturnal melatonin secretion was the first biological mechanism hypothesised to play an aetiological role in SAD. Melatonin is a hormone secreted rhythmically by the pineal gland in response to signals originating from cells forming the 'biological clock' in a region of the brain known as the suprachiasmatic nucleus (SCN). These signals are modulated by communications from light-sensitive ganglion cells in the retina, which enable the SCN to adapt its signals to the pineal gland in response to light exposure. Once released, melatonin binds to the G-protein-coupled melatonin receptors, MT_1 and MT_2 in the SCN, thereby modulating its action. While individual clock cells in the SCN have been shown to have their own internal rhythmical activity (running on a circadian rhythm of roughly 24 hours), their activity can be harmonised by external modulators (known as 'zeitgebers') such as body temperature and ambient light. The duration of nocturnal melatonin secretion is longer in winter than in summer and the response of various central and peripheral sites to this changing duration manifests itself in different adaptive measures to the seasonal environment.

Various initial studies supported an atypical melatonin response in SAD, the most significant of which was a comparison study by Wehr *et al*. of subjects diagnosed with SAD and a control group, which revealed a longer duration of melatonin secretion in winter in the SAD cohort.[11] Further analysis of aberrant melatonin levels in study populations revealed either an advance or a delay in the phase of circadian rhythm resulting in 'internal clocks' being out of sync with 'external clocks' or usual sleep/wake rhythms resulting in some of the symptoms associated with SAD. Lewy *et al*.[12] believe that this circadian misalignment is thought to be responsible for 35-65 per cent of the symptom variability in SAD.

The most widely used marker for endogenous circadian phase position is the measurement of plasma (or salivary) melatonin levels under conditions of dim light (dim light melatonin onset (DLMO)). Dim light is regarded to be the level of light that makes reading difficult without the assistance of artificial light and is not likely to suppress the evening rise in melatonin production.[13] A recent study using this technique revealed that roughly two-thirds of patients with SAD have a phase delay and the other third a phase advance.[13] For patients with a phase delay, the use of melatonin alone in the evening[13] or light therapy alone in the morning[14-16] in an effort to correct this delay have been shown to be of clinical benefit. For those with a phase advance, the use of light therapy in the evening is generally accepted to be useful. Interestingly, patients without circadian shifts may also benefit from light given 8.5 hours after the melatonin onset, suggesting that it is primarily the size of

the phase advance relative to an individuals sleep rhythm that is of prime importance.[16] However, not every individual with a circadian phase shift abnormality develops SAD, suggesting that other factors must play a role.

Genetics, clock genes and SAD

Due to the paucity of research on the heritability of SAD, it is difficult to form any concrete conclusions. The fact that there is an increased prevalence of other psychiatric conditions, most notably mood disorders and alcoholism,[10,17] in first-degree relatives of patients diagnosed with SAD suggests that there could be some shared genetic variants that might predispose these individuals to a seasonal variation in their symptoms. In addition, an increase in seasonality of mood symptoms in first-degree relatives of SAD patients[10] and the link between polymorphisms in the promoter region of the serotonin transporter gene and seasonal affective symptoms[18] has lent support to a genetic vulnerability, although the latter finding has been debated.[19]

The first clock gene (period or per) was discovered 30 years ago in the fly *Drosophila melanogaster* and since then multiple genes have been identified in humans, which together regulate the activity of the clock cells in the SCN through positive and negative feedback loops. The influence in SAD may arise from defective clock genes affecting the functioning of the clock cells in the SCN, as demonstrated in other chronobiological disorders such as familial advanced sleep phase syndrome and delayed sleep phase syndrome. As this is still an emerging field, reproducible precise delineation of the particular gene phenotypes remains a necessity prior to valid conclusions being drawn. However, the majority of interest appears to be focusing on polymorphisms in the genes CLOCK, period 2, period 3 and neuronal PAS domain protein 2 (NPAS2)[20] and more recently period circadian protein homolog 2 (per2) and aryl hydrocarbon receptor nuclear translocator-like (Arntl)[21] contributing to the pathogenesis of SAD. However, like mood disorders, SAD is a complex disorder with many environmental influences so it is likely to have a multifactorial aetiology with single genetic variants playing a small role.

Cognitive and behavioural influences

An integrative approach assessing genetic, psychological and environmental factors is already well established in guiding the diagnosis and management of a variety of mental illnesses. Of most relevance here is that maladaptive attitudes or assumptions, poor coping strategies, ruminative tendencies and negative attributional styles are widely accepted as vulnerability factors in the genesis and perpetuation of mood disorders. In common with non-seasonally depressed individuals, SAD sufferers display depressotypic attributes,[22,23] underlying dysfunctional attitudes,[23-25] similar levels of negative thinking and rumination[23,26] and selective Stroop interference.[27] However, in contrast, SAD sufferers do not show depressotypic mood congruent bias for negative words[28] or difficulties in accessing specific autobiographical memories.[29] There is a suggestion that rumination may represent a prominent risk factor for the development of SAD from autumn to winter.[30]

Role of neutotransmitters

It is widely accepted in the literature that the major neurotransmitters implicated in mood regulation (dopamine, noradrenaline and serotonin) as well as some of their receptors are influenced by circadian mechanisms. However, linking SAD with specific neurotransmitter abnormalities has been more challenging.

Serotonin

Considerable evidence in the literature has linked a seasonal variation in mood, suicide and appetite to changes in central and peripheral serotonergic function. As these features are prominent in SAD, it is understandable that interest has focused on whether some variations in serotonergic function are peculiar to patients with SAD or whether they represent normal physiological variations that may predispose an individual to any affective illness. Studies using metachlorophenyl-piperazine (m-CPP), a non-specific serotonin agonist, have shown that patients with SAD have reported subjective improvements in mood and energy levels.[31] This improvement was not replicated in a group of patients with non-seasonal depression.[32]

Tryptophan depletion has been shown consistently to precipitate a depressed mood in subjects with seasonal and non-seasonal depression and also to reverse the antidepressant effect of light therapy.[33] In addition, the carbohydrate craving associated with SAD has been shown to increase dietary intake of tryptophan, resulting in subjective reports of improved mood.[34,35]

The use of single photon emission computed tomography (SPECT) scanning has revealed a reduced thalamic and hypothalamic serotonin uptake in patients with SAD compared with healthy controls.[36] Unfortunately there are relatively few similar studies and it remains to be seen whether the use of

light therapy or antidepressants could improve outcomes measured by SPECT scanning.

Catecholamines
Although not as intensely studied as serotonin, both dopamine and noradrenaline are felt to play significant roles in the pathogenesis of SAD. Symptoms of a noradrenergic (and dopaminergic) deficit are characteristically those of fatigue, amotivation and reduced alertness – all prominent features of SAD. Studies have shown patients with SAD to be less responsive to exogenous noradrenaline and demonstrate an increased plasma level of noradrenaline following light therapy.[37]

The role of a dopamine deficit has been suggested by a reduction in the availability of dopamine transporters in SAD patients compared with healthy controls.[38] The dopaminergic system is also known to play a strong role in the natural reward pathway, suggesting a possible dual role with serotonin in the mechanism underlying the binge eating noted in SAD. Interestingly, dopamine is known to have a prominent role, through dopamine D_4 receptors on the retina, in light/dark adaptation, although no research to date has shown that a mutation in the genes coding for these receptors play a role in SAD.[39] Additional support for a dopaminergic deficit comes from neuroimaging studies, which have revealed decreased dopaminergic uptake in the striatum of patients with SAD compared with healthy controls.[39]

Current management strategies

Current management strategies centre upon the use of light therapy and antidepressants. In clinical practice, light therapy is suggested for those patients with a more typical SAD symptom profile, *ie* hypersomnia, weight gain and carbohydrate craving, in a seasonal pattern.[7] Antidepressants are advised for patients with predominant symptoms of weight loss, early morning wakening or episodes of non-seasonal depression.[7] Choice is often guided by patients who may prefer the non-drug option of light therapy as an initial intervention. Melatonin use is well documented in the correction of circadian-shift disorders, particularly the visually impaired, but there are few studies of its use as a sole agent in SAD. Lewy *et al*.[12] discovered that oral melatonin had an effect size in SAD similar to that of an antidepressant in a mood disorder, although this was not the focus of their study.

Light therapy
Following Rosenthal *et al*'s[1] initial description of the potential therapeutic benefit of bright light, attention has focused on demonstrating the efficacy of light therapy, as well as clarifying the optimum intensity, duration and timing of exposure. Initial randomised control trials were hampered by small trial numbers, short treatment duration and the difficulty in producing an adequate control for bright light. In addition, the patients involved in the trials were generally knowledgeable, self-diagnosed individuals expecting a response from bright light: a situation highly likely to produce a strong placebo response. However, the use of negative ion generators (either functional or deactivated) in trials with larger cohorts have produced more robust data.[40,41] More recent reviews using meta-analyses, in particular a review by Golden *et al*,[42] have supported the benefits of light therapy generally for seasonal (particularly sub-syndromal) as well as non-seasonal depression, and dawn simulation therapy specifically for SAD.

Current consensus is that light therapy is most effective in the early morning (based on the fact that most cases of SAD have a phase delay) and that an intensity as close to 10000 lux as possible should be used for a minimum of 30 minutes at a time.[7] Time to response is usually between two to four days and three weeks and the specifics of duration and intensity can be adjusted depending on response and side-effects. Most frequent side-effects are insomnia, headaches, blurred vision and overactivity, with rarer effects being overadvancement or hypomania/mania, although light therapy is generally very well tolerated. The most commonly used instruments are lightboxes but there is evidence for the efficacy of visors or dawn-stimulating alarm clocks.[7]

Antidepressants
Antidepressants as a treatment for SAD have not been studied as extensively as light therapy. Attention has focused primarily on the SSRIs and there is general consensus that fluoxetine[43] and sertraline[44] have enough evidence from large ran-

Key points

- There is significant evidence supporting the influence of seasonal and chronobiological mechanisms in mood disorders
- Recognising and effectively managing these components can substantially reduce morbidity
- There is evidence supporting the tailored use of psychotropic medication (bupropion and SSRIs), light therapy, cognitive behavioural therapy and melatonin in seasonal affective disorders
- The novel antidepressant agomelatine may be a useful option in this cohort

domised controlled trials to justify their use in SAD although neither has a licence that covers its use in this condition specifically. Smaller studies have suggested that other antidepressants including reboxetine, citalopram, and tranylcypramine are beneficial, as well as L-tryptophan and St Johns Wort but further replication is needed. Bupropion, a dopamine and noradrenaline reuptake inhibitor, was licensed in 2006 in the USA for the prevention of further depressive episodes in patients diagnosed with SAD. The CAN-SAD study,[45] a randomised controlled trial comparing light therapy and fluoxetine, revealed the two to be equally efficacious, with light therapy having a slightly quicker response rate and fewer adverse effects reported.

More recently, agomelatine, a potent melatonin-receptor agonist and $5HT_{2C}$ antagonist licensed for the treatment of depression, has refocused attention on the role of circadian dysfunction in depression. Despite having a different pharmacokinetic profile to melatonin, it has been demonstrated to cause phase advancement in circadian rhythms measured by body temperature and cortisol levels.[46] A significant improvement in sleep architecture has been noted as early as one week after starting treatment.[47] What remains unclear is whether agomelatine's antidepressant effect stems from its role as a $5HT_{2C}$ antagonist, through its modulation of circadian rhythms, or through its indirect effect of enhancing noradrenergic and dopaminergic neurotransmission within the prefrontal cortex. Recent evidence suggest that treatment of depression in patients diagnosed with SAD has been equally efficacious, suggesting that agomelatine may be a reasonable first-line agent in depressed patients showing a seasonal pattern in their presentation.[48,49]

Psychological approaches

Despite the fact that there is clear evidence of dysfunctional psychological mechanisms, both particular to SAD and shared with other mood disorders, there is currently a distinct lack of trials to support the role of psychological therapies in the treatment of SAD. Intuitively, a psychological approach should confer benefit particularly as an adjunctive intervention or possibly as an initial approach in mild cases. Of most relevance would be cognitive behavioural therapy (CBT) for which there is a large evidence base for its use in other mood disorders. Preliminary data by Rohan *et al*.[50,51] suggest that a tailored course of CBT is as efficacious as light therapy in the acute phase and better at preventing relapse;[52] however, there is a clear need for further study.

Conclusion

The validity of SAD as a specific syndrome continues to be questioned, primarily as a result of the use of the SPAQ as a diagnostic tool and the distinct heterogeneity of the patient group SAD encompasses. However, it is clear that there is a group of patients with atypical symptoms of an affective disorder who benefit from the use of light therapy with or without the additional use of an antidepressant or melatonin. A developing grasp of the chronobiological mechanisms underlying the seasonal aspects as well as the neurotransmitter deficits in this group has led credence to the 'dual vulnerability' model first proposed by Young *et al*. in 1991.[53] This model suggests that the interplay between a vulnerability to seasonal as well as depressive factors contributes to the SAD phenotype.

A modification of this model has more recently been suggested by Rohan *et al*,[30] incorporating more recent evidence and supporting a more integrative approach to the understanding and management of SAD. These models advocate that clinicians need a far clearer understanding of the underlying pathophysiology of the condition, as a precise and thoughtful intervention could result in a substantial reduction in seasonal morbidity. It is highly likely that SAD will become more acutely defined as co-ordinated research develops a clearer aetiological and phenotypical picture, and that newer treatment strategies such as agomelatine, CBT, negative ion treatment, more efficient light devices, exercise and dietary supplements may increase management options.

Declarations of interest

None.

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