

Can we prevent seasonal affective disorder (SAD) with melatonergic agents?[†]

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SUMMARY

Seasonal affective disorder (SAD) is a recurrent form of major depression, particularly occurring in the winter months with a generally spontaneous remission in spring/summer. The predictable nature of this condition provides a potentially unique opportunity to prevent recurrence in sufferers of SAD. The Cochrane Review discussed here examines the evidence for melatonin and agomelatine in preventing SAD, putting its findings into their clinical context.

KEYWORDS

Antidepressants; circadian rhythms; seasonal affective disorder; agomelatine; melatonin.

Seasonal affective disorder (SAD) is a form of depression with a seasonal pattern. It occurs particularly in the winter, with subsequent remission in the spring or summer, and displays a latitude characteristic, with a higher prevalence in northern latitudes (Monteleone 2008). In the UK, it has been estimated that 5.6% of patients attending general practices in the winter suffer from SAD (Thompson 2004).

ICD-10 classifies SAD as a subtype of major depressive disorder characterised by typical (e.g. lowered mood, anhedonia and anergia) but also atypical (hypersomnia, carbohydrate craving and weight gain) depressive symptoms with a characteristic seasonal nature (Rosenthal 1984; Magnusson 2005; WHO 1992). As with many other psychiatric disorders, SAD is a complex condition in which a multitude of genetic and physical environmental factors contribute to its manifestation. These include chronobiological mechanisms related to circadian rhythms, photoperiodism, melatonin and major monoamine neurotransmitters such as serotonin and dopamine (Levitan 2007; Lewy 2009). More generally, disrupted chronobiological mechanisms have been linked to major depressive disorder and, importantly, some of the more efficacious treatments of this disorder are therapies actively targeting the circadian system, such as morning bright

light and wake therapy (Walker 2020). SAD is a relatively stable condition in which two-thirds of patients continue to display symptoms in the long term, with only 20% demonstrating complete remission within a few years following first diagnosis (BMJ 2009).

As regards treatment, the National Institute for Health and Care Excellence (NICE; 2009) does not recommend treating seasonal depression any differently from major depressive disorder. No particular antidepressant is favoured and light therapy is also not actively encouraged (NICE cites a lack of evidence). However, findings have suggested that melatonin, a rhythm-regulating hormone, and circadian rhythms may play a role in SAD, with melatonin exhibiting chronobiotic properties and the ability to induce phase shifts (Hickie 2011). In this context, the antidepressant agomelatine, which was approved by the European Medicines Agency (EMA) in 2009 for the treatment of depression and has subsequently been demonstrated to be one of the more effective antidepressant agents (Cipriani 2018), is a melatonin receptor agonist (MT₁ and MT₂) and serotonin receptor antagonist (5-HT_{2C} and 5-HT_{2B}), and has been shown to restore disrupted circadian rhythms as well as being effective in treating people with SAD (Pjrek 2007; Srinivasan 2012). Thus, given the role of melatonergic systems on a neurochemical level in SAD, targeting these systems with melatonergic agents with the aim of preventing SAD appears reasonable. Further, with the predictable seasonal pattern of SAD arises a hopeful opportunity for prevention. The authors of this month's Cochrane Corner (Nussbaumer-Streit 2019a) thus wished to review the efficacy and safety of melatonin and agomelatine in preventing SAD, as this had not been previously accomplished.

The Cochrane Review

The review authors found only one study that met their eligibility criteria, and this compared agomelatine with placebo, providing data on 225 adults with a history of winter-type SAD who were symptom free at the beginning of the study. The analysis

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demonstrated inconclusive results, showing no clear effect either in favour or against agomelatine as a preventive treatment in SAD. Owing to the absence of studies on melatonin and the unclear evidence on agomelatine, no conclusion about the safety and efficacy of melatonin and agomelatine in the prevention of SAD may currently be inferred.

Definition of the clinical question

The review aimed to assess, in a population of adults with a history of SAD, the safety and efficacy of melatonin and agomelatine, whether in comparison with each other, placebo and other interventions (e.g. psychological and light therapy), in preventing a repeat onset of SAD.

A population of 225 participants over 18 years of age with a history of SAD but not displaying a current depressive episode at the start of the intervention were included. The sample was wholly derived from one study. SAD was defined in line with DSM-5 criteria as a seasonal pattern of recurrent major depressive episodes (American Psychiatric Association 2013). The definition, however, was then further restricted to the winter-type form, which is characterised by the depressive episode occurring in either the autumn or winter and then experiencing a full remission in either spring or summer. Summer-type SAD presents with different symptomatology and is a rarer form (Akram 2019). Participants with bipolar affective disorder were excluded, as were people demonstrating a depressive disorder from another medical condition, but studies that included people at risk of SAD and whose medical condition was not the direct cause for their depressive episode were considered. The sample, however, would have been increased had a population with bipolar disorder been included as well: it is estimated that around 25% of people with bipolar disorder fulfil criteria for SAD (Geoffroy 2013).

To assess efficacy, Nussbaumer-Streit et al considered only randomised controlled trials (RCTs), but for adverse events (i.e. tolerability) the intention was to include non-RCTs as well. The primary outcome measures were in relation to benefit and harm. Benefit was measured by the incidence of SAD. This was measured using the Structured Interview Guide for the Hamilton Depression Rating Scale – Seasonal Affective Disorders version (SIGH-SAD) with a score set *a priori* by the review authors at ≥ 20 or as defined by study authors themselves. The primary outcome for harm was defined as the rate of adverse events in relation to the intervention(s) employed (i.e. tolerability). The review authors also intended to study several secondary outcome measures, such as

quality of life and interpersonal and social functioning, the severity of the SAD episode, the proportion of people with serious adverse events and discontinuation rates (i.e. acceptability).

Methods

The search strategy included a review of multiple electronic databases as well as grey literature, including the European Medicines Agency (EMA), with no restrictions as to date, language or publication status. The references of identified studies were then scrutinised for any further relevant studies. Subject experts and trialists were contacted for information about ongoing or unpublished studies or to request additional trial data. In the case of the included study (which was unpublished), comprehensive data were obtained from the EMA. Two review authors independently reviewed the citations yielded by the search and, if required, resolved disagreements by consulting a third party.

The search initially returned 3745 citations but only one study, comparing agomelatine (25 mg/day) with placebo, met the set eligibility criteria. Specifically, of the 3745 records, 3619 were excluded during title and abstract review, leaving 126 titles for full text review and assessment for eligibility. Of these, 125 records were then rightly excluded for the following reasons: ineligible populations (54), ineligible publications such as editorials (25), ineligible interventions/controls (14), ineligible study designs (21), ‘does not answer a question of the review’ (3), conference abstracts only (2), and already included in other Cochrane Reviews on SAD – such as the review on light therapy (Nussbaumer-Streit 2019b) – and not relevant for inclusion in this review (6). Those studies that narrowly missed the inclusion criteria were rightly excluded for the following reasons: participants did not meet the criteria for SAD and were suffering from another form of depressive disorder, or participants were already displaying depressive symptoms at the start of the study. The review authors included only RCTs, in accordance with their inclusion criteria, and 21 studies were excluded owing to ineligible study designs. Potentially, and if available, non-randomised studies such as cohort studies and case-control studies could have been included in this review, with the ‘Risk of Bias in Non-randomised Studies – of Interventions’ (ROBINS-I) tool applied for assessing risk of bias in these non-RCTs.

Certainty of the evidence was assessed using the GRADE approach (Schünemann 2013). Risk of bias (Box 1 and Fig. 1) was assessed by two review authors using the Cochrane risk-of-bias tool as outlined in Higgins et al (2019). The review authors specifically assessed attrition and the reasons for it,

BOX 1 Bias, attrition bias and validity

A bias is a systematic error in results or inferences and can be defined as 'any process at any stage of inference which tends to produce results or conclusions that differ (systematically) from the truth' (Sackett 1979). It is systematic in that multiple replications of the same study would on average lead to the wrong answer.

Attrition bias can occur when people drop out of a study, leading to systematic differences between participants who leave the study and those who continue. This, in effect, can then weaken internal and external validity.

BOX 2 Intention-to-treat analysis

Intention-to-treat (ITT) analysis is the gold standard for randomised clinical trials. Under the ITT principle, participants taking part in the study are analysed as members of the group to which they were initially randomised, irrespective of whether they left the study, adhered to their treatment or switched to another one. ITT analyses are frequently used to assess clinical effectiveness as they mirror actual clinical practice, where adherence to the treatment is not always followed or where the treatment has to be changed according to the patient's clinical response.

as well as whether all relevant outcomes in these trials were published.

The statistical analysis of data used intention to treat (ITT) (Box 2) and risk ratios (RRs) (Box 3) as effect sizes for dichotomous data and mean difference (MD) for continuous data, all with 95% confidence intervals (CIs).

Results

Only one trial (225 participants) provided data for the outcomes presented in the review. Regarding the primary outcomes and the incidence of SAD, 199 participants were part of the analysis set. These were participants who had taken at least one dose of the intervention (agomelatine) and had at least one follow-up visit (26 people were excluded on this basis). The results were inconclusive, with wide confidence intervals that may encompass both relevant beneficial as well as harmful effects of agomelatine (RR = 0.83, 95% CI 0.51–1.34).

Assessing the impact of the excluded 26 participants, best- and worst-case scenarios (Box 4) were calculated, with the former yielding significance: best-case scenario (assuming that no one who dropped out was depressed) (RR = 0.42, 95% CI 0.18–0.96), worst-case scenario (assuming that everyone who dropped out was depressed) (RR = 0.96, 95% CI 0.66–1.38).

Regarding adverse events, 64 out of 112 people in the agomelatine group and 61 out of 113 in the placebo group displayed adverse events (RR = 1.06, 95% CI 0.84–1.34). The overall discontinuation rate saw 49 people in the agomelatine and 59 people in the placebo group leave the study (RR = 0.84, 95% CI 0.64–1.10).

Regarding secondary outcomes, the severity of SAD may be similar in both groups (MD = -1.80, 95% CI -4.58 to 0.98). No data were available for quality of life or interpersonal and social functioning.

The certainty of evidence for all outcomes was rated as very low because of high risk of bias, imprecision and indirectness.

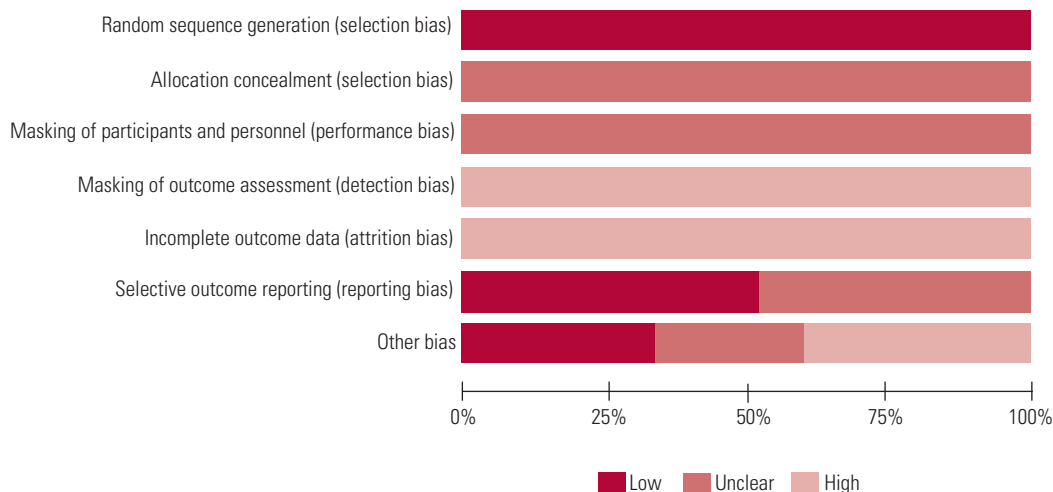


FIG 1 An example of a risk-of-bias chart.

BOX 3 Risk ratio

Risk ratio (RR) can be understood as a measure of the risk of an event occurring in the intervention group compared with the risk of the same event occurring in the control group.

RR = 1 means that there is no difference between the groups.

RR < 1 means that the risk of the event occurring has been reduced by the intervention.

RR > 1 means that the risk of the event occurring in the intervention group has been increased.

Discussion

In summary, this Cochrane Review did not demonstrate a beneficial role for agomelatine or melatonin in the prevention of SAD. It was based on only one study and was therefore in effect an appraisal of a single study. Although there is a good amount of research into the treatment of SAD using melatonergic agents, with some studies demonstrating their ameliorative effects, there is a marked lack of research into the actual prevention of SAD in the first place. This may be due to a lack of interest but also, importantly, due to the complexity of conducting such studies, especially in the recruitment of known individuals with SAD who are symptom free at the start of such an investigation.

The evidence on melatonergic agents

In the case of agomelatine, the evidence was uncertain and of very low quality. In the case of melatonin, a drug readily available over the counter in many countries, the review authors found no studies at all, and this may be a result of an inability to attain financing for such studies from bodies such as the pharmaceutical industry. In this context, the included agomelatine study was funded by the pharmaceutical industry.

BOX 4 Best-case and worst-case scenario

Missing outcome data are a frequent problem in systematic reviews, which may affect the validity of the study. The best-case scenario assumes that all missing participants have favourable outcomes in the intervention group and poor outcomes in the control group. The worst-case scenario assumes the opposite.

These scenarios are generally used as a sensitivity analysis and may generate unrealistic results in practice, in particular if attrition rates are elevated.

The review authors employed rigorous but necessary inclusion and exclusion criteria such as in differentiating participants with actual SAD from those with other depressive disorders and those who were symptom free at the start of the study from those who were already presenting with symptoms. In the end, only one study was included in the review. This 2008 study by Kasper et al, on the efficacy and safety of S 20098 (agomelatine) administered once a day for 1 year after an open period of at least 18 weeks, had not been published in a scientific journal and the review authors retrieved the complete trial data from the EMA, which is a credit to them.

The study itself suffered from a very high attrition rate (45% in the agomelatine group; 52% in the placebo group), which affected the results' validity (Box 1). The dose of agomelatine (25 mg) employed may have been appropriate but perhaps a higher dose may have seen a more beneficial effect. In the UK, dosing for depressive disorder starts at 25 mg/day and may be increased to up to 50 mg/day. Regarding the incidence of depression, Kasper et al used a SIGH-SAD score of ≥ 16 , which may have resulted in an overestimate of the incidence of depression. This is to be seen in the context, and as previously stated, that the authors of the Cochrane Review set a SIGH-SAD cut-off score of ≥ 20 *a priori*.

Limitations

There are some important limitations to this Cochrane Review. These include identifying only one eligible study, with a high attrition rate and employing a modified ITT analysis for the analysis of efficacy. Owing to the high attrition rate, it is unclear whether those who left the study could have developed depression and thus potentially altered the incidence rate in a significant way. Also, the setting does not reflect a real-world prevention experience with the participants being treated with agomelatine before winter starts and subsequently required to display stable remission for at least 2 months so as to be eligible for the study; therefore the generalisability of this study is poor.

Research into prevention of SAD

There is an evident lack of research on the topic of SAD prevention. Other Cochrane Reviews on SAD prevention but using the interventions of light therapy (Nussbaumer-Streit 2019b) and psychotherapy (Forneris 2019) also included only one study, which was at high risk of bias. However, a Cochrane Review on second-generation antidepressants in preventing SAD yielded more substantial results, demonstrating the effectiveness of

bupropion extended release (XL) in preventing SAD but also highlighting a higher risk of harm associated with the medication (Gartlehner 2019).

Conclusions

On the basis of this Cochrane Review, no conclusion on the clinical significance of melatonergic agents in the prevention of SAD can be reached. NICE guidelines recommend management of seasonal depression using the same treatment pathway as for a major depressive episode. No advice is given on the prevention of SAD. Overall, it is unlikely that this review will influence clinical practice in the UK. Further research is required on this topic and clinical practice should be guided as always by the evidence available and patients' preferences, highlighting the benefits and risks of any intervention employed.

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Declaration of interest

The views expressed here are the views of the author and not necessarily those of the National Health Service.

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