

STATE OF THE ART PSYCHOPHARMACOLOGICAL TREATMENT OPTIONS IN SEASONAL AFFECTIVE DISORDER

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SUMMARY

Seasonal affective disorder (SAD) is defined as a subtype of mood disorders in DSM 5, and it is characterized by a seasonal onset. SAD is proposed to be related to the seasonal changes in naturally occurring light, and the use of bright light therapy for depressive symptoms has been shown to reduce them in placebo controlled trials. Cognitive behavioral therapy has also been demonstrated to be effective in SAD. This review article aims to focus on the psychopharmacological treatment options for SAD. According to clinical trial results, first line treatment options seem to be sertraline and fluoxetine, and are well tolerated by the patients. There is some evidence that other antidepressants (e.g. bupropion) might be effective as well. Although clinical trials have shown that some of these antidepressants may be of benefit, a recent review has concluded that there is not enough evidence to support the use of any of these agents for the treatment of SAD yet. Moreover, more studies are still needed to evaluate the effectiveness of other treatment options, e.g., propranolol, melatonin, hypericum, etc. In addition to the above proposed treatments, patients with seasonal depressive symptoms should thoroughly be evaluated for any cues of bipolarity, and their treatment should be planned accordingly.

Key words: antidepressants – seasonal affective disorder – SAD - psychopharmacological treatment

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Introduction

Seasonal affective disorder (SAD) is not a distinct mood disorder other than major depressive disorder, bipolar disorder type I and type II. SAD is defined as a subtype of mood disorders in Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM 5), and has a seasonal onset (Osborn 2004). Mood symptoms emerge and cease spontaneously at specific periods during the year. Two subtypes of SAD have been described, one starting in winter, and the other in spring/summer (Partonen & Lönnqvist 1998). The winter onset subtype is more prevalent, and is characterized by atypical depressive symptoms, e.g. hypersomnia and increased appetite. On the other hand, the spring/summer onset type of SAD is less frequently encountered, and is associated with insomnia and loss of appetite. The prevalence of SAD varies among different populations, but is reported to be 1-10% (Roecklein 2005), and women seem to be more frequently affected than men (female to male ratio: 4/1). SAD is also reported to be more common among young adults (Miller 2005). In a study conducted in Turkey, the prevalence of syndromal and subsyndromal SAD were reported to be 2.21% and 9.22%, respectively (Noyan 2001). It has also been documented that seasonality is apparent in 15-22% of bipolar patients, and in 10-20% of recurrently depressed patients. Bipolar disorder has more frequently been associated with seasonality compared to major depression (Roecklein 2010). Similarly, another Turkish study revealed that 17% of bipolar patients also met the diagnostic criteria for SAD

(Dağdeviren 1998). The differential diagnosis of SAD includes major depressive disorder, bipolar disorder type I and type II, and dysthymia, all of which may not present features suggesting a seasonal pattern. It is also of importance to rule out any medical conditions, e.g. thyroid pathologies, before establishing the diagnosis as SAD.

Randomized controlled studies have confirmed that bright light therapy is the treatment of choice in SAD, which pointed out a direct relationship between the seasonal changes and the level of natural light (Golden 2005). Cognitive behavioral therapy has also demonstrated efficacy for the treatment of SAD (Rohan 2013).

This review article aims to summarize the state of the art psychopharmacological treatment of SAD.

Selective serotonin reuptake inhibitors (SSRI)

Randomized controlled trials (RCT) of SSRIs in SAD are limited in number. A placebo controlled randomized trial undertaken with 50-200 mg/day sertraline (n=187) showed that the winter onset subtype of SAD responded statistically significantly more to the active drug compared to placebo (Moscovitch 2004). Another placebo controlled study revealed that fluoxetine was superior to placebo, but the statistical significance was only modest. This study noted that although the treatment response was higher with the fluoxetine group, the scores obtained on the depression rating scales did not differ from the placebo group (Lam 1995). Further, a study where fluoxetine was compared

to moclobemide, both treatment groups were equally efficacious (Partonen & Lönnqvist 1996). Fluoxetine was also compared to bright light therapy in two other studies, and these studies showed no difference between the groups in terms of treatment response or change in depression scale scores (Lam 2006, Ruhrmann 1998). After a week of bright light therapy, when the depressive symptoms quickly diminished, treatment with citalopram seemed to prevent relapse more than placebo in two different studies (Thorell 1999, Martiny 2004). An open label, small study (n=20) has demonstrated that 10-20 mg/day escitalopram may be effective and well tolerated in SAD (Pjrek 2007).

Although the above summarized studies, the sertraline and fluoxetine studies in particular, have demonstrated that some SSRIs may be effective for the treatment of SAD, a recently published review concluded that these drugs do not have enough evidence to support their use in SAD (18). The authors suggested that more RCTs were needed, that side effects should be more systematically collected, and that a comparison to psychotherapeutic interventions was lacking.

Bupropion

In a randomized placebo controlled trial, patients with SAD were given bupropion 150-300 mg/day before the symptoms emerged in autumn. This prevention trial included 1042 patients, and the results showed that bupropion was significantly more effective in preventing SAD than placebo in both dosages (Modell 2005). Bupropion also remains the only licensed drug for this indication. In another open label study, where in addition to bupropion, tranylcypromine and desipramine were compared, all three drugs were found to be effective for the resolution of SAD symptoms (Dilsaver & Jaeckle 1990). A recent expert consensus report concluded that the extended release form of bupropion should be used for SAD due to its ease of use. Three other studies demonstrated that bupropion was effective for the treatment of SAD even before the symptoms arose, but the effect size was small. Therefore, more RCTs are needed to prove that bupropion is effective during the acute phase of SAD (Niemegeers 2013). The present evidence base supports the use of bupropion for the prevention of further SAD episodes rather than the treatment of the acute phase of the illness.

Other Antidepressants

Tranylcypromine

A 91% reduction in symptoms of depression during 4-week treatment of 14 patients with SAD was shown with tranylcypromine (Dilsaver & Jaeckle 1990). It is difficult to make any further comments about tranylcypromine, because of the limited number of patients, and since these findings have not been repeated.

Moclobemide

In a 3-week study that compared moclobemide with placebo, 34 patients with SAD were included. It was reported that in the first week of treatment, moclobemide showed superiority to placebo in terms of reducing the scores of atypical depression, but at the end of the 3-week treatment, moclobemide was superior to placebo in terms of reducing depression scores (Lingjaerde 1993).

Reboxetine

It was reported that the noradrenergic system also plays a role in the etiology of SAD. In an open-label study which included 16 patients with SAD, symptoms of atypical depression in 9 patients improved in the first week with 8 mg/day reboxetine treatment, and 11 of the patients achieved remission at the end of the 6-week treatment period (Hilger 2001). Although reboxetine seems to be a fast and effective option for the treatment of SAD, further research is needed.

Duloxetine

Twenty six patients with SAD were enrolled to an open-label study, and patients were given 60-120 mg/day duloxetine. At the end of the 8-week treatment, it was reported that 80% of patients responded to the treatment, and the remission rate was 76% (Pjrek 2008). Although duloxetine, which has a dual effect as an antidepressant, might be an effective option for the treatment of SAD, the findings of the study need to be replicated.

Mirtazapine

It was reported that in a pilot study which included 8 patients, at the end of the 4-week period of 30 mg/day mirtazapine treatment, 6 of the patients achieved remission without tolerability problems (Hesselmann 1999). Although mirtazapine may act quickly and is well tolerated, more research with more patients is needed.

Agomelatine

SAD patients' rhythmic secretion of melatonin changes seasonally. Agomelatine, a melatonin agonist, has antidepressant properties due to its effects on melatonin receptors, stabilizing circadian rhythms, and serotonergic function. Because of these reasons, although it was suggested that agomelatine would be an effective for treatment of SAD, there is no controlled study on its effectiveness in SAD. In an open-label study, which included 37 patients who were treated with 25 mg/day of agomelatine for 14 weeks, it was found that the symptoms of depression in the patients improved as early as the second week of treatment (Pjrek 2007). The response rate to treatment of SAD with agomelatine was 75%, and the remission rate was 70%.

Mood Stabilizers

In patients with bipolar disorder, 25% of the depressive episodes and 15% of the manic episodes exhibit

seasonal features (Geoffrey 2014). Mood stabilizers such as lithium and valproate might exert their therapeutic properties via their effects on circadian rhythms (Wirz-Justice 2003). Experts have recommended to use mood stabilizers for bipolar patients with seasonal features (Levitt 1999). Although there is not enough data about using mood stabilizers for the treatment of SAD in the literature, we think that it may be an appropriate treatment option, after questioning about bipolarity for patients who suffer from seasonal features during their depressive episodes.

Other Drugs

Beta-blockers

Beta-blockers have effects on melatonin secretion via decreasing melatonin in the morning. It was shown that 60 mg/day or less propranolol which is given just before sunrise (05:30-06:00 AM) was effective for winter onset SAD (Schlager 1994). Twenty four of 33 patients who were given propranolol met remission criteria. In a study with atenolol, decrease in the symptoms of SAD has been shown only in 3 of 19 patients (Rosenthal 1988). Although propranolol seems more effective than atenolol, the results have not been repeated.

Melatonin

There are differences at the beginning, during, and at the end of melatonin secretion in SAD (Srinivasan 2006). In addition to the role of melatonin in the pathogenesis of SAD, there are also some studies supporting the therapeutic use of melatonin. Treatment with 5 mg melatonin, given in the morning or evening, has been found to be ineffective for the treatment of SAD (Wirz-Justice 1990). On the other hand, much lower doses of melatonin (0.125 mg), given during afternoon, have been found to be effective for the treatment of winter depression in a small group of patients (Hesselmann 1999, Lewy 1998). These findings show that the place of melatonin for the treatment of SAD is controversial, and that more studies are needed.

Modafinil

In an open label study, 12 patients with SAD were treated with 100-200 mg/day modafinil, and 67% of patients responded well to modafinil, especially in terms of patients' fatigue and severe sleepiness (Lundt 2004). But the relatively small number of patients makes it difficult to generalize the results.

D-fenfluramine

Beneficial effects of D-fenfluramine on improving depressive symptoms in SAD patients has been shown in two small studies. On the other hand, it must be kept in mind that, d-fenfluramine was removed from the market due to its serious adverse effects (O'Rourke 1987, O'Rourke 1989).

L-Tryptophan

The effect of L-tryptophan was significantly greater than placebo, and L-tryptophan showed a similar effect like light therapy on 13 patients with SAD (McGrath 1990). In another study, L-tryptophan had similar response rates with bright light therapy, but the response time was 2 weeks in light therapy while it was 4 weeks in L-tryptophan treatment (Ghadirian 1998). The studies mentioned here show that L-tryptophan has similar response rates to light therapy, even though the number of participants in these studies is very low.

Metergoline

As expected, while a serotonin antagonist caused an increase in depressive symptoms, single-dose metergoline reversed them in 16 sufferers with SAD. However this effect was transient and not replicated (Turner 2002).

Vitamin D

Vitamin D levels were not found to be different from healthy controls (Oren 1994). In a small controlled study including 15 SAD patients, it was shown that vitamin D replacement demonstrated a better improvement relative to bright light in SAD patients (Gloth 1999). Yet, generalizing these results is not possible due to the small number of participants in the study. A recent double-blind randomized placebo controlled study indicated no response to vitamin D for the treatment of seasonal affective symptoms (Frandsen 2014).

Vitamin B12

Two weeks of cyanocobalamine treatment was investigated in a placebo-controlled study, however there was no significant difference between groups (Oren 1994). As the duration of treatment was short, and as they used cyanocobalamine instead of the methyl form of vitamin B12, which is used in most of the studies, it is hard to comment if vitamin B12 is of any benefit in SAD or not.

Hypericum perforatum (St. John's Wort)

Hypericum perforatum is a weak serotonin reuptake inhibitor. Studies indicate that *Hypericum perforatum* may be useful in the treatment of SAD as it is in major depression. *Hypericum perforatum* was as effective at least as light therapy (Kasper 1997, Martinez 1994). Additionally, hypericum alone was as effective as light therapy in conjunction with hypericum (Wheatley 1999).

Ginkgo-biloba

It is known that there is hypoperfusion in certain regions of the brain, and ginkgo-biloba has some positive effects on relieving hypoperfusion. From this viewpoint, it is considered that ginkgo-biloba might have beneficial effects on SAD. Nevertheless, in one and so far the only randomized, placebo-controlled study, ginkgo-biloba extracts were found ineffective in preventing winter depression (Lingjaerde 1999).

Alprazolam

Pharmacological efficacy of alprazolam was examined in two open studies including 6 patients (Yamadera 2001, Teicher & Glod 1990). Both studies suggested that alprazolam might be efficacious in the treatment of SAD, but as it is the case with other drugs, the number of patients in the studies were low.

Conclusion

According to clinical trial results, the first line treatment options seem to be sertraline and fluoxetine, and they are well tolerated by patients although the data for the usage of SSRIs is limited. There is some evidence that other antidepressants apart from SSRIs (e.g. bupropion) might be effective as well. Bupropion is the only drug approved in the treatment for SAD. But it should not be forgotten that the beneficial effect of bupropion in SAD is seen especially for the prevention of new episodes. Moreover, more studies are still needed to evaluate the effectiveness of other treatment options, e.g., propranolol, melatonin, hypericum, etc. In addition to the above proposed treatments, patients with seasonal depressive symptoms should thoroughly be evaluated for any cues of bipolarity, and their treatment should be planned accordingly. Thus, light therapy remains the treatment of choice for SAD, and can be combined with SSRIs for example to promote response.

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References

1. Dağdeviren N, Oral ET & Dedeoğlu S: Bipolar affektif bozuklukta mevsimsellik. *Düşünen Adam: Psikiyatri ve Nörolojik Bilimler Dergisi* 1998; 11:53-5.
2. Dilsaver SC & Jaecle RS: Winter depression responds to an open trial of tranlycypromine. *J Clin Psychiatry* 1990; 51:326-9.
3. Frandsen TB, Pareek M, Hansen JP & Nielsen CT: Vitamin D supplementation for treatment of seasonal affective symptoms in healthcare professionals: a double-blind randomized placebo-controlled trial. *BMC Research Notes* 2014; 7:528.
4. Geoffroy PA, Bellivier F, Scott J & Etain B: Seasonality and bipolar disorder: a systematic review, from admission rates to seasonality of symptoms. *J Affect Disord* 2014; 15:168-210.
5. Ghadirian AM, Murphy BEP & Gendron MJ: Efficacy of light versus tryptophan therapy in seasonal affective disorder. *J Affect Dis* 1998; 50:23-7.
6. Gloth FM, Alam W & Hollis B: Vitamin D vs broad spectrum phototherapy in the treatment of seasonal affective disorder. *J Nutr Health Aging* 1999; 3:5-7.
7. Golden RN, Gaynes BN, Ekstrom RD, Hamer RM, Jacobsen FM, Suppes T et al.: The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence. *Am J Psychiatry* 2005; 162:656-62.
8. Hesselmann B, Habeler A, Praschak-Rieder N, Willeit M, Neumaister A & Kasper S: Mirtazapine in seasonal affective disorder (SAD): a preliminary report. *Human Psychopharmacology: Clinical and Experimental* 1999; 14:59-62.
9. Hilger E, Willeit M, Praschak-Rieder N, Stastny J, Neumaister A & Kasper S: Reboxetine in seasonal affective disorder: an open trial. *Eur Neuropsychopharmacol* 2001; 11:1-5.
10. Kasper S: Treatment of seasonal affective disorder (SAD) with hypericum extract. *Pharmacopsychiatry* 1997; 30:89-93.
11. Lam RW, Gorman CP, Michalon M, Steiner M, Levitt AJ, Corral MR et al.: Multicenter, placebo-controlled study of fluoxetine in seasonal affective disorder. *Am J Psychiatry* 1995; 152:1765-70.
12. Lam RW, Levitt AJ, Levitan RD, Enns MW, Morehouse R, Michalak EE et al.: The Can-SAD study: A randomized controlled trial of the effectiveness of light therapy and fluoxetine in patients with winter seasonal affective disorder. *Am J Psychiatry* 2006; 163:805-12.
13. Levitt AJ, Lam RW & Ghadirian AM: Medication Treatment. *Clinical Guidelines for the Treatment of Seasonal Affective Disorder*. In Lam RW & Levitt AJ (eds): *Canadian Consensus Guidelines for the Treatment of Seasonal Affective Disorder*, 89-95. Clinical & Academic Publishing, 1999.
14. Lewy AJ, Bauer VK, Cutler NL & Sack RL: Melatonin treatment of winter depression: a pilot study. *Psychiatry Research* 1998; 77:57-61.
15. Lingjaerde O, Reichborn-Kjennerud T, Haggag A, Gartner I, Narud K & Berg EM: Treatment of winter depression in Norway. II. A comparison of the selective monoamine oxidase A inhibitor moclobemide and placebo. *Acta Psychiatr Scand* 1993; 88:372-80.
16. Lingjaerde O, Fjoreland AR & Magnusson A: Can winter depression be prevented by Ginkgo biloba extract? A placebo-controlled trial. *Acta Psychiatr Scand* 1999; 100:62-6.
17. Lundt L: Modafinil treatment in patients with seasonal affective disorder/winter depression: an open-label pilot study. *J Affect Disord* 2004; 81:173-8.
18. Martinez B, Kasper S, Ruhrmann S & Moller HJ: Hypericum in the treatment of seasonal affective disorders. *Journal of Geriatric Psychiatry and Neurology* 1994; 7(suppl):29-33.
19. Martiny K, Lunde M, Simonsen C, Clemmensen L, Poulsen DL, Solstad K et al.: Relapse prevention by citalopram in SAD Patients responding to 1 week of light therapy. A placebo-controlled study. *Acta Psychiatr Scand* 2004; 109:230-4.
20. McGrath RE, Buckwald B & Resnick EV: The effect of l-tryptophan on seasonal affective disorder. *J Clin Psychiatry* 1990; 51:162-3.
21. Miller AL: Epidemiology, etiology, and natural treatment of seasonal affective disorder. *Altern Med Rev* 2005; 10:5-13.
22. Modell JG, Rosenthal NE, Harriett AE, Krishen A, Asquarian A, Foster VJ et al.: Seasonal affective disorder and its prevention by anticipatory treatment with bupropion XL. *Biol Psychiatry* 2005; 58:658-67.
23. Moscovitch A, Blashko CA, Eagles JM, Darcourt G, Thomson C, Kasper S et al.: A placebo-controlled study of sertraline in the treatment of outpatients with seasonal affective disorder. *Psychopharmacology* 2004; 171:390-7.

24. Niemegeers P, Dumont GJ, Patteet L, Neels H & Sabbe BG: Bupropion for the treatment of seasonal affective disorder. *Expert Opin Drug Metab Toxicol* 2013; 9:1229-40.
25. Noyan MA, Karababa AO, Veznedaroğlu B, Elbi H & Korokoglu S: İzmir'de yarı-kırsal bir bölgede mevsimsel duygudurum bozukluğunun yaygınlığı. *Anadolu Psikiyatri Dergisi* 2001; 2:169-74.
26. O'Rourke D, Wurtman J, Brzezinski, Abou-Nader T, Marchant P & Wurtman RJ: Treatment of Seasonal Affective Disorder with d Fenfluramine. *Annals of the New York Academy of Sciences* 1987; 499:329-30.
27. O'Rourke D, Wurtman JJ, Wurtman RJ, Chebli R, Gleason R: Treatment of seasonal depression with d-fenfluramine. *J Clin Psychiatry* 1989; 50:343-7.
28. Oren DA, Schulkin J & Rosenthal NE: 1,25-(OH)₂-Vitamin D₃ levels in seasonal affective disorder: effects of light. *Psychopharmacology* 1994; 116:515-6.
29. Oren DA, Teicher MH, Schwartz PJ, Glod C, Turner EH, Ito YN et al.: A controlled trial of cyanocobalamin (Vitamin B12) in the treatment of winter seasonal affective disorder. *Journal of affective disorders* 1994; 32:197-200.
30. Osborn J, Raetz J & Kost A: Seasonal affective disorder, grief reaction, and adjustment disorder. *Med Clin North Am* 2004; 98:1065-77.
31. Partonen T & Lönnqvist J: Moclobemide and fluoxetine in treatment of seasonal affective disorder. *J Affect Disord* 1996; 41:93-9.
32. Partonen T & Lönnqvist J: Seasonal affective disorder. *Lancet* 1998; 352:1369-74.
33. Pjrek E, Winkler D, Konstantinidis A, Willeit M, Praschak-Rieder N & Kasper S: Agomelatine in the treatment of seasonal affective disorder. *Psychopharmacology* 2007; 190:575-9.
34. Pjrek E, Winkler D, Stastny J, Praschak-Rieder N, Willeit M & Kasper S: Escitalopram in seasonal affective disorder: results of an open trial. *Pharmacopsychiatry* 2007; 40:20-4.
35. Pjrek E, Willeit M, Praschak-Rieder N, Konstantinidis A, Semlitsch HV, Kasper S et al.: Treatment of seasonal affective disorder with duloxetine: an open-label study. *Pharmacopsychiatry* 2008; 41:100-5.
36. Roecklein KA, Rohan KJ & Postolache TT: Is seasonal affective disorder a bipolar variant? *Current Psychiatry* 2010; 9:42-54.
37. Roecklein KA & Rohan KJ: Seasonal Affective Disorder An Overview and Update. *Psychiatry* 2005; 2:20-6.
38. Rohan KJ, Evans M, Mahon JN, Sitnikov L, Ho SY, Nillni YI et al.: Cognitive-behavioral therapy vs. light therapy for preventing winter depression recurrence: study protocol for a randomized controlled trial. *Trials* 2013; 14:82.
39. Rosenthal K, Jacobsen FM, Sack DA, Arendt J, James SP, Parry BL et al.: Atenolol in seasonal affective disorder: a test of the melatonin hypothesis. *Am J Psychiatry* 1988; 145:52-6.
40. Ruhrmann S, Kasper S, Hawellek B, Martinez B, Hoflich G, Nickelsen T et al.: Effects of fluoxetine versus bright light in the treatment of seasonal affective disorder. *Psychol Med* 1998; 28:923-33.
41. Schlager NK: Early-morning administration of short-acting beta blockers for treatment of winter depression. *Am J Psychiatry* 1994; 151:1383-5.
42. Srinivasan V, Smits M, Spence W, Lowe AD, Kayumov L, Pandi-Perumal SR et al.: Melatonin in mood disorders. *World J Biol Psychiatry* 2006; 7:138-51.
43. Teicher MH & Glod CA: Seasonal affective disorder: rapid resolution by low-dose alprazolam. *Psychopharmacol Bull* 1990; 26:197-202.
44. Thaler H, Delivuk M, Chapman A, Gaynes BN, Kaminski A & Gartlehner G: Second-generation antidepressants for seasonal affective disorder. *Cochrane Database Syst Rev* 2011; 12:CD008591.
45. Thorell LH, Kjellman B, Arned M, Lindwall-Sundel K, Walinder J & Wetterberg L: Light treatment of seasonal affective disorder in combination with citalopram or placebo with 1-year follow-up. *Int Clin Psychopharmacol* 1999; 14(suppl):7-11.
46. Turner EH, Schwartz PJ & Lowe CH: Double-blind, placebo-controlled study of single-dose metergoline in depressed patients with seasonal affective disorder. *J Clin Psychopharmacol* 2002; 22:216-20.
47. Wheatley D: Hypericum in seasonal affective disorder (SAD). *Curr Med Res Opin* 1999; 15:33-7.
48. Wirz-Justice A, Graw P, Krauchi K, Gisin B, Arendt J, Aldhous M et al.: Morning or night-time melatonin is ineffective in seasonal affective disorder. *J Psychiatr Res* 1990; 24:129-37.
49. Wirz-Justice A. Chronobiology and mood disorders. *Dialogues Clin Neurosci* 2003; 5:315-25.
50. Yamadera H, Okawa M & Takahashi K: Open study of effects of alprazolam on seasonal affective disorder. *Psychiatry Clin Neurosci* 2001; 55:27-30.

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