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Review Article

Seasonal affective disorder

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CONTENTS

Abstract

Seasonal affective disorder (SAD) is a mood disorder characterized by recurrent episodes of major depression most frequently occurring during the winter months. A dysfunction in the serotonergic system has been implicated in the pathophysiology of SAD, together with an abnormal delay of circadian rhythms in winter. Therapy with bright light has been shown to be an effective treatment for SAD, although as many as 50% of individuals with SAD do not demonstrate clinically significant improvement with light treatment. There is some evidence that augmentation with cognitive-behavioral therapy or pharmacotherapy may improve responses or reduce subsequent relapse rates. The noradrenaline and dopamine reuptake inhibitor bupropion is the only drug approved by the U.S. Food and Drug Administration for the prevention of seasonal major depressive episodes. In terms of other pharmacotherapy for the treatment or prevention of SAD, very few randomized, controlled studies have been conducted. However, studies evaluating the selective serotonin reuptake inhibitors (SSRIs) sertraline and fluoxetine have demonstrated their efficacy in the treatment of this disorder.

Introduction

Seasonal affective disorder (SAD) is a mood disorder characterized by a recurrent, cyclical occurrence of major depression most frequently present during the winter months. It was first described during the 1980s (1). The longitudinal course of SAD is described by the seasonal pattern specifier of DSM-IV-TR (2); recurrent major depressive episodes are characterized by a regular temporal relationship between the onset of the episodes and a particular time of the year, and full remissions that also occur at a characteristic time of the year. Diagnostic criteria also include two major depressive episodes in the previous 2 years that demonstrate these temporal seasonal relationships, and no nonseasonal episodes during that same period. In addition, seasonal episodes should substantially outnumber the nonseasonal major depressive episodes that may have occurred over the individual's lifetime.

SAD is a relatively common condition, affecting 1-3% of adults, and it is more prevalent in women. Common symptoms, in addition to depressed mood, include an increased duration of sleep, fatigue, carbohydrate craving and subsequent weight gain (3). The pathophysiological mechanisms underlying SAD are incompletely understood, although a dysfunction in the serotonergic system has been implicated (4). Evidence for the effect of sunlight on brain serotonergic activity was demonstrated in a study in 101 healthy men, which showed that the turnover of serotonin in the brain was lowest in winter and that the rate of production of serotonin by the brain was directly related to the prevailing duration of bright sunlight (5). The role of circadian rhythms in SAD has also been investigated and the phase-shift hypothesis predicts that the symptoms of SAD will improve if circadian rhythms can be phase-advanced (photic entrainment) (6). Furthermore, circadian and serotonergic polymorphisms have also been identified in patients with SAD (7, 8). There is also some evidence for the role of G-protein-coupled signal transduction (9) and brain dopaminergic systems (10) in the pathophysiology of SAD.

The first comprehensive clinical guide to the diagnosis and treatment of SAD was published in 1999 by a group of Canadian researchers and clinicians. This represented a systematic review of all the available evidence regarding the diagnosis, clinical features, epidemiology, pathophysiology and treatment of SAD. Recommendations for treatment were based on levels of evidence, where level 1 evidence was based on randomized, controlled trials with sufficient numbers, or good-quality meta-analyses based on randomized, controlled trials (11).

Treatment approaches in SAD

Light therapy

Light therapy is an effective treatment for SAD, as shown by a recent meta-analysis of 23 studies (12). It is recommended as first-line treatment for SAD (level 1 evi-

dence) in the Canadian Consensus Guidelines (11). Appropriately timed treatment with bright light can redress the abnormal delay of circadian rhythms in winter, which is the basis of the phase-shift hypothesis for winter SAD (6, 13).

A small study showed that growth hormone (GH) responses to a challenge with the 5-HT_{1D} receptor agonist sumatriptan were blunted during winter depression in patients with SAD compared to healthy controls. Following symptom improvement achieved by treatment with light therapy, the GH responses were normalized to levels similar to in controls (14). In a group of 43 patients who received active light therapy using a fluorescent light box as part of a randomized, controlled study (15), there were significant improvements in the Structured Interview Guideline for the Hamilton Depression Rating Scale (HAM-D), SAD version (SIGH-SAD) (16), specifically including the 7-item atypical addendum score (HAM-D17+7). Subjects were outpatients aged 18-65 years with major depressive episodes with a winter pattern. They completed 8 weeks of treatment using a light box for 30 min daily on wakening (17). In a 3-week, parallel-design study in 26 patients, assessment of SIGH-SAD scores showed that narrow-band blue light-emitting diode light therapy was more effective than dimmer red light in reversing the symptoms of SAD (18).

Naturalistic dawn simulation has also been considered as an alternative to bright light therapy, and in a study including 94 patients with major depressive disorder with a winter seasonal pattern, post-treatment improvements in SIGH-SAD were broadly similar for dawn simulation, bright light and dawn pulse (19). In addition, a randomized, double-blind, crossover study demonstrated that bright light therapy might also be an effective treatment for pediatric SAD (20).

The Canadian Consensus Guidelines recommend the use of the fluorescent light box, with light intensities greater than 2500 lux. A recommended starting dose is 10,000 lux for 30 min/day, with early morning exposure on wakening being given to obtain maximum treatment response (all level 1 evidence) (11).

Augmentation of light therapy

Approximately 50% of individuals with SAD do not demonstrate clinically significant improvement with light treatment, particularly those with more severe symptoms and more typical depressive features (21, 22). Therefore, light therapy has also been evaluated in combination with cognitive-behavioral therapy (CBT) and with pharmacological augmentation. In a 6-week pilot study, light therapy, a novel SAD-tailored group CBT and their combination were compared in 23 patients. Depressive symptoms and remission rates were assessed post-treatment and at 1-year follow-up using SIGH-SAD and the Beck Depression Inventory (BDI). All three therapies significantly improved symptoms during the initial treatment period; however, during the subsequent winter, no CBT-treated subject, with or without light, experienced a full SAD relapse compared to over 60% of those treated with light alone (23).

In an open-label study, 16 partial and nonresponders to 2 weeks of a standard morning light therapy regimen were treated for a further 2 weeks with L-tryptophan while light therapy was continued. Augmentation of light therapy with L-tryptophan resulted in a significant reduction in mean depression scores measured by SIGH-SAD and significant improvements in Clinical Global Impression (CGI) scores (24).

Hypericum extract (St. John's wort) was evaluated in a randomized, single-blind study in 20 patients with SAD. After 4 weeks' treatment, *Hypericum* was associated with a significant reduction in the total score of the HAM-D. However, there was no significant difference when bright light therapy was combined with *Hypericum* compared with the group that received *Hypericum* plus dim light (25). In a population of 282 SAD patients with moderate depression, over 50% of patients responded to 1 week of bright light treatment. Responders were allocated to receive either citalopram or matching placebo for 15 weeks. The relapse rate was generally lower for citalopram (mean dose of 26.3 mg daily) than for placebo, but the differences only reached statistical significance based on the HAM-D 6-item depression subscale (HAM-D6) and the Melancholia Scale (26).

A summary of clinical studies assessing the efficacy of light therapies in SAD is given in Table I.

Pharmacotherapy

1. Bupropion

Bupropion was approved by the U.S. Food and Drug Administration (FDA) in June 2006 for the prevention of seasonal major depressive episodes. It is the first and only medication approved for SAD (27). Bupropion is a noradrenaline and dopamine reuptake inhibitor that was licensed for the treatment of major depressive disorder in the U.S. in 1989 (28).

Three prospective, randomized, placebo-controlled studies conducted in the U.S. and Canada investigated the possibility of preventing the onset of autumn-winter depression by initiating treatment early in the season. A total of 1,042 subjects with SAD were enrolled and received either bupropion 150-300 mg or placebo until spring and were then followed off medication for a further 8 weeks. Despite a high average number of previous seasonal depressive episodes, nearly 60% of the subjects had never received treatment for depression. In a combined analysis, bupropion reduced the risk of developing a seasonal major depressive episode by 44% relative to the placebo group (29).

2. SSRIs

Very few randomized, controlled clinical studies have been conducted in patients with SAD. The efficacy of sertraline, an SSRI, was evaluated in 187 outpatients with SAD in a randomized, double-blind, placebo-controlled study. Patients received either sertraline 50-200 mg once

Table I: Clinical studies assessing the use of light therapies in seasonal affective disorder (SAD) (from Prous Science Integrity®).

Design	Treatments	n	Conclusions	Ref.
Open	Light, 10,000 lux over 30 min o.d. x 3-6 wks	11	Light therapy normalized growth hormone response to sumatriptan challenge in patients with SAD	14
Multicenter Randomized Double-blind	Light, 10,000 lux over 30 min o.d. x 8 wks Fluoxetine, 20 mg/d p.o. x 8 wks	96	Light therapy and fluoxetine produced similar results in patients with SAD, except that light therapy showed an earlier onset of response and fewer adverse events compared with fluoxetine	15
Open Multicenter	Light, 10,000 lux over 30 min o.d. x 8 wks	43	Light therapy in patients with SAD showed a tendency for a quadratic relationship between phase angle difference and on-treatment depression rates, and a trend for a phase angle difference of 3 h	17
Open	Fluorescent light [4200ºK], 2664 μW/cm^2 over 45 min o.d. x 3 wks Blue light-emitting diode, 607 μW/cm^2 over 45 min o.d. x 3 wks Red light-emitting diode, 34 μW/cm^2 over 45 min o.d. x 3 wks	26	Narrow-band blue light at 607 μW/cm^2 was more effective than red light in reversing symptoms of major depression with a seasonal pattern	18
Randomized Comparative	Dawn light stimulation, 0.0003-250 lux o.d. x 3 wks Dawn light pulse, 250 lux over 13 min o.d. x 3 wks Light, 10,000 lux over 30 min o.d. [postawakening] x 3 wks Ionization, 4.5 x 10^{14} ions/s over 93 min o.d. x 3 wks Ionization, 1.7 x 10^{11} ions/s over 93 min o.d. x 3 wks	99	Higher response rates were associated with bright light therapy and dawn pulse, and were not significantly different from dawn stimulation; these therapies were all more effective than air ionization	19
Randomized Double-blind Crossover	Light, 2500 [age < 9 y] or 10,000 [age ≥ 9 y] lux over 1 h x 1 wk Placebo	28	Light therapy was effective for the treatment of pediatric patients with SAD	20
Randomized	Cognitive-behavioral therapy, 1.5 h 2x/wk x 6 wks Light, 10,000 lux over 45 min b.i.d. x 6 wks Cognitive-behavioral therapy, 1.5 h 2x/wk + Light, 10,000 lux over 45 min b.i.d. x 6 wks	26	Cognitive-behavioral therapy was beneficial in nearly half of the patients with SAD not responding to light therapy alone and was a useful adjunct or alternative therapy, especially for recurrence prophylaxis	23
Open	L-Tryptophan, 1 g p.o. t.i.d. + Light, 10,000 lux over 30 min x 2 wks	16	L-Tryptophan augmentation of light therapy could be effective in patients with SAD with limited or poor response to bright light therapy alone	24
Randomized Single-blind	St. John's wort extract, 900 mg/d p.o. x 4 wks St. John's wort extract, 900 mg/d p.o. + Light, 3000 lux o.d. x 4 wks	20	St. John's wort extract was effective for the treatment of SAD and no additional effect was obtained with concomitant light therapy	25
Randomized Double-blind	Light, 5000 lux over 2 h x 7 d → [if response] Citalopram, 20 mg/d → escalated to 40 mg/d or 60 mg/d [according to response] x 15 wks Light, 5000 lux over 2 h x 7 d → [if response] Placebo x 15 wks	282	Citalopram was able to prevent relapse in patients with SAD responding to 1 week of bright light therapy	26

daily or matching placebo for 8 weeks. Sertraline treatment resulted in significant improvement in scores compared with placebo based on the HAM-D and CGI scales (30). Another randomized, controlled trial conducted in Canada over three winter seasons compared the efficacy of light therapy with fluoxetine in 96 patients with SAD (15). Over the 8-week period, an overall improvement was observed, but there were no significant differences between the two treatments.

The Canadian Consensus Guidelines recommend sertraline and fluoxetine as effective, well-tolerated first-line pharmacological treatments for SAD (level 1 evidence) (11).

3. Drugs targeting melatonin

The melatonin-suppressing properties of propranolol were investigated in 33 patients with SAD. Following an open treatment period, 24 patients met remission criteria and entered a double-blind discontinuation phase receiving either propranolol or placebo for up to 2 weeks. Patients randomized to receive propranolol had a significantly greater increase in SIGH-SAD and HAM-D scores

at the end of the double-blind phase compared with those receiving placebo. The author proposed that the pre-sunrise administration of a short-acting β-blocker truncated the nocturnal secretion of melatonin and produced a "short-night" signal or physiological signal for summer (31). A recently completed study also investigated the efficacy of pharmacological suppression of melatonin secretion by propranolol in the treatment of up to 70 patients with SAD (32).

The novel melatonergic antidepressant agomelatine was tested in an open study in 37 acutely depressed SAD patients. Agomelatine was administered over 14 weeks and treatment resulted in a progressive and statistically significant decrease in SIGH-SAD, CGI-Severity and CGI-Improvement scores (33). The administration of melatonin was also investigated in a randomized, placebo-controlled trial in which 58 patients with seasonal, weather-associated mood/behavioral disorder were treated with a slow-release melatonin formulation. There was a significant improvement in sleep and overall symptoms compared with placebo (34).

4. Others

Small open-label studies have indicated that alprazolam (35), modafinil (36), nefazodone (37) and reboxetine (38) may be effective in the treatment of SAD. A small randomized, double-blind study in 27 patients with SAD showed no advantage for *Ginkgo biloba* extract compared with placebo in preventing the development of the symptoms of SAD (39).

The results of clinical studies with drug therapies investigated in SAD are summarized in Table II.

Table II: Clinical studies investigating drug therapies for seasonal affective disorder (SAD) (from Prous Science Integrity®).

Design	Treatments	n	Conclusions	Ref.
Multicenter Randomized Double-blind Pooled/meta-analysis	Bupropion-XL, 300 mg o.d. [titrated from 150 mg o.d.] p.o. [until first wk of spring] Placebo	1042	Extended-release bupropion started early in the season with the patients still asymptomatic prevented the recurrence of seasonal major depressive episodes in patients with SAD	29
Multicenter Randomized Double-blind	Sertraline, 50-200 mg [titrated from 50 mg/d] p.o. o.d. x 8 wks Placebo	187	Sertraline was well tolerated and effective for the treatment of SAD	30
Multicenter Comparative Randomized Double-blind	Fluoxetine, 20 mg/d p.o. x 8 wks Light, 10,000 lux over 30 min o.d. x 8 wks	96	Light therapy and fluoxetine produced similar results in patients with SAD, except that light therapy showed an earlier onset of response and fewer adverse events compared with fluoxetine	15
Randomized Pooled/meta-analysis	Propranolol, 20 mg [5:30-6:00 a.m.] → escalated to 60 [max.] mg/d [until response] x 14 d → Propranolol @ therapeutic dose x 2 wks or until relapse Propranolol, 20 mg [5:30-6:00 a.m.] → escalated to 60 [max.] mg/d [until response] x 14 d → Placebo x 2 wks or until relapse	33	A mean dose of propranolol of 33 mg/d produced remission in 73% of patients after the open-phase study. The Hamilton Depression Rating Scale score improved significantly in those patients who continued to receive propranolol in a discontinuation phase compared to those treated with placebo	31
Randomized	Propranolol, p.o. b.i.d. x 4 wks Placebo	70	A phase II study will determine whether the reduction of melatonin secretion with propranolol treatment can improve depressive symptoms in subjects with SAD	32
Open	Agomelatine, 25 mg o.d. x 14 wks	37	Agomelatine was well tolerated and effective in patients with SAD, yielding a response rate of 75.7% and a remission rate of 70.3%	33
Randomized Double-blind	Melatonin-SR, 2 mg p.o. 1-2 h before bedtime x 3 wks Placebo	58	Melatonin significantly improved sleep quality and vitality and improved overall symptoms compared with placebo in patients with SAD	34
Open	Alprazolam, 1.2-2.4 mg/d x 14-42 d	6	Alprazolam may have a role in the management of patients with SAD, although it is not very effective for atypical symptoms	35
Open	Modafinil, 100 mg/d [increased to 200 mg/d @ 1 wk if necessary and tolerated] x 8 wks	13	Modafinil was well tolerated and may be effective for the treatment of SAD/winter depression	36
Open	Nefazodone, 100-400 mg/d [titrated from 100 mg over 3 wks] p.o. x 8 wks	9	Nefazodone showed favorable antidepressant and anxiolytic effects and improved sleep efficiency and sleep latency in women with SAD	37
Open	Reboxetine, 8 mg/d p.o. x 6 wks	16	Reboxetine was well tolerated and effective for the treatment of SAD	38

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