FROM DRUG AND THERAPEUTICS BULLETIN

Management of seasonal affective disorder

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Low mood associated with a certain season (usually winter) is very common. For example, in the UK, up to 6% of adults have "recurrent major depressive episodes with seasonal pattern", commonly known as seasonal affective disorder (SAD).[1-3] People with SAD consult in primary care more often than age- and gender-matched control groups; patients also receive more prescriptions and are referred more often to secondary care.[4] Around 6-35% of patients require hospitalisation for SAD at some point.[5] Here we discuss the management of adults with SAD, and in particular light therapy.

About SAD

SAD involves symptoms typical for depression (eg, lowered mood, energy loss, fatigue) and also atypical symptoms (eg, hypersomnia, increased appetite and eating, carbohydrate craving, weight gain).[1 2 6] Some specialists have questioned the value of considering "SAD" as a separate diagnostic category from non-seasonal depression;[7] and of note it is classified as a subset of recurrent major depressive or bipolar disorder rather than as a separate category by both the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; see box 1) and the World Health Organization's International Statistical Classification of Diseases and Related Health Problems (ICD-10).[1 8]

What causes SAD?

Evidence suggests that SAD has a genetic element, with genes affecting serotonin metabolism (which has a seasonal pattern) being implicated in seasonal mood variations.[9 10] Melatonin, a hormone secreted by the pineal gland during darkness, has also been implicated in the aetiology of SAD. It is important in the regulation of daily or 'circadian' rhythms (eg, the sleep-wake cycle) and seasonal or 'circannual' rhythms (eg, regulating reproduction in many mammals).[11] The time at which the plasma melatonin concentration rises occurs later in patients with than without SAD.[12] Nocturnal melatonin secretion can be suppressed by light (eg, a light intensity of around 3000 lux suppresses melatonin secretion by around 70%; see box 2 for examples of light intensities measured in lux).[13 14]

Who gets SAD?

The mean age of onset of SAD is around 27 years; it can occur in childhood, when rates among girls and boys are similar.[5 16] Women are up to four times more likely than men to be affected during the reproductive years.[9 17] In older adults, prevalence rates decline and the genders are equally likely to be affected.

Clinical course

Episodes of SAD last around 4 months.[5 18] Around 60% of patients diagnosed with SAD continue to have a seasonal disturbance of mood and/or behaviour in the long term, while around 20% have complete remission within several years of first diagnosis.[9] Some patients have manic or hypomanic episodes in spring and summer.[19] SAD can markedly impair quality of life in winter, but this may return to normal in summer.[20 21]

Diagnosis

Various rating scales have been used to measure symptoms in SAD (eg, the 21-item and 17-item versions of the Hamilton Depression Rating Scale [HAM-D21 and HAM-D17, respectively] and the six-item depression subscale [HAM-D6]).[18] The gold standard of diagnosis is a

Box 1 | DSM-IV criteria for "with seasonal pattern" within recurrent major depressive disorder or major depressive episodes in bipolar disorder[1]

Regular temporal relationship between the onset of major depressive episodes and a particular time of the year (eg, fall [autumn] or winter)

Full remissions (or a change from depression to mania or hypomania) at a characteristic time of year (eg, spring)

In the last two years, two major depressive episodes that demonstrate the seasonal relationship and no non-seasonal episodes

Seasonal episodes substantially outnumber non-seasonal episodes that may have occurred over the individual's lifetime

Box 2 | Examples of light intensities measured in lux[14 15]

Moonlight: 0.2 lux
Winter's day: 20 000 lux
Bright sunny summer's day: 100 000 lux

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Previous Clinical Reviews
- Diagnosis and management of the antiphospholipid syndrome (*BMJ* 2010;340:c2541)
- Percutaneous endoscopic gastrostomy (PEG) feeding (*BMJ* 2010;340:c2414)
- Management of medication overuse headache (*BMJ* 2010;340:c1305)
- Screening and treatment of *Chlamydia trachomatis* infections (*BMJ* 2010;340:c1915)
- Paediatric obstructive sleep apnoea (*BMJ* 2010;340:c1918)

Box 3 | Structured Interview Guide Hamilton depression rating Seasonal Affective Disorder (SIGH-SAD): an interview covering HAM-D21 plus Atypical Depression Supplement of 8 items giving HAM-D29[22-24]

Current SAD episode criteria: total SIGH-SAD 20 or more, including HAM-D21 10 or more and Atypical Depression Supplement 5 or more

Response: a reduction of at least 50% from baseline

Remission: score falls to below 8[25]

structured interview to determine whether patients fulfil DSM-IV criteria (see box 3).[9]

Conventional antidepressants

Acute treatment of SAD

The suggestion that serotonin metabolism is disordered in SAD underlies the use of selective serotonin reuptake inhibitors (SSRIs) for acute treatment of patients with the condition; however, there have been few good-quality clinical trials of such intervention.[26]

One five-week randomised placebo-controlled trial, involving 68 adults with SAD, found a higher response rate with fluoxetine 20 mg daily (59% *v* 34% with placebo, P<0.05).[27] A second, eight-week, placebo-controlled trial, involving 187 adults with SAD and a mean baseline HAM-D29 of around 36, found a greater change in mean HAM-D29 with sertraline 50-200 mg daily (-17.90 *v* -13.39 with placebo, difference 4.51, 95% CI 0.76 to 8.28).[23]

Fluoxetine and sertraline are licensed for major depressive episodes, although SAD is not specifically mentioned in the summaries of product characteristics (SPCs) for these drugs.[28 29]

Prevention of SAD episodes

Given that SAD may recur, long-term and maintenance treatment may be needed.[30]

Pooled data from three randomised trials, involving a total of 1042 patients who started treatment before onset of SAD symptoms in autumn, suggested that compared with people on placebo, there was a lower recurrence rate among those on bupropion 150-300 mg daily (a noradrenaline and dopamine reuptake inhibitor not licensed in the UK for this indication, and not commonly used for SAD in UK practice; 16% *v* 28%; relative risk [RR] 0.56).[5 31] However, no P values were stated for this difference.

Light therapy

Why use light therapy?

No clear mechanism of action has been established for light therapy in SAD. One theory is that morning bright light counters disordered circadian rhythms in patients with SAD.[32 33] Other theories suggest that light may also have direct effects on some neurotransmitters (eg, serotonin).[10]

What does light therapy involve?

Light therapy involves daily scheduled exposure to fluorescent light boxes, dawn simulators (devices that slowly increase the room illumination over a period of around 90 minutes during sleep), or incandescent light visors (shaped like baseball caps with light sources shining from the brim down into the wearer's eyes). The "dose" of light is determined by the intensity and duration of exposure.[34]

Assessing light therapy

Methodological difficulties

Several factors make designing trials of light therapy difficult. For example, the appropriate "minimum dose" of treatment is unclear, and it is hard to find a credible control condition since patients are not "blind" to therapy, and treatment expectations may contribute to a positive outcome.[34 35] The acceptable maximum dose for a low-light control is not known.

In addition, it is difficult to combine the results of light therapy trials in a meta-analysis due to differences between studies in terms of the doses of light used; the methods of delivery (eg, light box, dawn simulation or visor); comparator treatments; and populations.[36]

Clinical efficacy of light therapy

A systematic review of randomised controlled trials of bright light therapy (at least 3000 lux-hours daily) for SAD found eight studies involving a total of 360 patients with a maximum of 300 lux for controls, and lasting 7-42 days.[37] The effect sizes for a significant reduction in depression symptom severity with bright light were consistently positive across the studies. However, there was significant heterogeneity among the studies, indicating that they should probably not be combined statistically.

The same review also identified five randomised controlled trials (involving a total of 133 patients) assessing dawn simulation (increasing light exposure from 0 lux to around 200-300 lux, over 1.5-2.5 hours) with controls receiving less than 5 lux and/or less than 15 minutes of treatment; the effect size for a significant reduction in symptom severity was reported as moderate to large.[37]

In a meta-analysis of five randomised controlled trials of light visors, no difference between light intensities of 3500–7600 lux, 400–650 lux, and under 100 lux was found; however, the authors stated that the combined statistical power of the studies was insufficient to demonstrate a significant effect.[35]

A recent update of the National Institute for Health and Clinical Excellence (NICE) guideline on the management of depression in adults has reviewed the data on light therapy for depression with a seasonal pattern.[36] This review included 20 randomised controlled trials, comparing light therapy (ranging from 176 lux to 15 000 lux daily) with waiting list control management, "attentional" control (eg, sham light box), or active treatment controls (eg, cognitive behavioural therapy [CBT], fluoxetine). Compared with waiting-list control, bright light reduced depressive symptoms more (eg, weighted mean difference [WMD] in SIGH-SAD score -10.4, 95% CI -15.99 to -4.81); however, bright light did not differ significantly from attentional control or active treatments. The review concluded that it was unclear whether the superior effectiveness of the light therapy compared with waiting list management was more than a placebo effect. Another possibility is that light therapy was as effective as fluoxetine or CBT. The NICE review

also concluded that dawn simulation did not reduce symptoms more than attentional control.[36]

No published randomised controlled trials have assessed the combination of light therapy and antidepressants in SAD.[33]

Unwanted effects of light therapy

Unwanted effects of light therapy include eye strain or visual disturbances (in 19-27% of patients), headache (13-21%), agitation (6-13%), nausea (7%), sweating (7%) and sedation (6-7%).[9] These effects are generally mild and subside with time or with reduction of the dose.[9] Hypomania can also occur.[9 24]

Practicalities of light therapy

Regulations

Light therapy devices intended as treatment for disease, which do not achieve their principal intended action on the human body by pharmacological, immunological or metabolic means, come within the scope of the Medical Device Directive and should carry a CE mark.[38]

Cost

Light boxes and other appliances are available for sale or hire in the UK both online and in high street stores (at around £200), but are not currently available on prescription in the NHS.[39] People defined as "chronically sick or disabled" do not have to pay VAT when they buy equipment (relating to the specific disability) supplied for their personal or domestic use.[40 41] Where required for treating SAD, light boxes are classified as zero-rated for VAT.[40 41]

Stopping and restarting light therapy

There are few data on stopping and restarting light therapy. Specialists suggest that patients on light therapy generally continue treatment until the time of their usual spontaneous remission; it can be stopped abruptly.[24] In rare cases where a patient experiences a relapse, treatment can be resumed for several weeks.

If light therapy is felt to be effective, it can be resumed in subsequent years before, or with the appearance of, the first symptoms (eg, difficulty waking, daytime fatigue, carbohydrate craving) prior to the onset of depression. However, this may be unnecessary, as patients do not always become depressed every winter.

Other treatments

Cognitive behavioural therapy

Two randomised controlled trials of CBT in patients with SAD have been published.[42 43]

The first was a pilot study involving 23 patients who received group CBT tailored to SAD (1.5 hour sessions twice weekly, with four to six participants per group), light therapy (10 000 lux for 45 minutes in the morning and 45 minutes in the evening), or both, for six weeks.[42] SIGH-SAD scores improved from pre- to post-treatment with no significant difference between groups (only graphical information presented). At the 1 year follow-up, no patients treated with CBT (with or without light therapy) the previous winter met SIGH-SAD criteria for relapse, compared with 62.5% of patients who had received light therapy only (P=0.005).

The second study, involving 61 patients with a mean pre-treatment SIGH-SAD score of around 28.6, compared four strategies for SAD: CBT (1.5 hour sessions twice weekly, with four to eight participants per group, for six weeks); light therapy (10 000 lux for 45 minutes in the morning and 45 minutes in the evening for one week, then flexible dosing for five weeks); both of these treatments for six weeks; and waiting list control management (minimal contact monitoring for six weeks; then treatment with light therapy).[43] All three active-treatment groups had a significant fall in SIGH-SAD scores (post-treatment scores: CBT only 12.9; light only 12.7; CBT plus light 8.5) and scores in all these groups were lower than that in the waiting list control group (23.1; P<0.05 for each active treatment).

Self-help and complementary treatments

An NHS Direct patient leaflet on SAD recommends lifestyle changes to reduce symptoms, including exercise, a healthy diet and trying to get as much natural sunlight as possible.[39]

A systematic review of complementary and self-help treatments for depression identified one randomised controlled trial that assessed vitamin D therapy as treatment for SAD (involving only 15 patients but suggesting the treatment was more effective than light therapy); one that assessed vitamin B12 as treatment for SAD (involving 27 patients, which found no benefit); and one that assessed ginkgo biloba for prevention of SAD relapse (involving 27 patients, which also found no benefit).[44]

One randomised trial, involving 27 patients with SAD, compared bright light (2500 lux between 2pm and 4pm daily), physical exercise (training on a stationary bicycle between 1pm and 2pm daily), and "no treatment" for one week.[45] The two active treatments reduced depressive symptoms (HAM-D21 fell by 64.5% with light and 68.5% with exercise, each P<0.001 *v* baseline) while "no treatment" did not (change in score 4.9%, not significant).

Negative ion generators

The environmental concentration of negative air ions varies greatly (for example, it is higher in humid, vegetated environments and at the seashore, and lower in urban environments and heated or air conditioned interiors).[24] It is thought that sustained exposure to negative air ionisation may elevate mood, although no definitive mechanism of action for this effect has been established.[25]

One double-blind randomised controlled trial involved only 25 patients with SAD, who received negative ions from an electronic device for 30 minutes shortly after rising (between 5.30am and 8.30am), for 20 days, at one of two doses.[46] More of those who received the higher density of ions achieved remission (58% with 2.7x106 ions/cm^3 *v* 15% with 104 ions/cm^3, P=0.025).

What do guidelines say?

American Psychiatric Association guidelines published in 2000 suggest that the entire range of treatments for major depressive disorder may also be used to treat patients with

SAD, either in combination with, or as an alternative to, light therapy.[47] As first-line treatment, the guidelines recommend light therapy as a time-limited trial, primarily in out-patients with clear seasonal patterns of symptoms. For patients with more severe depression, the guidelines recommend light therapy as a potential adjunct to psychopharmacologic intervention.

British Association for Psychopharmacology guidelines published in 2008 state that antidepressants are a first-line treatment for moderate and severe major depression in adults irrespective of depression type, and that CBT may be used in addition.[26] For SAD, the guidelines state that light therapy is a first-line acute treatment but that effective prophylaxis against relapse is then needed, including consideration of an antidepressant. The limited evidence available suggests that bupropion or CBT helps to prevent recurrence the following winter.

Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines published in October 2009 recommend "second-generation" antidepressants (eg, SSRIs) or CBT first line for major depressive disorder, and medication plus CBT as second-line treatment.[48 49] For SAD, they recommend light therapy first-line.[33]

The final draft of the NICE guideline on depression in adults, updated for publication in October 2009, suggests that people with depression with a seasonal pattern should be treated according to the strategy offered in the guideline for major depressive disorder in general.[36] Recommendations include an antidepressant (normally an SSRI) or CBT for mild to moderate depression, or both for moderate or severe depression; and that CBT should be offered for relapse prevention. The draft guideline also states that although there are a large number of studies that address the efficacy of light therapy in people with seasonal depression, they are difficult to interpret due to methodological differences. It goes on to propose that patients with winter depression who wish to try light therapy in preference to antidepressant or psychological treatment should be advised that the evidence for the efficacy of such therapy is uncertain.

The various guidelines appear to have reached different conclusions about light therapy because they included different studies and analysed primary data or published meta-analyses.[50]

Conclusion

Seasonal affective disorder (SAD) describes a subtype of major depression which has a seasonal pattern (usually winter depression and remission or hypomania during spring and summer). It includes atypical symptoms such as hypersomnia, carbohydrate craving and weight gain. A common approach is to treat the condition as for non-seasonal depression, for example, using SSRI antidepressants and/or cognitive behavioural therapy (CBT).

Light therapy has been suggested for treating people with SAD. Trials of such therapy are complex as they need a plausible control arm, and methodological differences between published trials have made the results hard to interpret. In addition, reviews and guidelines of light therapy have included different trials and reached contradictory conclusions. Nevertheless, bright light therapy in the early morning, using a light box or dawn simulation, appears to be a reasonable first-line approach to relieve depressive symptoms, instead of, or as well as, drug therapy and/or CBT when the patient has mild or moderate symptoms; people with more severe symptoms should be treated with antidepressant drugs, with or without light therapy and/or CBT.

For prevention of subsequent episodes, there is limited evidence for a benefit of CBT or bupropion (an unlicensed indication in the UK).

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ANSWERS TO ENDGAMES, p 1203. For long answers go to the Education channel on bmj.com

STATISTICAL QUESTION

Study design

Answer *d* is correct; answers *a*, *b*, and *c* are incorrect.

ON EXAMINATION QUIZ

A and B are appropriate actions; C, D, and E are not.

More questions on this topic are available from www.onexamination.com/endgames until midnight on Wednesday.

PICTURE QUIZ

Severe perianal ulceration

1 **Differential diagnoses are herpes simplex infection (HSV) of the genitals, tuberculosis, and infection with atypical mycobacteria. Other possibilities include inflammatory dermatoses such as metastatic Crohn's disease; pyoderma gangrenosum; vasculitis; lichen planus; Behçet's syndrome; autoimmune blistering disease, such as pemphigus vulgaris; and drug reactions. The history of lymphopenia and immunocompromise make HSV the most likely diagnosis.**
2 **A microscopy, culture, and sensitivity swab and viral swab of an ulcer, diagnostic punch biopsy from the edge of an ulcer for histology, immunofluorescence, culture, and colonoscopy to investigate the recurrent diarrhoea.**
3 **Treatment guidelines for chronic suppressive therapy for genital herpes in the immunocompromised patient recommend oral aciclovir 400 mg twice daily. The length of treatment has not been defined and depends on the patient and the disease course. Many patients will need suppression for a year or longer.**