Seasonal affective disorder (SAD), as originally described in 1984, is a condition characterized by the annual recurrence of depressive episodes in fall and winter followed by remission of depressive symptoms in spring and summer. Patients with SAD have to meet diagnostic criteria for major depression, recurrent, or bipolar disorder. In the latest version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), SAD is listed as a specifier of either bipolar or recurrent major depressive disorder, with a seasonal pattern of major depressive episodes. Subsyndromal SAD is a disorder with similar but milder symptoms that do not grossly disrupt patients' social and occupational functioning. The four central features characterizing SAD are listed in Table I. Patients with SAD have the usual symptoms of depression, including low mood, lack of drive, decreased concentration, and reduced interest. Typically, many SAD patients also tend to have a specific symptom cluster consisting of the so-called reverse vegetative or atypical depressive symptoms. These symptoms include increased sleep (70%-90% of SAD patients), increased appetite (70%-80%), carbohydrate craving (80%-90%), and weight gain (70%-80%).

Pathophysiology

The etiology of SAD remains unclear. It is thought that the decreasing daylight period as winter approaches triggers depressive episodes in individuals vulnerable to SAD. However, although bright light exposure is used in the treatment of SAD, no causal relation can be drawn between the occurrence of SAD and the shortage of light in fall and winter. Patients with SAD may be sensitive to factors that are common to various forms of recurrent depression.
affective disorder, and SAD can be seen as a disorder driven by endogenous annual rhythms and characterized by an imbalance of indoleamines, serotonin, and melatonin, as well as catecholamines, over the year.

**Light therapy**

Bright light therapy (BLT) has become a first-line clinical standard for treatment of SAD (Table II). The use of BLT as a therapy for SAD evolves directly out of neuroscience. In the early 1980s, knowledge that light could shift circadian and seasonal rhythms in animals, together with the heuristic idea of extending daylight during the winter months, led to the first clinical study on BLT in SAD.1 Since then, numerous studies have not only proven its efficacy, but also greatly refined our knowledge on treatment strategies, thereby allowing for astonishingly high response rates of 80% in selected patient populations.5 BLT is safe, effective, and it has few and benign side effects. It is generally well accepted by the patients,6 and indications other than SAD, eg, disturbances of circadian rhythm due to jet lag or shift work,7,8 circadian-phase–related disturbances in dementia,9,10 sleep disorders,11,12 and nonseasonal affective disorders,13-15 are expanding research fields.

**Efficacy**

The first controlled clinical trial1 already showed the beneficial effects of light against symptoms of SAD. Since then, more than 60 controlled studies and two meta-analyses16,17 have shown the efficacy of this treatment. Using stringent criteria, the meta-analysis of Terman et al16 found remission rates of up to 67% of patients with milder depression and up to 40% of more severely depressed patients. These benefits were seen as early as 1 week after beginning treatment. However, it is now known that improvement may sometimes be seen as late as 2 to 4 weeks after beginning BLT.18 The obvious obstacles in the search for plausible placebos and “blinded” designs for studying the efficacy of BLT have led to concerns about the adequacy of control conditions. Early studies mostly used dim-light of an intensity of 300 lux or less, delivered through a light source otherwise identical to that used in the active condition (mostly light of 2500 lux intensity). As it was still possible to distinguish between the bright and dim-light conditions, these studies have been questioned as to whether they measured real biological effects and whether they could reliably separate a true antidepressant effect from placebo effects. However, fantasy and creativity of researchers in the field has led to further studies, which now unequivocally prove that light is an active biological agent with antidepressant effects in SAD. Some of these studies used (deactivated) negative ion generators as placebo condition.16-20 Like a light box, the negative ion generator is a device, has a plausible mechanism of antidepressant action, and requires the subject to sit beside it. Light had the better antidepressant effect and produced significantly more remissions, although expectations were equal for both conditions. Interestingly enough, high doses of negative ions do seem to have an antidepressant effect as well.20

**Table I.** Features of seasonal affective disorder (SAD).

| Feature                                      |
|----------------------------------------------|
| Recurrent major depressive episodes that start around the same time each year (eg, fall and winter) and end around the same time each year (eg, spring and summer) |
| Full remission of symptoms during the unaffected period of the year (eg, summer) |
| Over the lifetime course of the illness, there are relatively more seasonal depressive episodes than nonseasonal episodes |
| Seasonal depressive episodes occur in at least 2 consecutive years |

**Table II.** Guidelines for bright light therapy (BLT).

| Guideline                                                                 |
|---------------------------------------------------------------------------|
| Light therapy is an effective first-line treatment for seasonal affective disorder |
| A fluorescent light box with light intensities greater than 2500 lux is the preferred device for light therapy |
| An optimal starting dose for light therapy is 10 000 lux for 30 min/day |
| Light boxes emitting 2500 lux are effective with a treatment duration of 2 h/day |
| Morning light is more effective than evening light. Patients should be encouraged to undergo light therapy as early as possible (eg, before/during breakfast). However, evening light may be effective for some patients |
| Many patients will respond as early as after 1 week. However, in some cases a response may occur after only 2 to 4 weeks |
| If there is no sufficient response after two treatment weeks, the dose should be doubled to 30 min in the morning plus 30 min in the evening |
| If this regimen does not lead to sufficient improvement, consider adding a pharmacological treatment (best evidence available for serotonin reuptake inhibitors) |
Another challenge for efficacy studies on light therapy is the “light-noise” inevitably encountered in a normal living environment. Depending on weather conditions, outdoor light intensities can easily surmount the intensities delivered by a light box, even in the winter. This has been compared to a study trying to prove the superiority of an antidepressant drug over placebo, with antidepressants occasionally delivered through the drinking water to all study subjects. Nevertheless, today there is sound evidence showing that antidepressant effects of light in SAD are real biological treatment effects.

Dose

Earlier studies have mostly used light intensities of 2500 lux. This is much more than the typical indoor illumination, ranging from 100 lux in average rooms to about 500 lux in brightly illuminated ones. Outdoor light intensities greatly vary with weather conditions ranging from about 2000 lux on a rainy winter day to 10 000 lux or more (usually 50 000 to 300 000 lux) in direct sunshine. Today, light treatment with intensity of 10 000 lux has become clinical standard. One great advantage of higher intensity light is that it allows for shorter exposure times. Current clinical guidelines recommend beginning treatment with 10 000 lux for 30 min in the morning. Nevertheless, intensities of 2500 lux have shown to have antidepressant effects when applied for 2 h daily.

Timing

A further finding that emerged from BLT studies is the superiority of morning light over light administered in the evening. By further refining timing of light administration in relationship to the position of the circadian phase, Terman and coworkers achieved remission rates up to 80% in selected patient populations. They were able to show that response to BLT critically depends on time of delivery relative to the position of the circadian phase as determined by the onset of melatonin secretion in the evening (dim-light melatonin onset). The study suggests that the ideal therapy time is around 8.5 h after melatonin onset.

Adverse effects

The adverse effects of light therapy include headache, eyestrain, nausea, and agitation. Usually, adverse effects are mild and subside spontaneously or with dose reduction. Bright light in the evening may be associated with sleep disturbances, and, occasionally, hypomania may arise during BLT. However, subjective benefits of light consistently outweigh its adverse effects. Altogether, it remains questionable whether the frequency of these symptoms under BLT significantly exceeds the frequency of side effects seen under placebo conditions.

Dawn stimulation

Many patients with SAD experience markedly increased duration of sleep during the winter months. Usually, most of these patients have to force themselves out of bed during the weekdays despite feeling excessively drowsy. Dawn stimulation is a form of light therapy involving gradually increasing bedside light in the morning before awakening. Dawn stimulation has shown to improve symptoms of SAD compared with placebo light signals. In addition, dawn stimulation appears to be effective in ameliorating the difficulty awakening and morning drowsiness in SAD. In a comparison study, dawn stimulation using 100 to 300 lux for 60 to 90 min every morning improved symptoms of SAD similarly to light therapy using 1500 to 2500 lux for 2 h every morning.

Risks

There are no absolute contraindications for light therapy. Animal studies suggest increased risk for retinal damage with lithium, β-blockers, tricyclic antidepressants, and tryptophan. However, no such interactions have been reported in humans, and there is no evidence that light therapy is associated with ocular or retinal damage in humans. Patients with severe ophthalmological conditions or patients taking photosensitizing medication should have

391
an ophthalmological examination before starting light therapy. However, it is important that the UV spectrum is filtered out of the therapeutic light source. Although suicidality is commonly regarded as being rather infrequent in SAD, our own group has reported severe suicidal ideation and suicide attempts in three patients after the initiation of light therapy. All three patients had suicidal thoughts before light therapy was started. As always when dealing with depressed patients, patients with SAD should be carefully assessed for suicidality before light therapy, and therapy outcome should frequently and regularly be evaluated by health care professionals.

**Treatment predictors**

Atypical depressive symptoms, specifically hyperphagia, hypersomnia, and carbohydrate craving, seem to be associated with favorable response to BLT. Younger age also seems to predict a good response, while comorbid personality disorders seem to compromise the response to BLT.

**Mechanism of action**

Theories on the mechanism of action of BLT are closely connected to what is known about the pathogenesis of SAD. Two main—mutually not exclusive—theories have been raised by researchers in the field: one concentrates on the evidence for reduced serotonin neurotransmission in SAD, the other theory relates light therapy–induced improvement to corrections of altered circadian rhythms during depression in SAD.

**Serotonin**

Several lines of evidence suggest an alteration in serotonin neurotransmission in SAD. A keystone of the serotonin hypothesis on the mechanism of action of light therapy is the finding that lowering brain serotonin by tryptophan depletion leads to a transient depressive relapse in patients with SAD who are in light therapy–induced remission. In line with this theory is the beneficial effect of selective serotonin reuptake inhibitors (SSRIs) in SAD. Although there is evidence for a seasonal variation in serotonin neurotransmission, and although there seems to be a close relationship between brain serotonin and atypical depressive symptoms, serotonergic alterations are not specific for the pathogenesis of SAD or the antidepressant action of light. They rather seem to constitute a pathway common to depressive syndromes and their treatment in general.

**Circadian phase shifts**

More specific for SAD are the theories concerning alterations in circadian and circannual rhythms. Neurons of the hypothalamic suprachiasmatic nucleus (SCN) act as the main “zeitgeber” in the mammalian organism. Having an intrinsic near to 24-h rhythm, they are also known as the “internal clock.” These neurons are reset by environmental light, and they are believed to be the main determinant for the position of the circadian phase. Several body functions, such as hormonal rhythms, including nocturnal melatonin secretion, sleep, or eating behavior, are subjected to a specific circadian rhythm. The best studied marker for the position of the circadian phase is the onset of melatonin secretion by the pineal gland. In humans, the beginning of melatonin secretion occurs in the evening, usually between 1 and 2 h before falling asleep. Light can shift the position of the circadian phase, and amount and direction of that shift greatly depend on the time of light exposure: light in the evening leads to a phase delay (eg, melatonin onset occurs later), morning light advances the circadian phase.

Early theories on the pathogenesis of SAD held that a delay in the circadian phase was responsible for the appearance of SAD symptoms. Although the phase-delay hypothesis on the pathogenesis of SAD did not hold up, as there does not seem a consistent pattern of phase alterations in SAD, recent work has shown the circannual variation in circadian phase to be altered in patients with SAD when compared with healthy control subjects. Recent work by Terman and colleagues showed a correlation between light-induced changes in the “phase angle” (the relationship between the circadian phase as measured by melatonin onset and, eg, sleep onset) and antidepressant response to light in SAD.

**Practical issues**

Sufficient and clear instructions to patients are critical for a satisfactory treatment response. Patients should be informed that the beneficial effects of light are not enduring, ie, that a relapse is to be expected after a few days when treatment is discontinued. Although one study suggested a transcutaneous effect of light on melatonin secre-
tion, these results have not been replicated. It is so far safe to state that the antidepressant effect of light is mediated by the eye. The patient therefore needs to make sure that light of sufficient intensity meets the eye. Light projection does not need to be foveal, ie, it is not necessary to look directly into the light source. The ideal is an angle of about 30° to 60° to let enough light meet the eye and allow for the patient to, for example, read or eat during light therapy. The intensity of light critically depends upon the distance from the light source. Light boxes should be powerful enough to deliver an intensity of about 10 000 lux at a distance of 60 to 90 cm. If the light box is less powerful, treatment time should be expanded (see above). Patients should be encouraged to seek exposure to environmental light on sunny days. Sunlight has much higher intensity than light delivered by a light therapy device (see above). Despite the fact that light therapy is now recommended as a treatment of choice for SAD, only in Switzerland has the economic argument that in the long run, light is cheaper than drugs, attained government endorsement and mandatory reimbursement by medical insurance. The fact that there is no reimbursement for light therapy has been widely criticized by patients with SAD, their relatives, and experts in the field of SAD. Case reports on SAD patients resistant to several antidepressants, but finally responsive to light therapy illustrate that, although depressive symptoms may often be only moderate, SAD can lead to severe impairment in occupational and social functioning and can precipitate catastrophic life events.

Pharmacotherapy

Although light therapy is recommended as the first-line option for SAD, some patients do not experience sufficient relief of depressive symptoms with light. BLT can then be supplemented with antidepressant drugs. Other patients with SAD feel unable to integrate light therapy into their daily routine, or other logistical difficulties in administering light therapy are present. The evidence of SAD being associated with a dysfunction in brain serotonin systems has guided the search for promising pharmacological treatments of SAD. Data emerging from multicenter placebo-controlled trials has led to the recommendation of the SSRIs sertraline and fluoxetine as first-line treatments of SAD. Other antidepressant compounds, like monoamine oxidase inhibitors, dopaminergic and noradrenergic agents, melatonin, β-blockers as melatonin antagonists, herbs, and nutritional supplements like l-tryptophan and vitamin D have been investigated in small studies. The efficacy of these medications has not yet been proven in SAD. Open trials, controlled studies, and placebo-controlled studies in SAD are listed in Tables III to V. New pharmacological agents are of potential value in the treatment of SAD, for example, agomelatine (Valdoxan). This new dual melatonergic and specific serotoninergic antidepressant has been shown to be efficient in the treatment of major depression: it exhibits a specific core action on circadian rhythms, and therefore could be of particular value in the treatment of SAD. More specific studies are underway to more obtain information about its activity in SAD.

Open studies

A survey of open studies in SAD is given in Table III. There is some suggestion from pilot data with small sample sizes that serotoninergic agents like fluoxetine, citalopram, and trazodone may be treatment options for SAD. Tranylcypromine, a nonselective monoamine oxidase inhibitor was effective in the treatment of 14 patients leading to an average 91% reduction in depressive symptoms within 4 weeks of initiation of treatment. A study in 20 patients indicates that St John’s wort (Hypericum perforatum) may be helpful in treating SAD. An add-on therapy with bright light in 10 of these patients treated with hypericum did not lead to a significantly better treatment outcome. Two studies in 6 patients each report beneficial effects of the benzodiazepine alprazolam. A 6-week open trial investigating efficacy and tolerability of reboxetine, a selective noradrenaline reuptake inhibitor, led to rapid full remission of depressive symptoms in 11 out of 16 patients. A rapid relief of preexistent severe atypical symptoms was observed in 9 patients within the

| Authors | Number of patients | Medication |
|---------|-------------------|------------|
| Jacobsen et al, 1989 | n=3 | Fluoxetine, trazodone |
| Dilsaver and Jaekle, 1990 | n=14 | Tranylcypromine |
| Teicher and Glod, 1990 | n=6 | Alprazolam |
| Wirz-Justice et al, 1992 | n=1 | Citalopram |
| Lingjaerde et al, 1993 | n=5 | Moclobemide |
| Martinez et al, 1994 | n=20 | Hypericum |
| Yamadera et al, 2001 | n=6 | Alprazolam |
| Hilger et al, 2001 | n=16 | Reboxetine |

Table III. Open studies of pharmacotherapy of seasonal affective disorder (SAD).
first week of treatment. This finding is of pathophysiological interest since, so far, atypical depressive symptoms like increased appetite, carbohydrate craving, and hypersomnia have been strongly associated with a dysfunction in brain serotonin systems.

**Controlled studies**

Controlled studies of pharmacotherapy in SAD are presented in Table IV. A study by Ruhrmann et al comparing the SSRI fluoxetine and light therapy in 40 patients with SAD found no significant difference in treatment outcome between the groups, but a faster onset of antidepressant action in the light therapy group. Because SAD is prevalent in winter when vitamin D stores are typically low, and because light therapy includes wavelengths that allow the skin to produce vitamin D, the potential role of vitamin D in SAD has been investigated in a small pilot study. Vitamin D was reported to lead to a greater improvement of depressive symptoms than light therapy. However, no difference in vitamin D levels has been observed between patients with SAD and healthy subjects, and the antidepressant effect of light therapy has been shown to be independent of changes in vitamin D levels. So far, any benefits of vitamin D on SAD remain unproven.

4 to 6 g daily doses of the amino acid L-tryptophan, the precursor of serotonin, were as effective as light therapy. In a postal survey using an 11-item rating scale, 301 patients with SAD treated with hypericum at 300 mg three times daily for 8 weeks were asked to report changes in their symptoms. Of these patients, 133 used additional light therapy. Significant overall improvement was reported in both treatment groups. Improvement in sleep was greater in the hypericum and light therapy group. However, double-blind research is needed to confirm the usefulness of hypericum (St John’s wort) for treating SAD.

**Placebo-controlled studies**

Table V presents placebo-controlled studies of pharmacotherapy in SAD. The best evidence for efficacy of antidepressants in SAD comes from studies of SSRIs. Multicenter, double-blind, randomized studies of fluoxetine and sertraline confirm that these medications are effective in the treatment of SAD. In the fluoxetine study (68 patients), significant improvement in mood was present in both fluoxetine and placebo-treated patients at termination of the study. However, there was significant superiority of fluoxetine over placebo in the clinical response rates (59% versus 34%, respectively). In the sertraline study (187 patients), a significant superiority to placebo in both clinical response rates (62% versus 46%, respectively) and depression scores was found. Although they have been widely cited, the data from the sertraline study have only been published as an abstract so far. A double-blind study by Lingjaerde et al investigating the efficacy of moclobemide, a reversible inhibitor of monoamine oxidase A, versus placebo over 14 weeks found no significant difference in depression scores between patients at study termination. However, within the first week of treatment, patients in the moclobemide group, but not in the placebo group, had a significant reduction in atypical depression symptoms. Testing the

| Authors           | Number of patients | Medication and study design                        | Outcome                                      |
|-------------------|--------------------|----------------------------------------------------|----------------------------------------------|
| McGrath et al,62  | n=13               | L-Tryptophan and LT versus L-tryptophan alone      | No significant difference                    |
| Ruhrmann et al,63 | n=40               | Fluoxetine versus LT                                | No significant difference, but faster onset of antidepressant action in LT group |
| Ghadirian et al,64| n=13               | L-Tryptophan versus LT, crossover study            | No significant difference                    |
| Gloth et al,65    | n=15               | Vitamin D versus LT                                 | Vitamin D superior to LT                     |
| Wheatley,66       | n=168              | Hypericum and LT versus hypericum alone            | Significant improvement in both groups, improvement in sleep greater in hypericum and LT group |

Table IV. Controlled studies of pharmacotherapy of seasonal affective disorder (SAD). LT, light therapy.
hypothesis that a dopaminergic deficiency plays a role in the pathophysiology of SAD, Oren et al conducted a small study investigating the efficacy of levodopa plus carbidopa as a treatment for SAD.\textsuperscript{68} No differences to placebo were found in the rates of response. The melatonin hypothesis of SAD was tested in two studies using the β-blockers atenolol\textsuperscript{67} and propanolol\textsuperscript{69} to suppress melatonin secretion. No difference in antidepressant efficacy was found between atenolol and placebo. Propanolol was superior to placebo in preventing a depressive relapse in patients with SAD who had previously responded to an open treatment with propanolol. Supplementation with melatonin has shown to be ineffective in patients with SAD when taken at night or in the morning.\textsuperscript{70} Melatonin has also been reported to even reverse the benefits of light therapy.\textsuperscript{80} However, a small pilot study with low doses of melatonin in the afternoon showed a significant decrease in depression ratings compared to placebo.\textsuperscript{72} The authors argue that a replication of this finding in an adequate sample with documentation of expected phase shifts would substantially support the phase shift hypothesis of SAD. A recent 1-year pilot study\textsuperscript{73} aimed at investigating possible advantages of combining light therapy with the SSRI citalopram. No significant group difference was found during the initial 10-day light therapy period. However, during the follow-up period depression ratings were significantly lower in the citalopram group compared with the placebo group. The authors conclude that light therapy with continued SSRI treatment may be a useful strategy to achieve beneficial long-term effects in patients with SAD. A study by Lingjaerde et al\textsuperscript{74} testing the hypothesis that \textit{Ginkgo biloba} extract may prevent the symptoms of winter depression in patients with SAD yielded negative results. In a recent study metergoline, a nonspecific serotonin antagonist, did not demonstrate a sustained significant effect on mood compared with placebo.\textsuperscript{75}

### General management issues

Since there is little evidence comparing light therapy with antidepressant medication, the choice between these alternatives relies on individual assessment of risks and benefits.\textsuperscript{23} Generally, light therapy is very well accepted by patients. Availability and costs of a light therapy device are sometimes limiting factors, as is the time patients need to commit for daily light therapy. However, BLT should be considered first-line treatment for moderately depressed

| Authors               | Number of patients | Medication and study design                      | Outcome                                      |
|-----------------------|--------------------|--------------------------------------------------|----------------------------------------------|
| Rosenthal et al,\textsuperscript{67} 1988 | n=19               | Atenolol versus placebo                          | No significant difference                    |
| Lingjaerde et al,\textsuperscript{58} 1993 | n=34               | Moclobemide versus placebo                       | No significant difference, but significant reduction of atypical symptoms in moclobemide group |
| Oren et al,\textsuperscript{68} 1994       | n=25               | Levodopa + carbidopa versus placebo               | No significant difference                    |
| Schlager,\textsuperscript{69} 1994        | n=23               | Propanolol versus placebo                        | Significantly higher relapse rates in placebo group |
| Oren et al,\textsuperscript{70} 1994       | n=27               | Vitamin B\textsubscript{12} (cyanocobalamine) versus placebo | No significant difference                    |
| Lam et al,\textsuperscript{71} 1995        | n=78               | Fluoxetine versus placebo                         | No significant difference, higher response rate in fluoxetine group |
| Lewy et al,\textsuperscript{72} 1998      | n=10               | Melatonin versus placebo                          | Melatonin superior to placebo                |
| Thorell et al,\textsuperscript{73} 1999    | n=8                | LT and citalopram versus LT and placebo           | No significant difference between citalopram and placebo during LT; after LT citalopram superior to placebo |
| Lingjaerde et al,\textsuperscript{74} 1999 | n=27               | \textit{Ginkgo biloba} versus placebo             | No significant difference; \textit{gingko} significant more effective in preventing new depressive episodes |
| Turner et al,\textsuperscript{75} 2002     | n=16               | Metergoline versus placebo                        | No significant difference                    |

Table V. Placebo-controlled studies of pharmacotherapy of seasonal affective disorder (SAD).\textsuperscript{58,67,71} LT, light therapy.
patients and patients with prominent atypical depressive symptoms. Generally, light therapy alone or in combination with antidepressants should be given for the duration of the dark time of year, ie, until April or May in the northern hemisphere. A trial of light therapy should last at least 2 to 4 weeks. A trial of antidepressants should last 4 to 6 weeks. Light therapy and medication trials should be applied sequentially, as combining them from the beginning on will lead to a loss of information about which treatment is beneficial, or which treatment is causing side effects. A combination of both treatments should be considered if there is insufficient response to either pharmacological or light treatment. If a depressive episode is resistant to the combination of BLT and an antidepressant, options are lengthening light treatment time, raising the dose of the antidepressant, or switching to a drug of a different class. Although there are no specific data available for SAD, treatment should follow algorithms for treatment-resistant depression if a sufficient response still cannot be achieved. Pharmacological augmentation strategies, electroconvulsive therapy, or sleep deprivation procedures should then be considered.
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