

# **LIGHT THERAPY IN BIPOLAR DISORDERS**

## **Protocol**

**Dutch Foundation for Bipolar Disorders: Chronotherapy Task Force**

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# 1. Introduction

## General introduction

Periodicity is a typical feature of mood disorders (Lieveise et al. 2012). In some patients mood episodes occur in certain seasons, such as with winter depression. Sometimes periodicity can also be seen at the symptom level, such as the diurnal fluctuation of a depressive mood, early morning waking and other sleep and sleep phase disorders. Research into the sleep-wake cycle and temperature cycles indicate that with mood disorders these cycles may be changed: in the case of depression slowed down and moved back and in the case of mania accelerated and moved forward. Research has been conducted into light therapy as a treatment for depression ever since the 1980s. Chronobiological changes seem to contribute to mood disorders, but it is not clear exactly how this occurs.

## Evidence base

Light therapy has proved to be effective primarily in the treatment of unipolar depression with a seasonal pattern (seasonal affective disorder or SAD), but it is also effective in depression without seasonal variation (Golden et al. 2005; Lam et al. 2016). A Dutch multidisciplinary depression guideline (*Multidisciplinaire richtlijn depressie*, Spijker et al. 2013) concludes that it is plausible that light therapy is effective in patients with depressive disorder with a seasonal pattern (particularly SAD) and therefore recommends light therapy for patients with SAD. Naturalistic research suggests that light has an antidepressant effect in bipolar depression (Benedetti et al. 2001a). Non-randomized and randomized studies of the effect of light therapy in patients with a depressive episode in the context of bipolar disorder have mainly been conducted in combination with sleep deprivation therapy; the intervention proved to be effective (Benedetti et al. 2001b en 2005; Colombo et al. 2000; Wu et al. 2009; Tseng et al. 2016). With light therapy a switch to hypomania, mania or a mixed episode has been described as a complication (Colombo et al. 1999; Dauphinais et al. 2012; Sit et al. 2007; Terman & Terman 1999). However, a review of 41 studies including 799 patients with bipolar disorder and treatment with – mostly morning – light therapy shows the risk of switch to be lower than the 4% found in a placebo condition (Benedetti 2018). In Dutch clinical practice a mood switch of this kind has only been observed very rarely in the treatment of seasonal bipolar depression and when it has occurred it has been short and slight (Rops L, Riemersma R, Schulte P., personal communication 2018). Patients who are already showing manic symptoms and patients with rapid cycling probably have a higher risk of switching to mania (Benedetti 2018).

Recently three small placebo-controlled, randomized studies have been conducted relating to the efficacy of light therapy in bipolar depression, without the criterion of a seasonal pattern (Sit et al. 2018; Yorguner Kupeli et al. 2017; Zhou et al. 2018). The patients were receiving antimanic medication or a mood stabilizer. In the first study the treatment consisted of 7000 lux of white light which was titrated up to 60 minutes and administered in the early afternoon for four to six weeks (Sit et al. 2018), in the second study two weeks of 5000 lux of white light for one hour in the morning (Zhou et al. 2018) and in the third study two weeks of 10,000 lux of white light for half an hour in the morning (Yorguner Kupeli et al. 2017). In all three studies light therapy proved to be more effective than placebo light. There was no occurrence of mania or

hypomania in any of the studies. Based on the studies by Tseng (2016) and Sit (2018) and without knowledge of the studies by Yorguner Kupeli (2017) and Zhou (2018), the new guideline for the treatment of bipolar disorders issued by the International Society for Bipolar Disorders concludes that light therapy is a third-line treatment in bipolar I depression (Yatham et al. 2018).

Seasonal depression (SAD) also occurs in the context of bipolar disorder. In practice light therapy is used frequently, but until now it has been insufficiently researched in relation to this condition. The Dutch Multidisciplinary Guideline for Bipolar Disorders concludes that light therapy can be considered as a treatment option for SAD in the context of bipolar disorder (Kupka et al. 2015). The randomized studies referred to above of the treatment of bipolar depression without the criterion of a seasonal pattern support this point of view, given that three quarters of the treatments in Sit's study (2018) took place in the autumn or winter and in Yorguner Kupeli's study (2017) a quarter of the patients had a seasonal pattern. These patients reached remission significantly more often with light therapy than those without this pattern. These findings support the assumption that light therapy is also – and possibly even particularly – effective in bipolar depression with a seasonal pattern.

The concerns regarding efficacy, eligibility and the risk of a switch are comparable to those relating to treatment with antidepressants. It should be borne in mind that with light therapy in bipolar depression, just as with treatment with antidepressants, a mood switch to hypomania, mania or a mixed episode may occur. It is therefore recommended that patients with bipolar I disorder should be given a mood stabilizer or antimanic agent at the same time.

## 2. Assessment of eligibility

### Eligibility for light therapy

Depressive episode, with or without a seasonal pattern, without psychotic or mixed features, in the context of bipolar I or II disorder. Light therapy may also have a beneficial effect on subsyndromal depressive seasonal symptoms which do not quite meet the criteria. In such cases there is often not so much a drop in mood as a seasonal energy problem (Haffmans et al. 1999).

## Absolute contraindications

- Manic symptoms or mixed episode

## Relative contraindications

- Pre-existing retinal conditions
- Systemic disease affecting the retina
- Taking photosensitive medication
- Depression with mixed features<sup>1</sup>
- rapid cycling in preceding year<sup>1</sup>

## Ophthalmic examination

It is not necessary to request an ophthalmic examination and advice as standard practice before starting light therapy. Visiting or consulting by telephone with an ophthalmologist should be considered if there are risk factors for the development of eye disease in the event that the patient is exposed to light as in the treatment. These risk factors are certain pre-existing physical disorders and taking certain medications which may make the retina more sensitive to light (see Table 1) (Lam et al. 2009 and Wirz-Justice et al. 2013). These risks are in fact estimated to be very low (Brouwer et al. 2017).

It is not known if there is a risk associated with long-term administration of light therapy or with risk factors as listed in Table 1. To date the available literature is reassuring, but there is too little research for a definitive conclusion (Brouwer et al. 2017). This means that the situation is similar to using newly registered medication for which the rare risks or risks of long-term use are also not yet known.

### Recommendation:

There are very few reports of complications occurring with light therapy (Brouwer et al. 2017). The recommended light therapy devices produce 10,000 lux of white light, which is comparable with the sun 45 minutes after sunrise. With these lamps UV light is filtered out, so that the light they produce is less harmful for the retina than sunlight. Since potential users usually also sit at pavement cafés at the height of summer (120,000 lux, Brouwer et al. 2017), it is reasonable to discuss the risks with the patient and leave the choice to them (informed consent). If there are risk factors, patients can request a visit to an ophthalmologist if they like.

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<sup>1</sup> Consistent with antidepressant use (Pacchiarotti et al. 2013).

## Table 1

### Risk factors for potential toxicity associated with exposure to bright light<sup>2</sup>

#### *Pre-existing eye and skin conditions*

- Retinitis pigmentosa
- Porphyria
- Chronic actinic dermatitis
- Urticaria due to sun exposure

#### *Systemic diseases affecting the retina*

- Diabetes mellitus
- Rheumatoid arthritis
- Systemic lupus erythematosus

#### *Photosensitive medication*

- Phenothiazines, e.g. promethazine, chlorpromazine, zuclopentixol and flupentixol
- Melatonin
- St John's wort (hypericum)
- Chloroquine
- 8-methoxypsoralen
- Amiodarone

## Medication strategy

With depression in the context of bipolar I disorder, the recommendation is to administer light therapy only in combination with a mood stabilizer or antimanic agent. It is important to watch out for the development of a mixed, hypomanic or manic episode (Wirz-Justice et al. 2013) and if this occurs to treat it appropriately. With a depressive episode in the context of bipolar II disorder the same strategy can be used as with giving antidepressants (see multidisciplinary guideline for bipolar disorders, Kupka et al. 2015).

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<sup>2</sup> This list is based on Lam et al. (2009) and Wirz-Justice et al. (2013) in consultation with Van der Pol (2017). After consultation with the Dutch Ophthalmological Society's guidelines subcommittee, the following conditions are no longer regarded as risk factors with regard to light therapy: retinal detachment, macular degeneration, a family history of macular degeneration, glaucoma or lithium treatment.

## 3. Dosage and type of light

### Dosage

The dosage can be controlled in 3 different ways:

1. The *light intensity* of the lamp (amount of lux)
2. The *duration of exposure* to light (number of minutes a day)
3. The number of days light therapy is given (*treatment duration*)

#### *Intensity*

According to the 'gold standard', light therapy should be done with a lamp which produces 10,000 lux of white light. The patient sits at a distance of about 30 cm from the lamp. It is not necessary to look at the lamp. The intensity of the light is reduced if the patient sits further away from the lamp. The rule of thumb is that if the distance from the lamp is doubled, the intensity is reduced by a factor of 4. In other words, 10,000 lux at a distance of 30 cm will be 2500 lux at a distance of 60 cm. During the treatment the patient can have breakfast, read a book or magazine, or use a laptop or tablet (Lam et al. 2009).

#### *Duration of exposure to light*

A 30-minute session with 10,000 lux has often proved effective in studies of unipolar seasonal depression and in the Netherlands the most experience has been gained with this duration and exposure. If treatment is with a 5000 lux lamp the treatment should be 45-60 minutes (Lam et al. 2009).

#### *Treatment duration*

There is no consensus in the literature as regards treatment duration. Usually the effect is apparent within a week and often this is even enough. If not, the therapy is prolonged for one or two weeks. In a study of the treatment of unipolar non-seasonal depressive disorder the effect of light therapy continued to increase over a period of six weeks (Lam et al. 2016). This was also found in the study of bipolar depression by Sit et al. (2018), but in that study the light dose was titrated up over four weeks. The light therapy can therefore optionally be extended to six weeks.

### Type of light

In recent years more and more types of light therapy lamps have become available. Not all lamps have been properly examined for efficacy and toxicity. When buying a light therapy lamp, either as a professional or a private user or patient, it is advisable to purchase a lamp which has been shown to be effective and not harmful. This can be done by means of peer-reviewed clinical trials or a study by an independent laboratory which looks at field size, light spectrum, intensity and UV screening (Wirz-Justice et al. 2013).

Most research has been done with lamps that produce bright white light which is largely similar to daylight. Unlike daylight, the light provided does not contain ultraviolet or infrared light, since these types of light have no therapeutic effect, but can be harmful (Haffmans et al. 1999).

### *Blue light*

There is evidence that the wavelength of blue light has the strongest effect on melanopsin in the retina and therefore on the circadian system. In theory this means that blue light might also have the strongest effect on mood and energy levels. Research has shown that blue light is just as effective as white light (Wirz-Justice et al. 2013; Meesters et al. 2011).

It has also been shown that intense blue light such as that of a welding torch is harmful to the retina. In the literature this is referred to as 'blue light hazard', meaning that acute retinal damage can be caused by exposure to intense light sources. Light therapy with white light has never been shown to be harmful to the retina. The reason for this is probably that the light intensity used is similar to the intensity of bright morning light. There are light therapy lamps which only produce blue light instead of bright white light. It has not been shown that these lamps are more effective than the standard lamps which produce white light. Because there is also potential toxicity and only limited research has been conducted into the long-term effects of these lamps, we do not recommend them (Lam et al. 2009 and Wirz-Justice et al. 2013).

### *LED light*

In recent years more and more light therapy lamps producing LED light have come onto the market. The advantage of these lamps is that they can produce a high light intensity on a smaller surface area, so that they are smaller and more convenient. They also use less power, often operate on batteries (sometimes rechargeable) and have a very long life. Studies have shown that LED light is effective in the treatment of seasonal unipolar depression. The intensity in lux of LED lamps is lower, but with the same duration (a maximum of 30 minutes) they appear to have the same efficacy as the lamps which produce bright white light (Desan et al. 2007). There may be other differences in the wavelength of the light which makes it more efficient. The drawback of these lamps is the relatively small area within which the light intensity is high, which means that if the position of the lamp changes slightly the intensity is quickly reduced. The user will have to bear this in mind (Lam et al., 2009).

## 4. When to start and what time of day

The starting time in relation to the appearance of the symptoms and the time of day at which the light therapy is given are very important. For seasonal depression in the context of unipolar or bipolar depression it is best to start as soon as the first depressive symptoms appear. No proper research has been conducted into preventive light therapy for people for whom it has previously been effective. Depending on the predictability of episodes, the speed at which symptoms appear and the speed of response to light therapy, the treating physician and the patient can make a decision about this together.



The time of day at which light therapy is given is also important. With unipolar seasonal depression it has been shown that light therapy in the early morning is the most effective. Light in the morning has a beneficial synchronizing effect on the circadian system and therefore also on sleep. Light in the evening pushes the rhythm back and therefore has a negative effect on sleep, which is often already disturbed, and is therefore not recommended.

There is evidence that people with bipolar disorder are more sensitive to light than people with unipolar depression and people without an affective disorder. Light therapy may cause agitation and hyperactivity, in which case adjustment of the light dose (shorter duration and/or greater distance from the light source) is usually the solution. However, for some patients with bipolar depression the administration of morning light causes a mixed episode. This occurs more frequently with bipolar I disorder (Lam et al. 2009). Research has shown that moving the time of the light therapy to noon also has a positive effect on the mood, with a lower risk of switch (Sit et al. 2007).

The recommendation is to start light therapy in the morning and if necessary – if agitation and/or mixed *symptoms* appear – to change the time to noon. If a mixed or manic *episode* occurs, the light therapy should be discontinued. Given that patients with bipolar disorder often have a positive response to light therapy, the small risk of disinhibition should not be a reason not to start light therapy. However, it is important to monitor for the appearance of any mixed or manic symptoms.

## 5. Side effects

Light therapy is generally well tolerated. Most side effects of light therapy are harmless, mild and temporary (Lam et al. 2009, Wirz-Justice et al. 2013).

Tired or irritated eyes, slight nausea, dizziness, headache and agitation or feeling 'wired' are the most commonly heard complaints, but they occur infrequently. If these complaints are a problem, an option is to reduce the dose of light by increasing the distance from the lamp or to shorten the duration of the session. As discussed in relation to the time of administration, the time can be shifted to noon if agitation is a problem or if a switch to mixed symptoms occurs. Administration in the evening can lead to difficulty falling asleep (Lam et al. 2009, Wirz-Justice et al. 2013).

If there are risk factors for potential toxicity of exposure to bright light, an ophthalmic examination can be considered (see Assessment of eligibility: ophthalmic examination).

## 6. Treatment process

### Presentation and screening

Patients with a seasonal depressive episode in the context of bipolar I or II disorder can be treated with light therapy. Light therapy can also be considered for patients with a non-seasonal bipolar depressive episode. The first time it is advisable to do this in an outpatient setting, under supervision of a professional. If the result is positive and there are no side effects, the patient can consider purchasing a light therapy lamp of their own. It is a good idea to check if this is covered by the patient's health insurance. In some cases part of the purchase costs will be included in additional cover.

Eligibility will be assessed by a psychiatrist or a treating physician under supervision of a psychiatrist. If a patient is assessed as eligible for light therapy, any possible contraindications will be identified and if necessary a specialist can be consulted. If a patient is eligible for light therapy, they will be informed about the background of the therapy and the practical ins and outs of the treatment.

### Administration of light therapy

Before the beginning of the first session the IDS-SR or QIDS is completed. Then an explanation is given about the operation of the light therapy device and the correct sitting position and distance from it. Light therapy should be started in the morning. In principle one treatment session lasts 30 minutes, with an intensity of 10,000 lux and a distance of 30 cm between the patient's eyes and the light source. The patient does not look directly at the lamp.

If there are complaints of agitation which are disruptive or if mixed *symptoms* appear, it is advisable to move the time of therapy to noon. If there is a switch to a mixed, hypomanic or manic *episode*, the light therapy should be discontinued. As discussed above, the risk of this happening is small.

### Evaluation and termination

After a week (for outpatient treatment 5 working days) the effect of the light therapy is evaluated by means of an assessment of the clinical picture and again completing the IDS-SR or QIDS. The further strategy is determined on the basis of the results:

- If the complaints are in remission, the treatment is finished.
- If there is insufficient or no response, the treatment is extended by one or two weeks. For outpatient treatment this means one or two times 5 working days. A treatment duration of six weeks can be considered.
- If mixed or manic symptoms appear, it is advisable to move the time of light therapy to noon.
- If a mixed episode, hypomania or mania occurs, the treatment should be discontinued.
- If detrimental side effects occur, the light dose can be reduced by increasing the patient's distance from the lamp or shortening the duration of the session.

On the last day of treatment a final exit interview will take place in which the effect of the treatment and the occurrence of any side effects will be evaluated. If the treatment was successful, the treating physician will explain to the patient that they will be eligible for further treatment if the complaints recur that same season or if there are new complaints a year later (in the case of seasonal depression). This can be included in the relapse prevention plan.

If the patient has completed light therapy with success and without side effects, it can also be suggested that they might try light therapy without supervision, with a rented or purchased lamp. In that case the patient must be carefully instructed about light intensity, the duration of the sessions, the total treatment duration, etc.

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