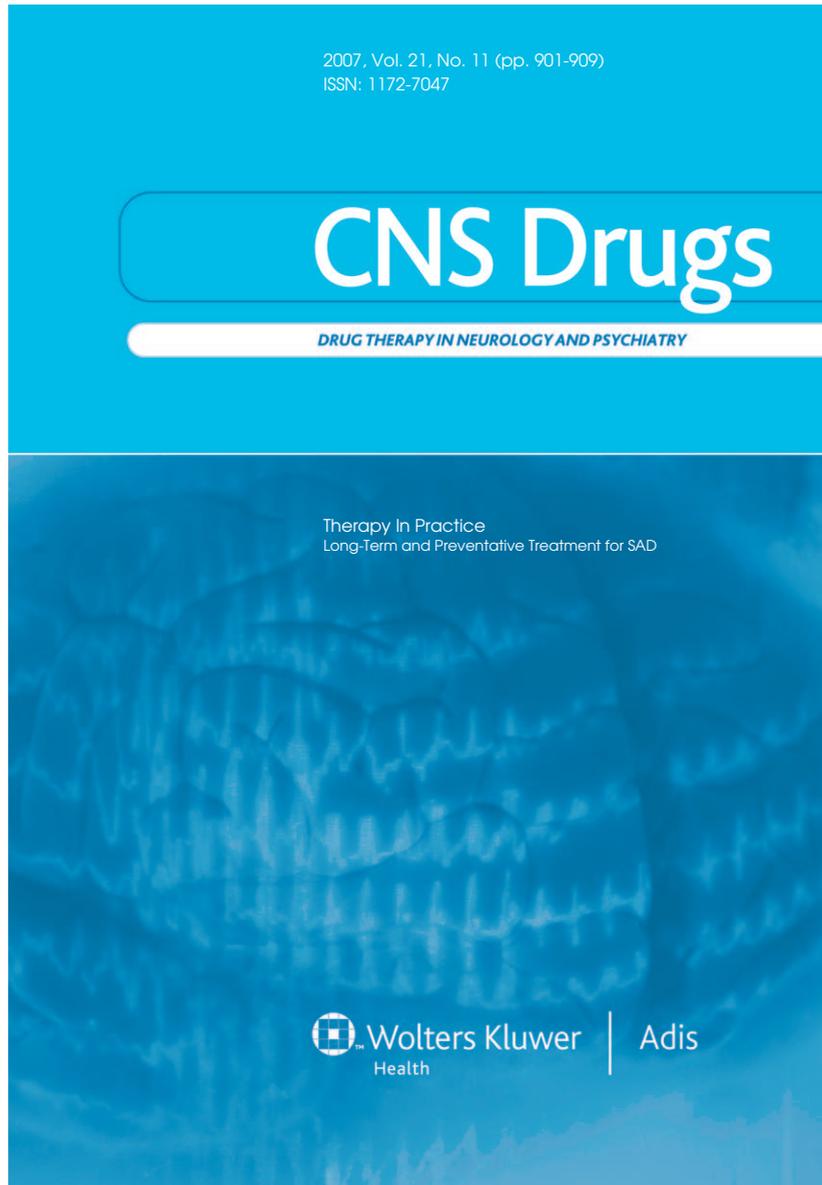


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Long-Term and Preventative Treatment for Seasonal Affective Disorder

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Abstract

Recurrent major depressive disorder with regular seasonal patterns, commonly known as seasonal affective disorder (SAD), has evoked substantial research in the last two decades. It is now recognised that SAD is a common condition with prevalence rates between 0.4% and 2.9% of the general population, and that patients with SAD experience significant morbidity and impairment in psychosocial function.

There is good evidence that bright light therapy and antidepressant medications are effective for the short-term treatment of SAD; however, given that SAD is characterised by recurrent major depressive episodes, long-term and maintenance treatment must be considered. Unfortunately, there are few studies of longer term (>8 weeks) and maintenance (preventative) treatments for SAD. The weight of evidence suggests that light therapy usually needs to be continued daily throughout the winter season because of rapid relapse when light is stopped too early in the treatment period. However, some studies support the use of antidepressants to continue the response from a brief (1–2 weeks) course of light therapy early in the depressive episode, as soon as the first symptoms emerge in autumn. Only small studies have examined preventative treatment (before onset of symptoms) with light therapy, all of which have methodological limitations. The best evidence for preventative treatment in SAD comes from antidepressant studies. Three large, randomised, placebo-controlled studies have shown that preventative treatment with bupropion XL reduces the recurrence rate of depressive episodes in patients with SAD.

Given the limitations in the evidence base and the inconsistent recurrence rate of winter depressive episodes, clinical recommendations for long-term and preventative treatment must individualise treatment choices and weigh potential benefits against possible adverse effects.

The DSM-IV describes seasonal affective disorder (SAD) as “recurrent major depressive episodes with regular seasonal patterns”.^[1] Such episodes occur most commonly during autumn and winter, and remit (or switch to hypomania or mania) during spring and summer.^[2] Some patients with SAD may experience nonseasonal depressive episodes during their lifetime, but these are substantially less frequent than the seasonal episodes. SAD is also associated with so-called atypical depressive symptoms, including hypersomnia, increased appetite and eating, carbohydrate craving and weight gain.^[3]

SAD is a relatively common condition. Epidemiological studies, based on diagnostic interviews and DSM criteria, found prevalence rates for this disorder in the general population of 0.4% in the US^[4] and 1.7–2.9% in Canada.^[5,6] Other studies, using self-report questionnaires, have shown community prevalence rates for SAD ranging from <1% to >10%.^[3] The aetiology of SAD remains unknown, but major theories of the pathophysiology of this disorder include circadian hypotheses, neurotransmitter dysfunction hypotheses and genetic hypotheses.^[7,8]

The depressive symptoms in SAD result in significant morbidity and impairment in psychosocial function. Patients with seasonal depression in a primary care clinic were found to have greater functional impairment than those with many other common medical conditions.^[9] Both social adjustment and quality of life in patients with SAD were significantly worse than in nondepressed community samples, with impairment comparable to patients with nonseasonal major depressive disorder.^[10,11] The progressive weight gain experienced by many patients with SAD may also lead to greater risk for obesity, diabetes and the metabolic syndrome.^[12]

The treatment of SAD is focused on light therapy (daily exposure to bright, artificial light)^[13] and

antidepressant medications.^[14] Despite some methodological issues in designing appropriate placebo conditions, several systematic reviews and meta-analyses have shown that light therapy is an effective short-term treatment for SAD.^[15,16] The most recent meta-analysis found a large effect size of 0.84 (95% CI 0.6, 1.08) for bright light therapy compared with control conditions.^[16] Similarly, while there are fewer studies of antidepressants in the short-term treatment of SAD, randomised controlled trials (RCTs) of SSRIs, such as fluoxetine (20 mg/day)^[17] and sertraline (50–200 mg/day),^[18] have shown evidence for efficacy in this disorder. Comparative studies and smaller, open-label studies suggest that other antidepressants, such as bupropion, reboxetine and moclobemide, may also be effective.^[19–22] A direct comparison study has shown that light therapy and fluoxetine have similar effectiveness in SAD,^[23] but unfortunately there are no studies of combination light and medication treatment.

These studies have all addressed the short-term treatment of SAD.^[15–23] In the management of depression, we now recognise that there are also continuation and/or maintenance phases of treatment in which the objectives of care are to prevent relapse and recurrence.^[24,25] In fact, most clinical practice guidelines recommend long-term maintenance treatment to prevent depressive episodes in recurrent depression.^[26–28] Since SAD, by definition, is a recurrent depressive condition, longer term studies (i.e. through a full winter season) and maintenance or prophylactic treatment studies (to prevent future depressive episodes) are very important. In this article, we review the evidence for longer term and prophylactic treatment of SAD, focusing on randomised trials or observational studies with larger sample sizes, and provide clinical strategies for prevention of depressive episodes.

1. Longer Term Treatment Studies

A major problem with light therapy acute treatment studies is their short duration of treatment, with placebo-controlled studies ranging from 1 to 5 weeks in duration.^[15,16] The short-term antidepressant trials and the comparative light versus fluoxetine study were also only 8 weeks in length.^[17,18,23] Few studies have examined treatment for >8 weeks over the course of the 4–6 month fall/winter season.

One exception is a 14-week, open-label study of agomelatine, a novel antidepressant with melatonin MT₁ and MT₂ receptor agonist and serotonin 5-HT_{2C} receptor antagonist properties.^[29] Thirty-seven outpatients with SAD, as defined by DSM-IV-TR, and meeting criteria for a moderate to severe depressive episode, were recruited between the first week of October and the second week of December. Patients with a baseline score of ≥ 22 on the 29-item version of the Structured Interview Guide for the Hamilton Depression Rating Scale (SAD version; SIGH-SAD) were treated with agomelatine 25 mg/day for 14 weeks. The SIGH-SAD scores improved significantly from week 2 onwards, and after 14 weeks 76% of the patients had responded to treatment (defined as >50% reduction of total SIGH-SAD score) and 70% reached the remission criteria (SIGH-SAD score <8). These results are promising but efficacy of agomelatine will need confirmation in a randomised, placebo-controlled trial.

Most studies of light therapy have shown rapid relapse (within a week or two) when light is discontinued,^[30] leading to clinical recommendations that light therapy be continued throughout the winter period of risk.^[31] However, in some studies, antidepressants have been used to maintain response after initial short-term treatment with light therapy. For example, in one pilot study, eight patients with SAD were randomised to citalopram 40 mg/day or placebo in combination with ten daily sessions of bright light treatment. After the light treatment they continued with citalopram or placebo for 1 year.^[32] Throughout the follow-up period, the patients treated with citalopram had significantly lower self-ratings on depressed mood than the patients receiving placebo, suggesting that citalopram can be

used to continue the therapeutic effect of a short course of light therapy.

A larger subsequent study also found beneficial effects of citalopram in continuation treatment of SAD after bright light therapy.^[33] Patients with SAD (n = 269) who were mildly to moderately depressed (scores of 13–22 on the 17-item Hamilton Depression Rating Scale [HAM-D]) were treated with bright light (5000 lux, 2 hours daily) for 7 days. Those who responded (n = 168 [62.5%]) with a reduction of $\geq 50\%$ of the baseline HAM-D score were then randomised to either citalopram 20–60 mg/day (n = 84) or placebo (n = 84) for 15 weeks. Relapse rates according to SIGH-SAD criteria were lower in the citalopram group compared with the placebo group (19.4% vs 31.6%, respectively), but this did not reach statistical significance. However, relapse rates for other outcome measures (core 6-item subscale HAM-D₆: 17.1% vs 31.7%, $p < 0.05$; Melancholia Scale: 16.2% vs 35.1%, $p < 0.05$) were significantly lower in the citalopram-treated group. While this suggests that citalopram can be used to maintain the initial effect of light, the low relapse rates in the placebo-treated group indicates that some patients with mild symptoms may not show full relapse after brief treatment with light therapy when followed over the course of a winter.

2. Maintenance and Prevention Studies

The regular pattern of depressive episodes in SAD suggests that prevention may be possible, with treatment started in early autumn before the onset of symptoms, or as soon as the first symptoms of depression appear; however, the depressive episodes of SAD may not be as predictable, as indicated by retrospectively assessed patterns of episodes. Studies show that only 50–70% of patients diagnosed with SAD in the summer months or in a previous winter will experience a major depressive episode on prospective follow-up.^[34–37] Depending on the study design, this means there is a risk of either over- or under-estimating the effect of a preventative treatment, since patients may not have a recurrence of depression during winter, whether treated or not. Finally, some patients with SAD will also

have occasional nonseasonal episodes, e.g. winter episodes that extend into the spring and summer, therefore it is important to determine whether a preventative treatment needs to continue year-round, or whether it is only required during the seasons of risk.

Table I summarises the studies on prevention of depressive episodes in SAD. Early studies suggested that a brief course of light treatment scheduled at the first onset of symptoms would be adequate to prevent relapses for the remainder of the winter season. In one study, 27 patients experiencing early symptoms were randomised to 5 days of light therapy (2500 lux, 3 hours daily) or to no treatment, and were followed for the rest of the winter.^[38] None of the 16 light-treated patients developed a depressive episode, in contrast to 5 of 11 of the nontreated control group. However, this result was not replicated in a study of 17 patients treated with 1 week of bright light (10 000 lux, 30 minutes daily) at the first onset of symptoms and then followed prospectively.^[39] Of the 15 responders to the brief treatment, all but two relapsed within the 8-week follow-up period.

Two other small studies examined the preventative effect of a brief course of light treatment prior to the onset of symptoms. In one study, 12 patients with SAD (previously treated with light therapy during a winter depressive episode) were randomised in September to either start light treatment when they were still well ($n = 6$) or to start it when their first symptoms of depression occurred ($n = 6$).^[41] Bright light (3300 lux, 1 hour daily) was administered for as long a period as the patient wished. During the winter follow-up, SIGH-SAD scores were significantly lower in the group treated with bright light in advance, and none of these patients relapsed during the study period.^[41] However, a previous study with a similar design did not find any relapse prevention effect of light treatment administered in September before patients were symptomatic.^[40] Fifteen patients with SAD who had a full remission to light treatment the previous season were treated with bright light (2500 lux, 3 hours daily) for 5 days and then followed weekly through

the winter. Of the 11 patients who completed the study, eight (73%) reached the relapse criteria on the self-rated Beck Depression Inventory.

A prevention study using continuous light treatment involved 38 patients with SAD who had been successfully treated with fluorescent light boxes in previous winter seasons.^[42] In the early autumn, when not yet depressed, these patients were randomly assigned to one of three treatments: (i) light visors using bright white incandescent light (2500 lux, 30 minutes daily); (ii) identical light visors using infrared light (not known to be an active treatment); and (iii) no light treatment. Patients continued with their treatment assignment throughout the winter and outcome was assessed weekly for 24 weeks using a self-rated version of the SIGH-SAD, with recurrence defined as scores ≥ 20 for 2 consecutive weeks. Of the 30 patients who completed the study, 6 of 14 (43%) receiving bright light, 5 of 15 (33%) receiving infrared light and 6 of 9 (66%) receiving no treatment had recurrence of a depressive episode. Using survival analysis, the infrared treatment was significantly superior to no treatment ($p < 0.02$), the bright light had a trend to superiority ($p < 0.07$) against no treatment and there was no significant difference between the two light conditions. This study is limited by the small sample size and the unexpected result with infrared light, given that it was not expected to be an active treatment. Unfortunately, no other studies have examined the use of infrared light for SAD.

In contrast to the very small, methodologically-limited studies of light therapy, there are large, well designed studies of antidepressants for the prevention of depressive episodes in SAD. Preventative treatment with bupropion XL was examined in three double-blind, placebo-controlled, multicentre studies in Canada and the US.^[43] In total, 1042 patients with SAD diagnosed by clinical history were included in the studies, all of which had identical designs. Patients entered the studies between September and November when they were asymptomatic, and were seen at least every 4 weeks until the first week of spring in late March, unless a depressive episode occurred. Patients were randomised to receive

Table I. Studies on the prevention of depressive episodes in seasonal affective disorder

Study (year)	Treatment(s)	Sample size (n)	Study design	Outcome
Meesters et al. ^[38] (1993)	Bright light (fluorescent, 2500 lux, 3h daily) for 5 days No treatment	27	RCT Brief treatment given at first onset of symptoms Patients followed through one winter	0/16 (0%) light-treated patients relapsed during follow-up compared with 5/11 (45%) nontreated patients
Terman et al. ^[39] (1994)	Bright light (fluorescent, 10 000 lux, 30 min daily) for 1wk	17	Open-label treatment with prospective follow-up Brief treatment given at first onset of symptoms Patients followed for 8wk	13/15 (87%) responders to brief treatment relapsed during follow-up
Meesters et al. ^[40] (1994)	Bright light (fluorescent, 2500 lux, 3h daily) for 5 days	11	Open-label treatment with prospective follow-up Brief treatment given before onset of symptoms Patients followed through one winter	73% of patients had recurrence of depression during follow-up
Partonen and Lonqvist ^[41] (1996)	Bright light (fluorescent, 3300 lux, 1h daily) for as long as the patient wished	12	RCT Treatment started either before onset of symptoms or at first onset of symptoms Patients followed for 24wk	Clinical remission was significantly more frequent in the group with bright light given before onset of symptoms
Meesters et al. ^[42] (1999)	Bright white light visor (incandescent, 2500 lux, 30 min daily) throughout winter Infrared light visor (>700nm, 0.18 lux, 30 min daily) throughout winter No light treatment	38	RCT Treatments started before onset of symptoms Patients followed through one winter	Recurrence rates were significantly lower in the infrared light group (33%) compared with placebo (66%) No difference between bright light (43%) and infrared light (33%) conditions
Modell et al. ^[43] (2005)	Bupropion XL (150–300 mg/day) throughout winter Placebo	1042 (pooled sample)	RCT, three studies with identical design Treatments started before onset of symptoms Patients followed through one winter	Recurrence rates significantly lower in the bupropion-treated group (16%) compared with placebo (28%)
Lingaerde et al. ^[44] (1999)	Ginkgo biloba 120 mg/day for 10 weeks Placebo	27	RCT Treatments started before onset of symptoms Patients followed for 10wk	No significant differences between groups in the recurrence of depressive episodes or key mood symptoms

RCT = randomised controlled trial.

bupropion XL 150 mg/day or placebo for the first week, following which those receiving bupropion XL were increased to 300 mg/day (if the 300 mg/day dosage was not tolerated, it could be reduced to 150 mg/day). In the first week of spring, the dosage was reduced to 150 mg/day for 2 weeks and then discontinued, after which the patients were followed off medication by telephone interviews for 8 weeks. A recurrence of a depressive episode was defined as a SIGH-SAD ≥ 20 , or fulfilling DSM-IV criteria for major depressive episode.

Results for the three individual studies, as well as a pooled analysis since the study designs were identical, are summarised in figure 1. Recurrence rates were significantly lower for the bupropion XL group than for the placebo group in all three studies (19% vs 30% for study A, 13% vs 21% for study B, 16% vs 31% for study C and 16% vs 28% for the pooled sample, respectively). However, survival analyses for time to onset of depression, comparing bupropion XL with placebo, only reached significance in study C and in the pooled sample. Furthermore, it should be noted that the recurrence rates of depressive episodes were low overall, even in the placebo-treated groups.

In these studies, dropout rates for any reason (24% vs 22%) and because of adverse events (9% vs 5%) did not differ between bupropion and placebo. Frequencies of adverse events were low overall, with bupropion showing slightly higher frequency

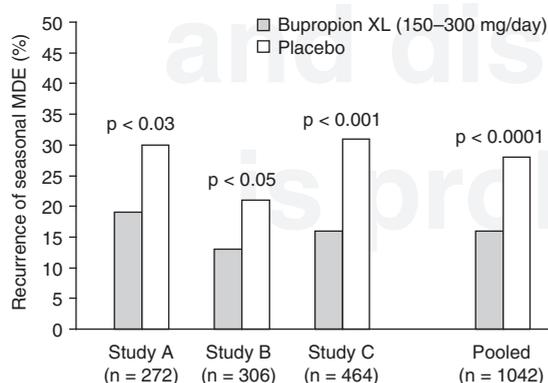


Fig. 1. Bupropion XL vs placebo in the prevention of seasonal major depressive episodes (MDE) in seasonal affective disorder (reproduced from Modell et al.,^[43] with permission).

of dry mouth, nausea, constipation and flatulence than placebo. Together, these three studies provide good evidence for the efficacy and tolerability of bupropion XL as a preventative treatment for depressive episodes of SAD when commenced before the onset of symptoms.

Of interest is that this is the only SAD study examining discontinuation of treatment in the spring. In the 8-week follow-up after bupropion was stopped, there was no evidence for discontinuation-emergent adverse events. Additionally, depression recurrence rates after stopping medications were very low and no different than placebo (2.7% and 2.1%, respectively). This indicates that medication can be successfully discontinued during the spring and summer months.

Finally, some studies with small sample sizes have investigated novel treatments for prevention. In an RCT ($n = 27$), the herbal remedy ginkgo biloba did not differ from placebo as a preventative treatment for SAD.^[44] Another study randomised 23 patients with SAD to 6 weeks of treatment with light therapy, a group-based cognitive behaviour therapy (CBT) intervention, and the combination of light therapy and CBT, and then examined outcomes during the subsequent winter season.^[45] All three treatments demonstrated significant but similar responses in the short-term treatment trial. However, at naturalistic follow-up during the subsequent winter, patients who had CBT, particularly in combination with light therapy, had better outcomes, as measured by symptom severity, remission rates and relapse rates. This was not a true prevention trial because of the naturalistic follow-up in which patients were allowed to use other treatments, but it suggests that CBT may offer some benefits beyond the short-term treatment phase, in the same way that CBT may help prevent episodes of nonseasonal depression.

3. Clinical Recommendations

Seasonal depression is a common and recurrent condition that causes significant morbidity and impairment of psychosocial function, therefore it is reasonable to consider prophylactic and mainte-

nance treatments to prevent depressive episodes. Complicating the issue, however, is the fact that some patients, even with a history of consecutive winter depressive episodes, may not experience a depressive episode in any particular winter. Unfortunately, there are still limited data to guide clinical recommendations for the prevention of SAD. Therefore, the decision to use a preventative treatment must take into account a variety of factors, including individual course and severity of illness, predictability of episodes and their onset, patient preference and motivation, and availability of resources.

Similarly, the choice of preventative treatment requires individual assessment to weigh potential benefits against risks of adverse effects. For example, light therapy may be the treatment of choice for patients who prefer nonpharmacological treatment, have relative contraindications to drug therapy (e.g. hepatic disease) or are intolerant to medication adverse effects. On the other hand, medication treatment may be the treatment of choice for patients who cannot make the time commitment for light therapy, have relative contraindications to light therapy (e.g. retinal disease, macular degeneration, use of photosensitising medications) or are intolerant to the adverse effects of bright light.

There are only limited efficacy data for longer term and preventative treatment with light therapy. Because light therapy has a fast onset of action (from a few days to 1 or 2 weeks), it is reasonable to recommend starting light therapy at the time of first onset of symptoms in the autumn; however, some patients have rapid onset of symptoms or may not recognise the insidious onset of depression until they are in a full episode. These patients may want to restart their light therapy at least 2 weeks (the typical time period for response to light) ahead of their usual onset of depressive symptoms. There is no good evidence that a brief course of light therapy can prevent relapse, therefore light treatment should be continued throughout the winter season and discontinued during spring and summer. Alternatively, a brief course of light treatment can be followed by continuation treatment with antidepressant medication through the winter months.

Better evidence exists for the preventative efficacy of antidepressants, but only bupropion XL has been adequately studied and approved for the prevention of episodes of SAD by regulatory agencies (in the US). It is certainly possible that other antidepressants (e.g. SSRIs such as fluoxetine and sertraline, which show efficacy in short-term treatment) are also effective. For antidepressants, preventative treatment should be started in the early autumn at least 4 weeks (the typical time period for response to medications) prior to the usual onset of symptoms. Extrapolating from the results of the bupropion XL studies, it appears that antidepressants can be safely tapered and discontinued in the spring (at the time of usual remission) and summer. Discontinuation symptoms, however, may vary among different antidepressants and it is important to distinguish these from depressive symptoms, indicating recurrence. It may be more prudent to continue the antidepressant year-round for individual patients if they have usual remission of symptoms later in the spring, require longer taper periods (e.g. those on higher doses or those who experience significant discontinuation symptoms), or have subsyndromal symptoms in the summer, as the time off medication will be very short. In this situation, patients should be cautioned about the possibility of spring/summer hypomania.

In clinical practice it is also common to combine light and antidepressant treatment.^[46] Unfortunately, no studies have examined the effect of combination use of light therapy and antidepressants, either for short-term or maintenance treatment. In addition, there is a suggestion that CBT may also offer benefits for the prevention of SAD. These will be important future research directions for the field.

4. Conclusions

Longer term and preventative treatments for patients with SAD are indicated because of the duration and recurrent pattern of winter depressive episodes. Unfortunately, there is less evidence for efficacy of light therapy and antidepressants in continuation and maintenance phases than for acute treatment of SAD. Hence, clinical recommendations

are based on a limited number of quality studies and by extrapolating from acute studies. A complicating factor is the variable predictability of self-reported seasonal patterns of illness, since prospective monitoring indicates that only about 30–70% of patients with SAD will have recurrence of a winter depressive episode. Therefore, the need for, and choice of preventative treatment relies on clinical judgement and consideration of various factors, including individual course and severity of illness, predictability of episodes and their onset, patient preferences and motivation, and availability of resources.

Given the significant personal and psychosocial impairment associated with SAD, it is important to conduct further studies to determine which patients need maintenance treatment and how to optimise preventative treatment with light therapy and/or antidepressants.

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