

Bright-Light Therapy in the Treatment of Mood Disorders

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Abstract

Bright-light therapy (BLT) is established as the treatment of choice for seasonal affective disorder/winter type (SAD). In the last two decades, the use of BLT has expanded beyond SAD: there is evidence for efficacy in chronic depression, antepartum depression, premenstrual depression, bipolar depression and disturbances of the sleep-wake cycle. Data on the usefulness of BLT in non-seasonal depression are promising; however, further systematic studies are still warranted. In this review, the authors present a comprehensive overview of the literature on BLT in mood disorders. The first part elucidates the neurobiology of circadian and seasonal adaptive mechanisms focusing on the suprachiasmatic nucleus (SCN), the indolamines melatonin and serotonin, and the chronobiology of mood disorders. The SCN is the primary oscillator in humans. Indolamines are known to transduce light signals into cells and organisms since early in evolution, and their role in signalling change of season is still preserved in humans: melatonin is synthesized primarily in the pineal gland and is the central hormone for internal clock circuitries. The melatonin precursor serotonin is known to modulate many behaviours that vary with season. The second part discusses the pathophysiology and clinical specifiers of SAD, which can be seen as a model disorder for chronobiological

disturbances and the mechanism of action of BLT. In the third part, the mode of action, application, efficacy, tolerability and safety of BLT in SAD and other mood disorders are explored.

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In the early 1980s, the observation that light is able to shift the circadian phase and seasonal rhythms in animals, and the concept of extending daylight during winter months in order to interfere with these rhythms resulted in the first trial of bright-light therapy (BLT) in seasonal affective disorder (SAD) [1]. Since then, a remarkable number of studies have been able to prove the relevance of BLT in the treatment of seasonal and non-seasonal mood disorders. Moreover, BLT was also investigated in other problems and disorders associated with circadian rhythm disturbances (jet lag, shift work or dementia) [2–5], sleep disorders [6, 7], bulimia nervosa [8–11] and adult attention-deficit/hyperactivity disorder [12]. The purpose of this article is to give an overview on up-to-date chronobiology research, and to try to elucidate the links that exist between basic and clinical aspects relevant to light treatment in psychiatry. Moreover, recent studies on BLT in SAD and other mood disorders will be discussed together with new findings concerning the mode of action of BLT, wavelength, intensity, and the so-called placebo problem in light-therapy studies.

Circadian and Seasonal Adaptive Mechanisms and Their Disturbances in Mood Disorders

The Suprachiasmatic Nucleus

Almost all physiological functions of the body, like secretion patterns of hormones, sleep-wake cycle or core body temperature, follow specific rhythmic changes throughout the day [13]. These highly specialized functions are driven by the master clock, the suprachiasmatic nucleus (SCN), and can be seen as the core of an adaptive system reacting to predictable everyday demands of life. The SCN consists of approximately 10,000 neurons located within the anterior hypothalamus and allows mammals, including humans, to maintain this circadian cycle in body functions, even when totally isolated from zeitgebers [14]. This function is lost if the SCN is destroyed [15]. The circadian system is primarily entrained by the zeitgeber light. Information on the light-dark cycle is perceived and transduced by melanopsin-containing retinal cells [16]. These cells are directly connected to the SCN via the retinohypothalamic tract and are not part of the visual system. Entrainment depends on time of presentation, duration, wavelength and dose of light [17]. In addition, the SCN is modulated by serotonergic neurons originating in the raphe nuclei [18]. The SCN receives direct feedback from the pineal gland via MT_1 and MT_2 melatonin receptors [19, 20]. However, the majority of cells in the human organism follow their own circadian rhythms and zeitgebers. These rhythms are synchronized with the primary oscillator, SCN, to a varying extent [21–23].

Melatonin

Melatonin (N-acetyl-5-methoxytryptamine), a central hormone of internal clock circuitries [24], was first identified by Lerner et al. [25] in 1958. It is secreted primarily by the pineal gland in a specific circadian pattern in accordance with the light-dark cycle (high at night, low during the day) [26] and the seasonal cycle (longer peak in winter, shorter peak in summer) [27, 28]. Melatonin is synthesized from its precursor serotonin before it is rapidly distributed within the body [29]. The pace of secretion is controlled by the SCN and its main efferent pathway to the paraventricular nucleus through polysynaptic pathways of the sympathetic nervous system [30, 31]. Melatonin works as a biochemical marker transducing photoperiodic information and signalling seasonal variations of the light-dark cycle to all cells [32]. Peripheral effects of the circadian system are mainly mediated by the paraventricular nucleus and corticotropin-releasing factor secreting neurons enhancing periodical adaptation of body functions in anticipa-

tion of diurnally varying requirements [33]. In 1980, Lewy et al. [24] were able to show that exposure to light had the potential to alter circadian rhythms and to suppress the secretion of melatonin in humans.

Serotonin

The predominant role of serotonin (5-hydroxytryptamine) in modulating behaviour, emotions, and circadian rhythms [31] made it one of the best-researched transmitters in the human brain. Serotonergic neurons originate in the raphe nuclei of the brainstem. A number of studies showed seasonal changes in serotonergic parameters, including brain serotonin concentration and turnover [34–38]. Furthermore, serotonin-related behaviours change with the seasons in clinical and non-clinical populations [34, 39–47]. The most important physiological mechanism controlling synaptic serotonin levels is reuptake of serotonin into the presynaptic neuron via the serotonin transporter (5-HTT) [48, 49]. High 5-HTT density is associated with low extracellular serotonin, and vice versa [50]. In a study in healthy subjects, Praschak-Rieder et al. [51] have recently shown that 5-HTT binding in the living human brain varies with the season, with peak differences being as high as 40%. 5-HTT binding potential values, an index of 5-HTT density, varied along a sinusoidal curve in all investigated brain regions during the course of the year. The highest 5-HTT binding potential values occurred during the dark months in autumn and winter, while the lowest values were found around the summer solstice. Moreover, 5-HTT binding potential values were negatively correlated with the duration of daily sunshine, with reductions in 5-HTT binding paralleling the increase in sunlight during spring. These results are in line with findings on the impact of light on serotonergic processing in rodents [52–56] and they offer a potential explanation for the regular reoccurrence of depressive episodes in patients with SAD and for the spring peak in suicide rates found in temperate and polar zones [57–61].

Chronobiology of Mood Disorders

Alterations of circadian rhythms in mood disorders can be classified into three groups: shift of phase (phase advance, phase delay), diminution of amplitude, and day-to-day variability to entrainment [62, 63]. Typical changes of circadian rhythms in depression apply to sleep [64–68], hormones [69–78], and core body temperature [78–83], and results from a large meta-analysis of psychopathological symptoms of circadian rhythm disorders were able to distinguish depressed patients from normal controls [78, 84]. Although chronobiological abnormali-

Table 1. Diagnostic criteria of the seasonal pattern specifier according to the Diagnostic and Statistical Manual of Mental disorders, ed. 4, text revision adapted from ref. 87

A	Regular temporal relationship between the onset of major depressive episodes and a particular time of the year (unrelated to obvious season-related psychological stressors)
B	Full remission (or change from depression to mania or hypomania) also occurs at a characteristic time of the year
C	Two major depressive episodes meeting criteria A and B in the last 2 years and no non-seasonal episodes in the same period
D	Seasonal major depressive episodes substantially outnumber non-seasonal episodes over the individual's lifetime

ties in major depression are highly variable, the most characteristic chronobiological abnormality in depression is presumably phase advance [85].

Seasonal Affective Disorder

SAD can be seen as a model disorder for chronobiological disturbances and BLT. A first milestone was set by Rosenthal et al. [1], who characterized a subset of patients suffering from annually recurrent depressive episodes followed by spontaneous remission. Before this report, Lewy et al. [86] had published a case report of a bipolar patient with seasonal mood cycles. Today, the *Diagnostic and Statistical Manual IV, text revision* (DSM-IV-TR), lists SAD as a specifier of recurrent unipolar or bipolar affective disorders with a seasonal pattern of major depressive episodes [87]. The four central clinical features characterizing SAD are summarized in table 1. Winter depression, also termed fall-winter depression, constitutes the most common form of SAD [88]. In 1989, Kasper et al. [89] reported the occurrence of subsyndromal mood fluctuations in the general population. Since then, seasonality has been appraised as a dimensional process rather than a distinct syndrome by most authors. Patients suffering from SAD exhibit typical depressive symptoms like low mood, lack of drive, decrease in interest and lack of concentration [90]. In addition, patients tend to exhibit a specific symptom cluster related to atypical depression. These symptoms are hypersomnia (70–90% of SAD patients), increased appetite (70–80%), carbohydrate craving (80–90%) and weight gain (70–80%) [91]. Furthermore, about three quarters of patients show increased irritability in fall/winter, and anger attacks seem to be especially preva-

lent in SAD [91, 92]. Interestingly, almost half of the female patients with SAD suffer from premenstrual dysphoric disorder. Hence, a pathogenic connection between these two cyclic disorders has been proposed [93, 94]. In epidemiological studies, the prevalence of SAD patients amounts to 2–5%. The prevalence of the subsyndromal form of the disorder ranges between 5 and 10%. SAD accounted for approximately 11% of all major depressive episodes in a Canadian community sample [95]. According to Winkler et al. [96], the female-to-male ratio in SAD (3–5:1) is even higher than in non-seasonal depression, where women are affected twice as often as men.

Pathophysiology of SAD

Chronobiological Hypothesis

In the literature, two main etiological pathways are discussed, which should be further illustrated: a chronobiological hypothesis and an altered monoaminergic transmission hypothesis [97].

The first hypothesis focuses on light and the circadian system, as previously presented in this review. Since it is evident that exposure to light is a matter of latitude, a number of studies tried to verify this assumption. However, while one large study [98] and one meta-analysis [99] came to the conclusion that there is a positive correlation between Northern latitude and prevalence of SAD, others failed to show such an association [100]. However, two putative explanations for negative results are migration, which allows vulnerable individuals to move to more temperate climate zones, and gene-environment interactions. Similarly, the data concerning the melatonergic system are not consistent. A number of studies provide evidence for abnormal melatonin levels in patients with SAD: high melatonin levels during daytime [101], prolonged nocturnal melatonin secretion in winter [102] and a phase delay of melatonin release [103]. However, there are also studies which could not discriminate between patients and healthy controls on the basis of melatonin secretion patterns [104, 105]. The phase shift hypothesis is nonetheless remarkable as many SAD patients are phase delayed in their chronobiological cycle. Morning BLT, as a strong external zeitgeber, is able to restore this disruption [106–108].

Role of Monoamines

The second hypothesis, the pathophysiological role of monoamines in SAD needs further consideration. As mentioned before, there is substantial evidence for a seasonal fluctuation in brain serotonin function [37, 51]. Recently, an enhanced 5-HTT turnover rate (defined as the number of uptake events of one 5-HTT molecule per sec-

ond) in platelets of medication-free depressed patients with SAD could be demonstrated by Willeit et al. [109]. One of the rare brain-imaging studies in SAD, also published by Willeit et al. [110], using [^{123}I]- β -CIT single-photon emission tomography showed decreased 5-HTT availability in the thalamus/hypothalamus of patients during winter depressive episodes. This finding could be replicated in patients suffering from non-seasonal atypical depression [111]. Further evidence for the role of serotonin in SAD, and the mode of action of BLT, comes from studies by Neumeister et al. [112], showing a depressive relapse in BLT-treated, remitted patients during depletion of the serotonin precursor tryptophan. Similar findings were also detected in patients with SAD during stable summer remission [113], although these results could not be replicated in another study [114]. However, two catecholamine depletion studies in BLT-treated remitted patients [115] and patients during summer remission [116] suggest a possible role of norepinephrine and dopamine in the pathophysiology of SAD. A number of genetic studies aimed at investigating vulnerabilities to SAD and seasonality. Most studies focused on the 5-HTT-linked polymorphic region (5-HTTLPR, SLC6A4) described two [117] or three [118] common functional polymorphisms. Results from a study by Caspi et al. [119] indicate that the 5-HTTLPR short (*s*) allele, in contrast to the long (*l*) allele, is associated with depressive episodes and suicidal behaviour after traumatic life events. However, a recent meta-analysis questioned the finding of a gene-environment interaction of 5-HTTLPR genotype and traumatic life events [120]. Findings in SAD are contradictory as well: while two earlier studies found associations between 5-HTTLPR and SAD/seasonality [121, 122], a large meta-analysis yielded negative results [123]. Another SAD study found evidence for an association of 5-HTTLPR with atypical and melancholic depression subtypes, suggesting that the low-expressing 5-HTTLPR *s*-allele is associated with atypical symptoms rather than with a diagnosis of SAD [124]. The association of the 5-HTTLPR *s*-allele and the atypical depression subtype could be replicated in patients with non-seasonal depression [125].

Bright-Light Therapy

Today, the administration of BLT is the first-line therapy for SAD [126]. BLT represents a potent, non-pharmacological treatment modality whose efficacy and tolerability have been a matter of extensive research. Mode of action and administration of BLT will be addressed first.

Mode of Action

The exact mechanism of action of BLT remains unclear. The effect of BLT seems to be mediated through the eyes: extraocular administration has failed to show any significant antidepressant qualities [127]. Studies in the 1990s became the basis of a widely cited benchmark for BLT with light intensities of up to 10,000 lx and a duration of 30 min/day [128–130]. However, melanopsin, a short-wavelength light-sensitive G-protein-coupled receptor located in human retinal ganglion cells, is known to transduce short-wavelength light signals into neural signals [131]. Since melanopsin is primarily responsible for resetting the timing of the SCN, suppressing pineal melatonin secretion, and improving alertness and electroencephalogram-derived correlates of arousal [16, 132], it has been hypothesized that short-wavelength light with a low light intensity might be a better stimulator for melanopsin-containing retinal ganglion cells and the behaviours mediated via this photoreceptor system [133, 134]. In a study by Anderson et al. [134], blue-appearing light at 98 lx was compared to blue-enriched white-appearing light at 700 lx in patients with SAD. Both light sources emitted fewer lux than traditional BLT sources, but emitted equivalent numbers of photons within the short-wavelength range. Depression rates decreased significantly in both groups after 3 weeks. However, this study was underpowered and did not include a non-treatment group. Another study tested short-wavelength blue light against short-wavelength red light (an intended placebo) with promising results for the blue-light condition [135]. However, since these studies did not compare blue light to standardized BLT with high-intensity white light at 10,000 lx, low-intensity light is not established as uniquely effective in the treatment of SAD.

Whether the antidepressant effect of light is also related to its alerting property is unclear [136]. However, the acute alerting and performance-enhancing effects of light are increasingly taken into account for the design of indoor light standards in office environments [133, 137].

Administration

Commonly, BLT is applied using a light box containing fluorescent lamps, a reflector and a diffusing screen. There are different models with varying light intensities available on the market [88]. Further application forms are light visors and dawn simulators, both of which are not widely used. Light visors (or helmets) are portable head-mounted light sources [138, 139], a dawn simulator offers morning-light stimulation simulating natural dawn conditions [140]. For adequate treatment conditions, light

Table 2. BLT guidelines adapted from ref. 88, 90

Parameter	Information
Intensity of bright-light device	Fluorescent light box using light intensities from 5,000 to 10,000 lx (measured at the level of the eyes of the patient)
Wavelength of bright-light device	Full-spectrum visible light
Distance from light source	Patients should remain positioned at approximately 60–80 cm from the light source Staring into the light source is not necessary
Time of day for application	Morning light therapy is more effective than evening light However, in some patients evening light therapy may be more successful
Dose	30 min at 10,000 lx or 2 h at 2,500 lx as a starting dose
Onset of therapeutic effect	3–7 days
Maintenance of therapeutic effect	Effect will vanish shortly after discontinuation of therapy
In case of non-response	Application of double dose, administered in the morning and evening Consider psychopharmacological treatment

intensities of 5,000–10,000 lx, measured at the level of the eyes, and a therapeutic distance of 60–80 cm from the light box can be seen as standard requirements [141].

At this point, it is important to mention that patients need not stare directly into the light source as long as the light is able to meet the eye at an angle of 30–60°. Treatment is started with a dose of 30 min using a light intensity of 10,000 lx, the duration of treatment is extended in case of insufficient response [142]. When using less powerful light boxes, the exposition time should be extended [90]. Morning administration of BLT offers greater chances for remission as pointed out in the following section.

However, compliance is the primary factor of success of the treatment, and extensive information and clear instructions concerning utilization and duration of BLT should be provided. According to a small pilot study by Michalak et al. [143], patients' adherence to a set light treatment regimen is as important as adherence to antidepressant medication. The effects of treatment do not persist after discontinuation of BLT, thus a relapse can be anticipated few days after stopping the treatment. Some SAD

patients may profit from a prophylactic initiation of BLT [144, 145]. In this context, psycho-educational training for the detection of early symptoms (difficulties in awakening, daytime fatigue and carbohydrate craving) may help to prevent the onset of a full-blown episode of SAD. Useful tools for maintaining the patients' cooperation are a stringent therapeutic setting with frequent clinical assessments and constant patients' reports about exposure time and psychopathological status. For clinical trials as well as daily practice, the Structured Interview for the Hamilton Depression Rating Scale – Seasonal Affective Disorder Version (SIGH-SAD) has been implemented to cover the specific symptom cluster of SAD [146]. It consists of the 21 items of the Hamilton Depression Rating Scale [147], 8 additional items characterizing atypical depressive symptoms and 2 unscored items assessing difficulties in awakening and temperature discomfort [126]. A summary of application principles is presented in table 2.

Light Therapy in SAD and Non-Seasonal Mood Disorders

When assessing the efficacy of BLT, researchers encounter obvious obstacles in developing study designs. While it is relatively simple to produce placebos for randomized and controlled psychopharmacological trials, developing a placebo for BLT led to controversies in the scientific community. During the 1980s, the usual placebo condition was a light box delivering intensities of ≤ 300 lx, often of a different color. These studies were criticized by some authors with regard to the adequacy of the control condition. Although a pooled analysis of these data showed that BLT is superior to dim light controls, expectations of the subjects sometimes predicted the clinical outcome.

Other studies used negative-ion generators as placebo condition, a device that similarly to a light box requires the patient to sit next to it. The superiority of both morning and evening BLT over low-density negative air ionization, or sham negative air ionization, respectively, as placebo conditions could be demonstrated in two large studies using a balanced, randomized cross-over design [148, 149]. These findings from two independent centres are remarkable in so far as the advantage of antidepressant drugs over placebo in controlled trials is so small that only multicenter studies can answer questions of relevance [150]. Surprisingly, high doses, but not low doses, of negative air ions were found to have an antidepressant effect as well [151]. In both studies, expectation ratings within groups were not correlated with clinical response.

The most recent meta-analysis on the efficacy of BLT was published by Golden et al. [152] in 2005, following a

request of the American Psychiatric Association in order to systematically gather efficacy data following the principles of evidence-based medicine. The authors initiated a systematic review of all existing data of trials using BLT in seasonal and non-seasonal depression, using dawn simulation for SAD and using BLT as adjunctive therapy to psychopharmacological treatment in non-seasonal depression. Twenty-three of 173 studies qualified for inclusion (age 18–65, DSM diagnosis, Rosenthal criteria, standardized BLT conditions, plausible and defined placebo conditions) into the meta-analysis. Results show impressive effect sizes, i.e. 0.84 (CI 95%: 0.60–1.08) for BLT in SAD, 0.73 (CI 95%: 0.37–1.08) for dawn simulation in SAD and 0.53 (CI 95%: 0.18–0.89) for BLT in non-seasonal depression. These effect sizes are equivalent or superior to most psychopharmacological trials. In the meta-analysis, there was no evidence in favour of adjunctive BLT to psychopharmacological treatment in non-seasonal depression. However, there are also positive data from a subsequent placebo-controlled randomized trial of BLT augmentation in a sample of 102 patients with non-seasonal depression treated with sertraline [153].

In a review of 332 patients with SAD from 14 different study centres, Terman et al. [154] found remission rates of up to 67% in patients suffering from milder depression, and up to 40% in patients with severe depression. Moreover, the latter review could substantiate a faster onset of action of BLT compared to treatment with antidepressants.

Three studies published in 1998 were able to conclusively demonstrate that early morning administration of BLT is associated with higher remission rates than evening administration. Nevertheless, a small subset of patients preferentially benefited from evening light [149, 151, 155]. One explanation for this is that, according to the phase shift hypothesis, there are two kinds of internal circadian misalignment in SAD: while the typical depressed patient is phase-delayed, a small subgroup of phase-advanced patients may preferentially benefit from a corrective phase delay provided by evening BLT [156, 157].

Patients with bipolar depression have been shown to respond robustly to BLT [158]. Response rates did not differ significantly between bipolar and unipolar patients with SAD [159]. Another study found non-seasonally depressed bipolar patients to improve more with BLT than unipolar depressed patients [160]. These data suggest that BLT is a valuable treatment modality in bipolar-depressed patients. Like other biological treatments for bipolar depression, BLT can precipitate manic/hypomanic and mixed states in susceptible patients [161–163], although the potential advantage of BLT in patients with bipolar

Table 3. Indications for psychopharmacological treatment in SAD adapted from ref. 88

Patient's choice
Missing compliance using BLT
Non-response to BLT
Adverse reactions to BLT
Ophthalmological contraindications (e.g. macular degeneration)
Bipolar disorder (switch to hypomania/mania)
Severe depression (e.g. psychotic depression)
Suicide risk (consider hospitalization)

depression is that the light dose can be titrated against emergent symptoms of hypomania. However, as of yet, there are no specific BLT guidelines for patients with bipolar disorder other than the need for additional anti-manic-agent coverage. In a small dose-ranging safety and efficacy study in depressed women with bipolar disorder, 3 of 4 subjects treated with morning BLT developed mixed states [164]. This was not the case in subjects receiving midday light. The authors conclude that women with bipolar depression may be highly sensitive to morning BLT, and that initiating treatment with a brief course of midday light is advisable. Another recent study in patients with non-seasonal bipolar depression could demonstrate that a chronotherapeutic intervention with one night of sleep deprivation, BLT, and sleep phase advance as adjunctive treatment to lithium and antidepressants lead to accelerated and sustained antidepressant responses when compared to a medication-only group [165].

BLT has also been found to be effective in chronic depression [166]. Preliminary studies of BLT in antepartum depression, a condition where non-pharmacological treatment options are urgently needed, show promising results [167, 168]. In non-seasonal depression, BLT is sometimes combined with other chronotherapeutic interventions (wake therapy and phase changes of sleep) because they are hypothesized to act through complementary mechanisms [169–171]. Neumeister et al. [172] were the first to show that morning BLT can help maintaining the antidepressant effects of therapeutic sleep deprivation, a finding which could be replicated in a number of subsequent studies [158, 173]. There are few data on BLT in premenstrual dysphoric disorder. Results of these studies remain controversial [94, 174, 175].

In case of non-response, side effects or patients' inability to integrate BLT into their daily routine psychopharmacological treatment, preferably using an antidepressant with serotonergic or noradrenergic properties, is in-

licated [88, 176]. Reviewing clinical courses of 553 SAD patients, Pjrek et al. [177] found that 49% of patients were receiving psychotropic medication, with 35.4% being treated with an antidepressant drug. Indications for psychopharmacological treatment in the context of BLT are summarized in table 3.

Safety and Tolerability of BLT

Generally, BLT is well tolerated and well accepted by patients [99]. Side effects are rare; the most common ones are headache, eyestrain, nausea and agitation. Side effects tend to remit spontaneously or after dose reduction [178, 179]. Evening administration of BLT can increase the incidence of sleep disturbances; bipolar patients may switch to hypomania during therapy [180]. Suicidality may sporadically occur early in the treatment course [181, 182], menstrual irregularities have been reported [183]. Although there is some evidence for retinal degeneration after prolonged exposure to intensive visible light in rodents [184], this was not confirmed in humans [185].

However, patients with a (family) history of retinal damage or patients needing photosensitizing medication are advised to consult their ophthalmologist before initiating treatment. In any case, UV light must be avoided.

Conclusion

BLT represents a non-pharmacological, efficacious, well-tolerated, well-accepted and probably underestimated biological therapy which should be part of the therapeutic repertoire of all psychiatrists and general practitioners. There is no solid medical reason for non-reimbursement of BLT for all patients profiting from it. Ideally, light boxes should primarily be lent to patients by physicians and health care professionals in order to assess diagnosis and treatment response. Consequently, patients with beneficial treatment responses ought to have fair access to BLT similarly to psychopharmacological treatment.

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