REVIEW ARTICLE

# Phototherapy: Role in Sleep Disorders


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## Abstract

In the natural world, the light/dark cycle entrains our rhythm. Light is a very effective "zeitgeber." In the presence of environmental time cues, sleep–wake physiology and gene expression continue to exhibit a near-24-hour circadian rhythm regulated by the suprachiasmatic nucleus in the hypothalamus. Phototherapy is an accepted modality for the non-pharmacological management of circadian disorders, such as delayed sleep phase syndrome, insomnia, and mood disorders. This review discusses the clinical repercussions of circadian rhythm disorders, the physiological principle of phototherapy, and its application across the spectrum of sleep disorders.



**Keywords:** Circadian rhythm disorders, phototherapy, circadian rhythm and diabetes, seasonal affective disorders.


## Introduction

Living organisms exhibit a biological periodicity. This rhythm when occurs on a 24-hour cycle is known as "circadian rhythm." A rhythmic biological cycle that displays an endogenous, entrainable oscillation of less than 24 hours in known as ultradian rhythm and that lasts for more than 24 hours is known as infradian rhythm.

Circadian rhythms generate rhythmic cycles of sleep patterns, food intake, sexual behavior, core body temperature, and secretion and release of hormones such as adrenocorticotropic hormone (ACTH), prolactin, gonadotropin, and melatonin. Circadian rhythms are generated by the suprachiasmatic nucleus (SCN) of the anterobasal hypothalamus[1].

Pineal gland regulates the rhythmic production and release of melatonin. The duration, phase, and amplitude of melatonin and cortisol secretion are influenced by changes in light/dark cycles. The plasma levels of melatonin are low during daytime and are high at night. This rhythm is maintained by the SCN and is entrained by the light/dark cycle. Low light intensities (100–500 lux) also have been shown to suppress the levels of melatonin[2]. Phototherapy or light therapy uses light boxes that are typically LED square bright lights, ranging from 8–12 ′ 12–24 in. that emit up to 10,000 lux light. "Cool" color temperature light acts as natural sunlight without the harmful effect of ultraviolet rays. This mode of entraining the sleep–wake cycle is an accepted modality and mainstay treatment in the non-pharmacotherapeutic management of circadian rhythm disorders.


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## Pathway of Phototherapy

### *Melatonin*

Light

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Activates Retinal Ganglion cells

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Stimulates hypothalamic SCN via Retinohypothalamic tract

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Regulates Melatonin and Cortisol function

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Maintains day and night cycle

**Cortisol**

Corticotrophin- releasing hormone secreted by Hypothalamus

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I.e. PVN (Paraventricular Nucleus)

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Acts on CRH receptor

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Releases ACTH and acts on Adrenal Cortex

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Releases Cortisol

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CRH activates Locus Ceruleus (LC) and utilizes Norephinephrine (NE)

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Elevated NE and CRH implicated in

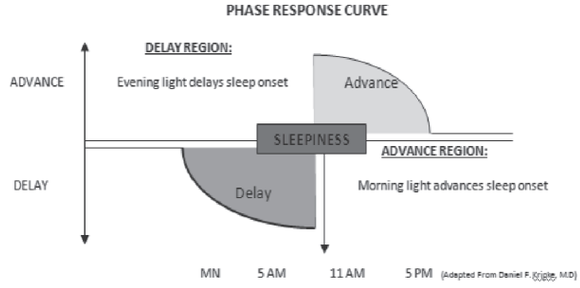
Primary Insomnias

## Principles of Phototherapy

The circadian rhythm aims to maintain a bridge between sleep patterns and the internal clock that is set at an optimally synchronized time. This results in a normal sleep–wake pattern.

### *Phase–response curve*

The phase–response curve (PRC) is modulated by two efficacious modalities (i.e., light and melatonin), both of which are exploited to entrain the circadian cycle. Bright light is very helpful in synchronizing the human rhythms, and melatonin serves as a "dark pulse" helping to induce nighttime behaviors. Bright morning light advances circadian rhythms whereas bright evening light delays them. Melatonin in the evening advances circadian rhythms whereas that in the morning delays them[3].




### *Circadian disturbances and insulin resistance*

Pathogenesis of type 2 diabetes mellitus is multifactorial and circadian disturbances are a contributing factor. Sleep disturbances including sleep insufficiency, sleep loss, and sleep fragmentation are connected to abnormal glucose metabolism and thus, increase the risk of type 2 diabetes mellitus. Studies in rodent models suggest that disruption of circadian rhythms leads to impaired glucose homeostasis and â-cell failure, culminating in increased susceptibility to type 2 diabetes mellitus. Disturbed circadian rhythm is a causative factor in the recent epidemic "obesity." In controlled clinical studies, acute 1–3 week circadian misalignment (alone) or in combination with sleep restriction resulted in dysregulation of glucose homeostasis and consequent glucose intolerance attributed in part to loss of â-cell function as well as decline in insulin sensitivity[4,5].

### Circadian rhythm and inflammatory diseases

Inflammatory bowel disease (IBD), including ulcerative colitis and Crohn's disease, is a chronic and recurrent inflammatory disorder of the intestinal tract. Sleep disturbances are implicated in the pathogenesis of the patients with IBD. In addition, melatonin contributes to regulation of inflammation as well as the immune system and antioxidant systems in the intestinal disorders[6,7].

### Circadian rhythm and visual impairment

Bright light has been shown to suppress melatonin secretion even in visually impaired subjects, which substantiates the fact that nonvisual photoreceptors in the eye help mediate the circadian rhythm[8].

### Circadian rhythm and immunity

Sleep restriction and sleep deficit increase susceptibility to disease. Sleep is not only regulated by the circadian drive but also partly by immune system factors known as cytokines. Blood counts of T cells and levels of proinflammatory cytokines (such as IL-12) are high during the night, whereas levels of leukocytes and anti-inflammatory cytokines (such as IL-10) go up during daytime[9]. The immune system is connected to the sleep regulatory system and actions of the immune system to fight disease.

For those with chronic inflammation, however, the immune system keeps them tired for long periods, which may explain symptoms of fibromyalgia and chronic fatigue disorder. It is becoming increasingly evident that disruption of daily rhythms, such as from sleep deprivation, affects the immune response.

## Role of Phototherapy

### Sleep quality in healthy individuals

Studies report that it is possible to reactivate the SCN and improve "sleep–wake rhythm" by applying extra light. Light therapy provides a safe treatment option in improving mood functioning and normal well-being[10]. In addition, bright light exposure improves sleep quality in 7–18% subjects ($n$ = 1154, meta-analysis of 13 interventional studies)[11].

### Delayed sleep phase syndrome

Delayed sleep phase syndrome (DSPS) is a circadian disorder that involves a shift in the biological cycle. The major sleep episode is delayed in relation to the conventional clock time, therefore resulting in symptoms of sleep-onset insomnia and difficulty in awakening at the desired time. The core body temperature minimum and peak of the melatonin rhythm both are shifted to later in the morning than normal time[12]. Bright light has phase-shifting effects on human circadian rhythms. Patients with DSPS were administered 2 h of bright light exposure in the morning together with light restriction in the evening, thus successfully phase advancing circadian rhythms of core body temperature[13]. Evening melatonin administration in addition to morning light treatment for circadian phase advance was additive[14].

### Advanced sleep phase syndrome

Advanced sleep phase syndrome is a disorder in which the biological clock is timed too early, that is, all sleep episodes are advanced in relation to the conventional clock time, which therefore results in symptoms of evening sleepiness, an early sleep onset, and an awakening that is earlier than normally desired. The core body temperature minimum and peak melatonin rhythm occur earlier in the morning than usual. On the basis of human PRC, a phase delay will take place, if the subject is exposed to light soon after the dim light melatonin secretion onset or core body temperature maximum, usually in the evening[12].

### Non-24-hour sleep–wake syndrome

Non-24-hour sleep–wake syndrome is a chronic circadian rhythm syndrome in which the internal or biological clock does not reset adequately and also fails to stay balanced. The circadian period differs every 24 h, thus patients with non-24-hour sleep–wake syndrome fall asleep at varying times each day. Core body temperature cycles may be greater in length than normal. Non-24-hour rhythm is commonly observed in blind individuals in which the normal sleep–wake cycle may be longer than 24 h; if no light reaches the SCN, there may not be natural resetting of the circadian clock to 24 h.

## Jet lag

Jet lag syndrome causes distress to travelers impairing sleep, mood, and cognitive performance. Timed exposure to bright light and melatonin administration can help reduce symptoms. Specific recommendations using bright light and melatonin for eastward and westward travel before and after departure are recommended for time zone changes of up to 6–10 or more hours, can help adjust underlying circadian rhythms, and can mitigate symptoms of jet lag. Light therapy also helps reduce the mood, cognitive, and behavioral symptoms that result from desynchronized rhythms[3].

## Shift work syndrome and its effect on cognitive functioning

Light intensity has an impact not only on the cognitive performance but also on the alertness and on the subjective feeling of sleepiness. Light intensity is also a factor, if increased intensity is proportional to the alertness levels and memory scales. Artificial light is used to phase shift circadian rhythm and help improve performance, sleep, and well-being during shiftwork simulations. This study was designed for NASA personnel during the prelaunch week. The treated subjects, self-exposed to 10,000 lux, showed a positive result reporting better sleep, performance, and physical and emotional well-being than control subjects and rated the treatment as highly effective for promoting adjustment to their work schedules for the study[15].

In a crossover design study conducted on 12 night-shift nurses with three treatment procedures [room light, bright light (BL), and bright light with sunglasses (BL/S)], the same nocturnal light exposure as in BL was done with light attenuation in the morning. Nocturnal alertness was measured using a visual analog scale. Daytime sleep was recorded with actigraphy. The results showed that nocturnal alertness was the highest in the BL/S. This improvement was maximized by attenuating morning light. Hence, it is clear that nocturnal alertness, daily performance, and daytime sleepiness could be improved by light exposure of tolerable intensity and duration in a real workplace[16].

## Sundowning phenomenon

Sundowning is a clinical psychological phenomenon in which the patient shows increased neuropsychiatric symptoms such as confusion, disorientation, anxiety, agitation, aggression, pacing, wandering, resistance to redirect screaming, and yelling that are observed late afternoon or when the sun is setting (i.e., in the evening or at night) and most commonly occurs among cognitively impaired, demented, or institutionalized elderly patients[17]. In a double-blind, placebo-controlled, crossover trial, the bright light therapy (10,000 lux bright light) in addition to melatonin administration had positive effect on motor restlessness in subjects with dementia[17]. Ten patients with Alzheimer's disease (AD) showing sundowning behavior and sleep disturbances, who received 2 h/day of exposure to bright light between 7 pm and 9 pm, were studied for a week. The results showed that the proportion of total daily activity occurring during the nighttime decreased during the light-treatment week. The relative amplitude of the circadian locomotor activity rhythm, a measure of its stability, increased during the light-treatment week. This kind of effect mediated through a chronobiological mechanism[18].

## Mood disturbances

*Manic-depressive illness (MDP)*: It is recurrent illness in which episodes of mania and depression occur and remit spontaneously. Several clinical studies say that disturbance in the circadian rhythms play a crucial role in its pathophysiology. Melatonin secretion shows abnormal levels in some bipolar patients (MDP). Patients with MDP exhibit circadian sleep–wake rhythm in which they spent one complete sleepless night in between two nights of normal sleep. In a study, 143 patients with a major depressive episode (*DSM-IV* criteria) were treated with three consecutive total sleep deprivation cycle (each composed of 36 h awake followed by recovery sleep), light therapy, and lithium, which rapidly decreased the depressive suicidality and prompt antidepressant response in patients with drug-resistant major depression in the course of bipolar disorder[19]. An open study assessed 13 female patients with borderline personality disorder (BPD) for the effectiveness of bright light (10,000 lux) in addition to selective serotonin reuptake inhibitors in drug-resistant depressed patients with comorbid BPD, and it was found that the application of bright light leads to a significant improvement as compared to the use of antidepressants alone[20].

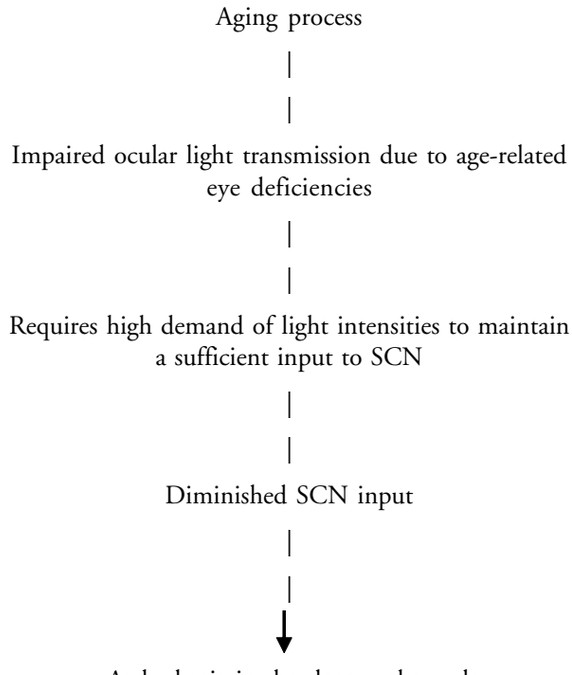
*Seasonal affected disorder (SAD)*: Phototherapy acts through retinal melatonin or rhodopsin help regulate the release of dopamine in the eye where it acts as the main

neurotransmitter. In patients with SAD, the retina–SCN–pineal gland link is disturbed. By suppressing retinal melatonin, phototherapy has been suggested to correct the underlying biochemical abnormality seen in SAD, thereby inducing clinical remission. Recently, it has been noted that exposure of patients with SAD to natural sunlight in the morning hours resulted in complete remission of depressive symptoms. In patients with SAD, instability of circadian rhythms may be due to the high-amplitude PRC, linked to impaired serotonergic function in the afferent pathways to the SCN. Following administration of phototherapy ($N$ = 24; 12 SAD and 12 control), a phase advance of melatonin rhythms was seen in patients with SAD. Hence, there is an association between phase position and phase shift in patients with SAD[21]. This seems to be a significant advancement in the etiology of SAD that links light with mood disorders. SAD is common when vitamin D stores are typically low. Wavelengths between 280 and 320 nm, which are included in broad-spectrum light therapy, allow the skin to produce vitamin D. In a prospective, randomized controlled trial of 15 subjects with SAD, 8 subjects received 100,000 IU vitamin D and 7 subjects received phototherapy. At the onset of treatment and after 1 month of therapy, depression scales of the subjects were assessed and their vitamin D levels were also checked. The phototherapy group showed no significant change in depression scale measures but showed an improvement in the vitamin D levels. The vitamin D group showed an improvement in the vitamin D level as well as the depression scale. Hence, vitamin D may be an important treatment for SAD[22].

*Attention deficit hyperactivity disorder (ADHD):* In patients with ADHD, morning bright light therapy helps reduce both subjective and objective measures of core ADHD pathology, improve mood symptoms, and phase advance in circadian preference. Multiple regressions showed that the shift toward an earlier circadian preference with light therapy was the strongest predictor of improvement on both subjective and objective ADHD measures[23].

*Mood disturbances in the elderly*: The risk of developing depression increases with old age: 20–25% patients have major depressive episode in AD and 20–30% have minor depressive symptoms[24]. In a randomized, double-blind, placebo-controlled trial, patients with early AD, mild cognitive impairment, and subjective memory complaints were exposed to~10,000 lux for 2 years. Neuropsychological, behavioral, physiological, and endocrine measures were assessed at baseline and follow-up every 5–6 months. The evaluation showed long-term daily bright light prevented worsening of sleep–wake rhythms and depressive symptoms in elderly people with memory complaints[24].

## Factors Contributing to Impaired Sleep Wake Cycle in Aging




### *Side Effects of Phototherapy*

No major side effects were observed with light intensity of 10,000 lux for 1250 h spread over 5 years[12]. In a study, $N$ = 83, analysis of side effects of light therapy showed symptoms such as jitteriness (8.8%), headache (8.4%), and nausea (15.9%)[25]. In another study in which bright white light (10,000 lux) versus dim red light (<500 lux) was used in healthy adults, bright light exposure did not show any kind of reported side effects than was the placebo control condition. The only side effect observed in both the groups that was statistically significant was eye strain and blurred vision[26].

## Summary

The circadian rhythm (i.e., the sleep–wake cycle) is important in maintaining immunity, insulin sensitivity, and hormonal balance of the body. Phototherapy is an accepted non-pharmacological therapy for circadian

disorders such as DSPS, advanced sleep phase syndrome, and jet lag, which also helps in improving mood disturbances in SAD, sundowning, and cognitive issues in ADHD and AD. Phototherapy is a relatively nontoxic, non-pharmacological therapy and should be used as an adjunctive therapy at its greatest capacity in the management of chronic sleep disorders.

## References


1. **Srinivasan V**. Melatonin, biological rhythm disorders and phototherapy. Indian J Physiol Pharmacol 1997;41(4):309–328.
2. **Shechter A**, Boivin DB. Sleep, hormones, and circadian rhythms throughout the menstrual cycle in healthy women and women with premenstrual dysphoric disorder. Int J Endocrinol 2010;2010:259345.
3. **Parry BL**. Jet lag: Minimizing it's effects with critically timed bright light and melatonin administration. J Mol Microbiol Biotechnol 2002;4(5):463–466.
4. **Rakshit K**, Thomas AP, Matveyenko AV. Does Disruption of circadian rhythms contribute to beta-cell failure in type 2 diabetes? Curr Diab Rep 2014;14(4):474.
5. **Reutrakul S**, Van Cauter E. Interactions between sleep, circadian function, and glucose metabolism: Implications for risk and severity of diabetes. Ann N Y Acad Sci 2014;1311:151–173.
6. **Takagi T**, Inada Y, Naito Y. [Circadian rhythm and inflammatory bowel disease.] Nihon Rinsho 2013;71(12):2165–2170.
7. **Voigt RM**, Forsyth CB, Green SJ, et al. Circadian disorganization alters intestinal microbiota. PLoS One 2014;9(5):e97500.
8. **Czeisler CA**, Shanahan TL, Klerman EB, et al. Suppression of melatonin secretion in some blind patients by exposure to bright light. N Engl J Med 1995;332:6–11.
9. **Lange T**, Dimitrov S, Born J. Effects of sleep and circadian rhythm on the human immune system. Ann N Y Acad Sci 2010;1193:48–59.
10. **Terman M**, Terman JS. Light therapy for seasonal and nonseasonal depression: Efficacy, protocol, safety, and side effects. CNS Spectr 2005;10(8):647–663.
11. **Tamrat R**, Huynh-Le MP, Goyal M. Non-pharmacologic interventions to improve the sleep of hospitalized patients: A systematic review. J Gen Intern Med 2014;29(5):788–795.
12. **Chesson AL**, Littner M, Davila D, et al. Practice parameters for the use of light therapy in the treatment of sleep disorders. Sleep 1999;22:641–660.
13. **Rosenthal NE**, Joseph-Vanderpool JR, Levendosky AA, et al. Phase-shifting effects of bright morning light as treatment for delayed sleep phase syndrome. Sleep 1990;13(4):354–361.
14. **Paul MA**, Gray JW, Lieberman HR, et al. Phase advance with separate and combined melatonin and light treatment. Psychopharmacology (Berl) 2011;214(2):515–523.
15. **Stewart KT**, Hayes BC, Eastman CI. Light treatment for NASA shiftworkers. Chronobiol Int 1995;12(2):141–151.
16. **Yoon IY**, Jeong DU, Kwon KB, Kang SB, Song BG. Bright light exposure at night and light attenuation in the morning improve adaptation of night shift workers. Sleep 2002;25(3):351–356.
17. **Khachiyants N**, Trinkle D, Son SJ, Kim KY. Sundown syndrome in persons with dementia: An update. Psychiatry Investig 2011;8:275–287.
18. **Satlin A**, Volicer L, Ross V, Herz L, Campbell S. Bright light treatment of behavioral and sleep disturbances in patients with Alzheimer's disease. Am J Psychiatry 1992;149(8):1028–1032.
19. **Benedetti F**, Riccaboni R, Locatelli C, Poletti S, Dallaspezia S, Colombo C. Rapid treatment response of suicidal symptoms to lithium, sleep deprivation, and light therapy (chronotherapeutics) in drug-resistant bipolar depression. J Clin Psychiatry 2014;75(2):133–140.
20. **Prasko J**, Brunovsky M, Latalova K, et al. Augmentation of antidepressants with bright light therapy in patients with comorbid depression and borderline personality disorder. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2010;154(4):355–361.
21. **Thompson C**, Childs PA, Martin NJ, Rodin I, Smythe PJ. Effects of morning phototherapy on circadian markers in seasonal affective disorder. Br J Psychiatry 1997;170:431–435.
22. **Gloth FM**, Alam W, Hollis B. Vitamin D vs broad spectrum phototherapy in the treatment of seasonal affective disorder. J Nutr Health Aging 1999;3(1):5–7.
23. **Rybak YE**, McNeely HE, Mackenzie BE, Jain UR, Levitan RD. An open trial of light therapy in adult attention-deficit/hyperactivity disorder. J Clin Psychiatry 2006;67(10):1527–1535.
24. **Most EI**, Scheltens P, Van Someren EJ. Prevention of depression and sleep disturbances in elderly with memory-problems by activation of the biological clock with light-a randomized clinical trial. Trials 2010;11:19.
25. **Terman M**, Terman JS. Bright light therapy: Side effects and benefits across the symptom spectrum. J Clin Psychiatry 1999;60(11):799–808.
26. **Botanov Y**, Ilardi SS. The acute side effects of bright light therapy: A placebo-controlled investigation. PLoS One 2013;8(9):e75893.