Light therapy is increasingly applied in a variety of sleep medicine and psychiatric conditions including circadian rhythm sleep disorders, seasonal affective disorder, and dementia. This article reviews the neural underpinnings of circadian neurobiology crucial for understanding the influence of light therapy on brain function, common mood and sleep disorders in which light therapy may be effectively used, and applications of light therapy in clinical practice.

**Light and Circadian Neurobiology**

A circadian rhythm is a self-sustaining biological activity oscillating with a periodicity near 24 hours. Circadian rhythms have been detected in living organisms under natural conditions, as well as during isolation in artificial circumstances, including space travel. Circadian rhythms tend to move into phase synchrony with environmental rhythms, mainly the day/night cycle. While the persistence of circadian rhythms under experimental decoupling from the environment points to rhythmicity generated by an internal biologic clock, the widespread phase synchronization with the rotation of the planet (circadian from the Latin, meaning about a day) underscores the capability of the biologic clock to reset. We present a summary of the relevant physiologic processes pertinent to understanding the relationship between chronobiology and the light-dark (LD) cycle, followed by a discussion of light use as a therapeutic tool in medicine.

**The Biologic Clock**

Scientific evidence mounting over the last decades has unveiled the location of the mammalian “master biologic clock” in the paired suprachiasmatic nuclei (SCN) of anterior hypothalamus. Lesions of the SCN in animal experiments have been linked to disruptions of circadian rhythms of hormones and complex behavior such as drinking and locomotion. Specific genetic mutations targeting SCN abolish the circadian sleep rhythm. Consistent with their clock function, the SCN neurons exhibit an internal rhythmic activity, which is generated by cyclic expression, transcription, and feedback regulation of recently identified genes (CLOCK, PER, and others), arrested by the inhibition of protein synthesis, and preserved in isolation from the surrounding brain tissue in cell cultures. Posttranslational modifications are the proposed mechanism for the periodicity of the biologic clock.

The resulting endogenous circadian period varies in different species and between individual subjects. The average endogenous circadian period of humans is slightly longer than the clock day, measuring approximately 24.2 hours.

**Setting the Biologic Clock**

The endogenous circadian period of the biologic clock may lack phase synchrony with the surrounding environment. One would expect that the discrepancy between the 24.2-h intrinsic human circadian period and the 24-h terrestrial day would cause a continuous phase delay relative to the calendar day. However, certain external stimuli, known as zeitgebers (literally, from the German, time-givers), exert a synchronizing effect on the circadian rhythm of biological organisms, producing and sustaining an in-phase temporal progression of the endogenous circadian period and Earth’s 24-h rotation. The process of establishing phase synchronization between biological and planetary periodicities, i.e., setting the biologic clock, is referred to as entrainment. Daily entrainment of the biologic clock by environmental zeitgebers prevents inadvertent drifting or divergence from the 24-h day. Although less crucial synchronizing stimuli such as physical exercise have been identified, the principal entraining zeitgeber of the human endogenous circadian period is the LD cycle. The entraining influence of the LD cycle upon the human central nervous system is mediated through the light-sensitive receptors of the retina.

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**Keywords:** Light therapy, circadian disorders, insomnia, mood disorders, physiology

**Citation:** Shirani A; St. Louis EK. Illuminating rationale and uses for light therapy. J Clin Sleep Med 2009;5(2):155-163.

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Submitted for publication May, 2008
Submitted in final revised form November, 2008
Accepted for publication November, 2008
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The release of norepinephrine from the postganglionic noradrenergic fibers of SCG promotes the synthesis of melatonin from serotonin in the pineal gland.25 Melatonin is secreted into the blood stream and detected by the melatonin 1 and 2 receptors (MT-1, MT-2) in the SCN, further reducing and modulating its electrical activity in a negative feedback loop.26 In the presence of intact retinal photoreceptors, light inhibits while darkness promotes, melatonin secretion from the pineal gland.25 Under natural conditions, plasma melatonin concentration surges after dusk and returns to low daytime values with the onset of dawn.

CLINICAL APPROACH TO THE BIOLOGIC CLOCK

Light therapy targets the biologic (subjective) clock and attempts to reset the phase of the clock’s activity relative to the LD cycle and/or influence its amplitude. Since improved quality and quantity of sleep coincides with sleep at subjective night,27 common goals of light therapy include: (1) synchronizing the sleep-wake cycle with the subjective night; (2) shifting the biologic clock phase to facilitate sleep at a desired time of day/night; and (3) advancing the biologic clock phase to attain indirect effects on mood (see discussion below on light therapy of mood disorders). The biologic clock is, however, not equally amenable to phase shifts throughout its circadian period. Successful light therapy, therefore, requires the identification of circadian windows of opportunity for clinical intervention.

Timing of Light Therapy

The responsiveness of the biologic clock (SCN) to an intervention is represented by the magnitude of the ensuing shift in the clock’s phase. SCN phase shifts obtained by systematic exposure to a zeitgeber of defined magnitude at various biologic clock times (under exclusion of other zeitgebers) may be measured in minutes and subsequently plotted against the biologic time of exposure as the phase response curve (PRC, Figure 2). The sinusoidal shape of the PRC reveals a remarkable property of the biologic clock: any zeitgeber can yield phase advancement (positive shift), delay (negative shift), or be entirely phase neutral depending on the biologic clock time at which that zeitgeber is administered. Since no direct measures of SCN activity phase exist, the biologic clock time must instead be inferred from indirect markers of SCN activity in a negative feedback loop: any zeitgeber can yield phase advancement (positive shift), delay (negative shift), or be entirely phase neutral depending on the biologic clock time at which that zeitgeber is administered.

While the sleep-wake cycle is generally phase synchronized with the biologic clock in healthy subjects who are following a normal circadian rhythm,27 the sleep-wake cycle is not a wholly...
reliable indicator of biologic clock time, since a reset, phase-shifted biologic clock may not substantially alter the sleepwake cycle itself.33

Plasma melatonin levels are relatively low throughout the subjective day given tonic suppression of pineal gland activity by the SCN. Dim light melatonin onset (DLMO) refers to a surge in plasma melatonin concentration correlated with diminishing SCN neuronal firing, usually occurring in the first part of the subjective night. Maximal phase delay of the biologic clock can be induced by light administration prior to the core body temperature minimum, or during the melatonin concentration surge (generally in the first half of subjective night). In contrast, maximal phase advancement of the biologic clock is achieved by light administration following the core body temperature minimum, or during the melatonin concentration fall (generally in the second half of subjective night).12,32 Due to practical difficulties, measurement of DLMO and core body temperature minimum for optimal timing of therapeutic light administration have not been adopted into routine clinical practice. For instance, core body temperature may be falsely elevated due to physical exercise or ambient temperature, and measuring DLMO would require night time blood/saliva sampling. Simplified algorithms (discussed below) designed to assist clinicians in identifying the subjective day and night (i.e., individual circadian rhythm) and selection of proper timing for light therapy await replacement by more accurate and user-friendly tools.

**Figure 2**—The PRC to the bright light stimulus using melatonin midpoints as the circadian phase marker. Phase advances (positive values) and delays (negative values) are plotted against the timing of the centre of the light exposure relative to the melatonin midpoint on the pre-stimulus constant routine (defined to be 22 h), with the core body temperature minimum assumed to occur 2 h later at 0 h. Data points from circadian phases 6-18 are double plotted. The filled circles represent data from plasma melatonin, and the open circle represents data from salivary melatonin in subject 18K8 from whom blood samples were not acquired. The solid curve is a dual harmonic function fitted through all of the data points. The horizontal dashed line represents the anticipated 0.54 h average delay drift of the pacemaker between the pre- and post-stimulus phase assessments. Reproduced from: Khalsa SBS, Jewett ME, Cajochen C, Czeisler CA. A phase response curve to single bright light pulses in human subjects. J Physiol 2003; 549: 945–952 (with kind permission of Wiley-Blackwell, Oxford, UK).

**Types and Dosing of Light Therapy**

The biologic valence of light therapy is determined by 2 inherent features—wavelength and intensity. Visible light has an approximate wavelength spectrum of 380 (violet) to 760 (red) nm. Early studies of light generally utilized bright white light (a mixed spectrum of wavelengths similar to day light) to examine light effects on human circadian rhythm. Recent studies, however, have demonstrated that short wavelength blue light (~ 460 nm) possesses greater phase shifting properties than the rest of the visible light spectrum.34–37 Hence, blue light therapy may obviate the need for high intensities to influence the biologic clock.

The unit of intensity for visible light is lux. For example, the intensity of sunlight at midday measures over 100,000 lux. Early research in light therapy operated under the assumption that bright white light (7,000-12,000 lux simulating the ambient outdoor light intensity just after dawn) was necessary to produce discernible biologic effects.33-38 Subsequent research, however, proved that much lower intensity sources, such as ordinary room light (~180 lux) were sufficient to reset the human biologic clock.39 implying that exposure to ordinary room light on the opposite side of the Y-axis of the PRC may interfere with logical design and desired outcome of prescribed light therapy.40-41 One strategy to compensate for the undesired effects of ordinary room light on the SCN is to administer a higher dose (intensity × duration) of therapeutic light. The
elargated S-shaped dose-response curve (DRC) correlates the resultant circadian phase shift in minutes with a particular light dose (Figure 3). The DRC is nonlinear, slopes maximally between 50 and 550 lux and plateaus thereafter, indicating that high-intensity stimuli exceeding 550 lux are only slightly more effective than lower intensity stimuli. For instance, the net biologic effect of 9000 lux over 6.5 h may only be twice that of 100 lux over the same period.\textsuperscript{44} Although possible in principle, it may, therefore, be difficult to overcome the effects of ordinary room light on circadian rhythm by administering a higher intensity light for a longer duration. Moreover, sensitivity of the SCN to various light intensities is dependent on previous light exposure history.\textsuperscript{52,41} Extended prior exposure to dim light sensitizes the SCN to light, generating greater melatonin suppression following exposure to light of modest intensity, while baseline exposure to high light intensities produces the opposite effect.\textsuperscript{44,45} A thorough history of the nature, amount, and timing of daily light exposure of each patient may prove essential for the appropriate design and prescription for optimal light therapy.\textsuperscript{46,47} In some cases, successful therapy may necessitate a combination of light exposure and light restriction by wearing dark goggles (see delayed sleep phase type below) or even employ light restriction solely.\textsuperscript{38}

**DISORDERS RESPONSIVE TO LIGHT THERAPY**

Light therapy has been used to treat a number of disorders that can be classified in three broad categories: (1) disorders caused by desynchronization between the circadian rhythm, sleep-wake cycle, and the external environment; (2) mood disorders; and (3) disorders that entail elements of both.

**Circadian Rhythm Sleep Disorders**

Circadian rhythm sleep disorders are misalignments between the timing of an individual’s circadian rhythm of sleep propensity and the natural or societal rhythms of the individual’s environment. Circadian rhythm sleep disorders may arise when the physical environment is altered relative to internal circadian timing (as in rapid air travel across several time zones) or when intrinsic circadian timing is out of phase with the individual’s environment. The hallmarks of all circadian rhythm sleep disorders are tenacious insomnia and/or hypersomnia relative to the environmental clock time.

Circadian rhythm sleep disorder, delayed sleep phase type (DSPT) is common in adolescents and young adults, and is characterized by delayed bedtime and impaired ability to arise early or entrain to a usual daytime work schedule. Attempts to realign the sleep cycle often fail, resulting in sleep-onset insomnia and excessive daytime sleepiness. Advancing the circadian rhythm requires light exposure following the nadir of core body temperature. Exposure to white light of 2500 lux for 2 h in the early morning, combined with light restriction after 16:00 (dark goggles) is an effective treatment for DSPT.\textsuperscript{50} Alternatively, a light mask offering exposure to gradually escalating light intensities through closed eyelids over the last 4 h of habitual sleep time can be used to advance the circadian rhythm in DSPT patients.\textsuperscript{50} In a clinical trial, one week of morning blue light therapy succeeded in advancing the dim light melatonin onset by 2.5 h but failed to induce a similar shift in the sleep-wake cycle.\textsuperscript{51} Despite limited evidence, the American Academy of Sleep Medicine currently considers timed phototherapy as “a rational and effective intervention for DSPT.”\textsuperscript{52,55}

Circadian rhythm sleep disorder, advanced sleep phase type (ASPT) represents an undesirably early onset of sleep in the evening followed by an excessively early morning awakening. Patients with ASPT, usually older adults, are plagued by inability to stay awake for social events in evening hours. Evening light therapy (prior to core body temperature nadir) can be used to phase delay patients toward a later bedtime. Information on light treatment for this condition is, however, very limited.\textsuperscript{52-55}

Circadian rhythm sleep disorder, nonentrained type is common in blind, but rare in the sighted population. A complete lack of circadian rhythm phase synchronization with the 24-h day enables the sleep-wake cycle to follow an approximate 24.2 h endogenous period length, resulting in a gradual drift of the sleep-wake cycle in successive phase delays over the entire calendar day. Bright light may succeed in entraining a subpopulation of patients who retain functional melanopsin containing retinal ganglion cells. Such patients display intact plasma melatonin suppression in response to bright light exposure, a property that allows the identification of potential therapy candidates.\textsuperscript{18,56}

A mismatch between the work and sleep-wake cycle schedule and the endogenous circadian rhythm gives rise to circadian rhythm sleep disorder, shift work type. Light therapy may assist in realigning the circadian rhythm with the desired work schedule, provided the work shift changes sufficiently infrequently.\textsuperscript{57} Habitual night shift workers demonstrate improved nocturnal alertness under bright light exposure in the work place, and restriction of daytime light, indicating a sustained biologic clock phase reversal.\textsuperscript{58,59}

Circadian rhythm sleep disorder, jet lag type represents the sudden misalignment of a previously entrained circadian rhythm and a new geographic time zone imposed by rapid transmeridian air travel. Sleep deprivation in the course of travel may further contribute to the sleep-wake disturbance in this condition. Given the endless possibilities in combining the disorder parameters (number of time zones crossed, direction of travel, baseline phase of the circadian rhythm relative to local time, light exposure history, etc.), it is difficult to provide general recommendations for light therapy in jet lag disorder.\textsuperscript{60} Computer algorithms based on the PRC have been devised to calculate the optimal timing of light therapy.\textsuperscript{61} A simplified approach to treatment could involve pre-flight phase advancement for eastward travel and phase delay for westward travel. Using this paradigm, a study reported significant benefit in light therapy for jet lag disorder.\textsuperscript{62} In addition to light exposure, timed light restriction may prove to play an important role in treating this disorder.\textsuperscript{63}

**Dementia**

Severe disturbances of circadian rhythms due to deteriorating SCN function,\textsuperscript{64} diminished exposure to zeitgebers (e.g., reduced daily variation in environmental light), and/or impaired visual reception are commonly encountered in elderly institu-
tionalized patients. Prolonged wakefulness and wandering at night are compensated by daytime napping. Nocturnal agitation and wandering have been related to the amount and circadian distribution of light exposure. In a population with dementia and behavioral problems, daytime exposure to diffuse bright light reduced the variability of rest/activity cycle, as documented by actigraphy. Evening bright light administration (19:00-21:00) assisted in consolidating sleep in elderly with Alzheimer disease, sundowning, and nocturnal agitation. Morning bright light exposure increased the total nocturnal sleep time in another group of dementia patients without affecting behavior. Behavioral parameters improved following morning bright light therapy, yet sleep quality and quantity remained unchanged in another study. A rigorous study of demented nursing home residents also failed to improve nocturnal sleep by light therapy, but did not rate the behavioral impact of the treatment. In another trial, total agitation ratings in institutionalized patients with severe Alzheimer disease were unchanged following light therapy, although effects on circadian rhythms of these patients were not reported. Conflicting results may be attributed to heterogeneity of the studied population with respect to underlying diagnosis, stage of disease, visual impairment and/or methodological questions such as timing of light exposure with respect to core body temperature or baseline light conditions affecting light sensitivity (light history). Additional large controlled, prospective trials are warranted to clarify the value of light therapy in the treatment of behavioral problems accompanying dementia.

Mood Disorders

Mood disorders are highly prevalent and frequently associated with alterations in hypothalamic and pituitary hormones and disturbance of sleep architecture and sleep-wake cycle, suggesting a concomitant disruption of biologic clock function. Conversely, the temporal relationship between the sleep-wake cycle and biologic clock phase affects circadian mood variations in healthy individuals in a complex fashion. The precise nature of neurobiological actions of phototherapy in mood disorders remains unclear. Parallelizing general concepts underlying pharmacotherapy of depressive disorders, one postulated mechanism for the antidepressant effect of light is mediation by biogenic amines, since depletion of tryptophan, the amino acid precursor of the neurotransmitter serotonin, reverses beneficial effects of light therapy on mood.

Reduced retinal light sensitivity secondary to disturbances of the retinal neurotransmitter, dopamine, has been proposed as a potential culprit in seasonal affective disorder (SAD). Exposure to intense light increases retinal dopamine activity and favors day vision over night vision. Another controversial hypothesis holds that light’s antidepressant effects are conferred through phase advancement of the biologic clock. Phase advancement of the biologic clock may even be implicated in the antidepressant properties of selective serotonin reuptake inhibitors such as fluoxetine, as supported by an in vitro study. More complex interactions of antidepressant medications with clock genes in a synergistic or complimentary fashion to light are also possible. For instance, in an animal model, fluoxetine induced the expression of clock genes in brain regions beyond the SCN.

Phototherapy was introduced in 1984 as a treatment for mood disorders with a seasonal pattern (seasonal affective disorder or SAD). Seasonal pattern is a standard DSM-IV-TR specifier for the depressed portion of mood disorders, requiring a temporal relationship between the onset of the depressive episodes and a particular time of year, followed by full remission associated with another time of year, observed over a minimum time span of 2 consecutive years. The seasonal pattern specifier may be used to qualify unipolar or bipolar depression. Patients with SAD often display the atypical neurovegetative symptoms of hypersomnia and hyperphagia, 2 positive predictors of response to light therapy. The onset of winter depression may also be associated with a tendency to circadian phase delay termed eveningness. The classical phototherapeutic approach to SAD uses a morning dose of 5000 lux/h (10,000 lux for 30 min, or 2500 lux for 2 h). As the clinical benefits of light therapy in SAD appear to stem in part from a phase advancement of the circadian rhythm (represented by the earlier DLMO), the proper timing of the administration of the light treatment relative to DLMO is crucial. To achieve the best results, light therapy should be administered in the morning hours, approximately 8.5 h after the DLMO. In case the measurement of DLMO is not readily available, the following surrogate algorithm may be used. For every half-hour of nocturnal sleep beyond 6 h, light therapy should be scheduled 15 min prior to the habitual awakening time, to a maximum of 1.5 h. For instance, a patient who habitually sleeps 8 h (i.e., 4 × 30 min beyond 6 h) has to be awakened 4 × 15 minutes, or 1 h, prior to the usual awakening time to receive light treatment. This is, however, merely a rough estimate based on data obtained from patients with SAD. The same regimen has also been successfully applied to patients with delayed sleep phase disorder and nonseasonal depression. Fluoxetine did not offer an advantage over light therapy in SAD, underscoring the value of light therapy as a cost-effective first-line treatment in this condition. Up to 20% of patients with nonseasonal unipolar depression are treatment resistant to antidepressant medications, in part attributable to the inclusion of a subgroup with undiagnosed bipolar disorder in this population. Not surprisingly, phototherapy as a sole therapeutic tool, and in combination with other measures, has been studied for treatment of both nonseasonal unipolar and bipolar depressive disorders. In general, the efficacy of light therapy in nonseasonal depression appears to be lower than in SAD. When used as stand-alone treatment (without concomitant antidepressant medication), the outcome is inconsistent and unpredictable. Mood improvement following total sleep deprivation may be a positive response predictor to phototherapy in nonseasonal depression. Light therapy as an adjuvant measure (combined with pharmacotherapy), however, offers more robust results. Regimens for light administration in non-seasonal depression are similar to those customary for SAD.

Insomnia

Insomnia is the most common sleep-wake related complaint. In addition to medical etiologies such as chronic pain or sleep related breathing disorders, the International Classification of Sleep Disorders (ICSD-2) identifies psychological and behavior-
Light Application in Clinical Practice

Various light stimuli covering a range of intensities and spectrums have been used for therapeutic intervention, although not all have been adequately tested. The optimal duration of light therapy cycles in various conditions has not yet been established. The majority of published studies of light therapy protocols do not exceed one month duration. Only one trial reviewed for this paper extended over 60 days.10 At the present time, decisions regarding the number of therapeutic cycles and their duration must therefore be deferred to clinical judgment.

Traditionally, investigators have resorted to multiple fluorescent tubes to emit intensities from 2,500 to 12,000 lux for light therapy. The light source is placed 1-3 feet from the patient. A diffusion screen placed over the fluorescent tubes ensures even distribution of light and protects from ultraviolet wavelengths. The patient is instructed to use the light for illumination while performing desk work or reading and to avoid gazing at the light source directly. As the lower portion of the retina appears to have a greater propensity to communicate with the biologic clock, positioning the light source above eye level is recommended.

Unsupervised early morning light exposure performed at home raises the question of sleepy patients’ compliance. Naturalistic dawn simulation was devised to minimize the need for reliance on the patient’s active participation and practically reduce the necessary time investment for the treatment to zero. The patient, while still asleep, is exposed to a light source starting at near complete darkness and growing over approximately 3 h to a maximum intensity of 250 lux, effectively reproducing the natural sleep conditions under a tree cover in the northern hemisphere spring.115 The light source is placed above the head of the bed and faces the pillow. Maximum intensity is programmed to coincide with the habitual waking time and to subsequently fade out rapidly. The benefit is presumably due to the interaction of light with the retinal receptors through the closed eyelids.116 In addition to easing compliance, naturalistic dawn simulation eliminates possible ocular adverse effects due to excessive exposure and/or preexisting retinal disease.

Bright light could pose dangers to patients with known retinal pathology, and in those using photosensitizing medications. Excluding these cases and excessive exposure, however, light therapy overall appears to have a very favorable risk-benefit ratio.117 Although reported in SAD, switching depression to mania and inducing suicidal ideation are rare.118,119 Complaints of decreased sleep, dry mouth, headache, weakness, and fatigue are as commonly reported as in fluoxetine therapy.120 Ocular adverse effects in individuals who were previously free of ocular disease were not detected, even after extended exposure. Nevertheless, ophthalmologic evaluation every few years may be a reasonable precaution.

Side effects of light therapy overdose may include agitation, headache, or nausea. Insomnia, particularly initial insomnia, may also be encountered.117 Side effects can be obviated by reducing the light dose (intensity, duration, or both), increasing the distance between the patient and the light source, or by moving morning therapy sessions to a later time or evening treatments to an earlier time to diminish the light efficacy according to the PRC.

Conclusion

Light is the main zeitgeber for the human circadian rhythm. Light exerts its influence on the central nervous system through interaction with retinal ganglion cells. The capacity of light to advance or delay the circadian rhythms of melatonin, core body temperature, and corticosteroids can be utilized for clinical purposes. The main clinical applications of light therapy are in circadian rhythm sleep disorders, dementia, mood disorders, and insomnia. In bright light therapy, 5000 lux/h administered daily over several weeks is usual. Lower light intensities yield similar efficacies, if presented as naturalistic dawn simulation or short wavelength blue light. Given the widespread influences of light upon circadian brain functions, the spectrum of clinical disorders in which light therapy can be considered is likely to expand, with early evidence pointing toward potential efficacy in subsyndromal mood and certain eating disorders.121,122 Large randomized, controlled clinical trials are necessary to identify response predictors and better characterize optimal administration parameters including duration and timing of light therapy. Additionally, clinical trials evaluating the longitudinal efficacy and safety of light therapy for chronic medical conditions would help refine future clinical applications of light therapy. Practical application of light therapy would also be aided by efforts to educate clinicians concerning the scientific basis of light therapy and its clinical applications.

DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.
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