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What Are Circadian Rhythms and How Can They Go Wrong?

An Introduction

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CENTER FOR Environmental Therapeutics

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What Are Circadian Rhythms and How Can They Go Wrong?

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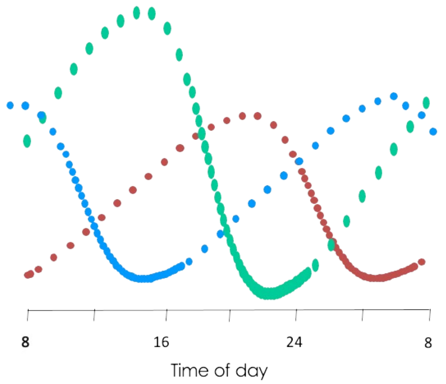
Contents

WHAT ARE CIRCADIAN RHYTHMS?

Many textbooks already explain the properties of daily (circadian) rhythms, so let us here just focus on the concepts that are important for daily life and for understanding chronotherapeutics.

Circadian rhythms describe predictable oscillations in the patterns of behavioral, psychological, physiologic and biochemical functions over 24 hours. They occur in all living organisms, from the most primitive cyanobacteria, to fungi, plants, and animals. Nearly everything we measure has a peak and a minimum that fits with optimal timing of its function. We will talk mainly about the sleep-wake rhythm, as the most obvious one, and the core body temperature rhythm, as a marker of the internal clock.



Schematic examples of three rhythms with different timing of peaks and minimum.

HOW DOES LIGHT REACH THE BIOLOGICAL CLOCK?

The mammalian circadian clock is located in a small area of the brain's hypothalamus, the suprachiasmatic nuclei (SCN), which are reached by a direct pathway from the retina, separate from the optic nerve, the retino-hypothalamic tract [1, 2]. This means that light entering the eye follows two routes. First, via the classic photoreceptors — the rods and cones — light transmits visual information through the optic nerve to the brain that leads us to see the world in color, shape, and movement. Second, light also hits a novel photoreceptor in a small group of intrinsically photosensitive retinal ganglion cells (ipRGCs) that then synchronizes the clock in the SCN to the 24-hour day via the retino-hypothalamic tract. This function of light to entrain rhythms is called "zeitgeber" (time-giver). Light affects sleep, alertness, performance, and even pupil size through this pathway.

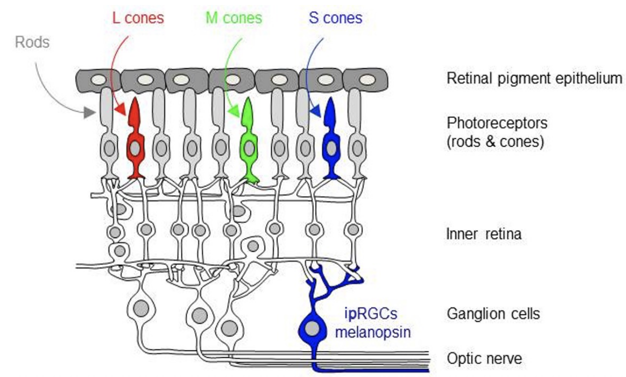


DIAGRAM OF THE HUMAN RETINA: the classical photoreceptors, rods and cones, and the newly discovered intrinsically photosensitive retinal ganglion cells (ipRGCs) containing melanopsin. (S. PEIRSON)

LIGHT DIRECTLY AFFECTS MOOD

An exciting discovery has been that the mood-enhancing effects of light (well-known from clinical applications), are mediated via these ipRGCs, but not only through the SCN. A second pathway goes from the ipRGCs directly to a region of the brain called the perihabenular nucleus (PHb), itself close to regions involved in mood and stress regulation. The PHb also influences learning. So perhaps we now have a clue how light can be antidepressant.

The circadian system is driven by so-called "clock genes." These are found not only in the SCN, but in all neurons of the brain and cells of the body. The elucidation of how these clock genes tick was awarded the Nobel Prize for Physiology or Medicine in 2017, a noble recognition of the important role of circadian rhythms.

JEFFREY C. HALL

MICHAEL ROSBASH

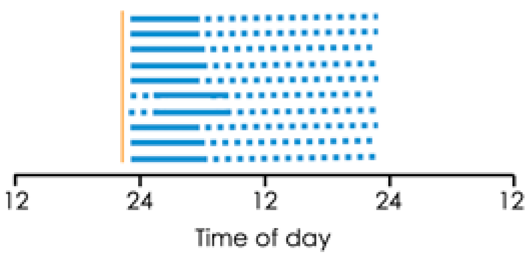
MICHAEL W. YOUNG

Illustrations: Niklas Elmehed. Copyright: Nobel Media AB 2017

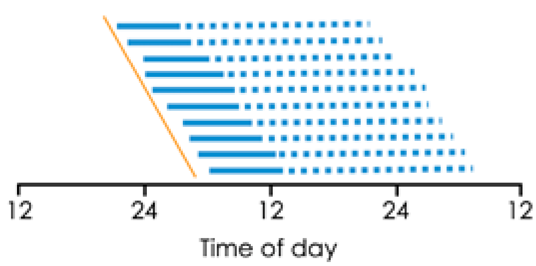
DIFFERENT PATTERNS OF THE CIRCADIAN REST-ACTIVITY (SLEEP-WAKE) CYCLE

We begin with a simple diagram, using the sleep-wake cycle as an (indirect) indicator of the circadian system. A full line denotes sleep, a dotted line the duration of wakefulness, and 10 successive days are shown one below the other.

Let us consider a “normal” rhythm: bedtime before midnight, waking around 7 a.m., often with a delay on weekends. This stable pattern of a 24-hour rhythm [orange line] is called synchronization or entrainment.

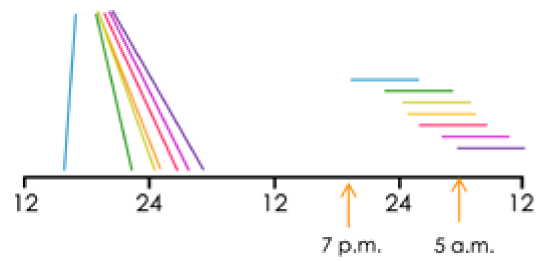


Without light perception (as in the blind), or under controlled experimental near-darkness conditions without information about time of day, the circadian clock loses entrainment, and sleep-wake cycles drift a few minutes later each day. This is called free running (with the circadian period indicated by the orange line fitted to sleep onsets).

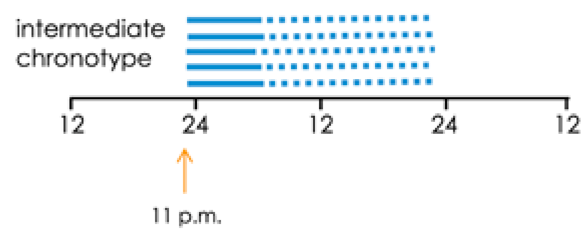


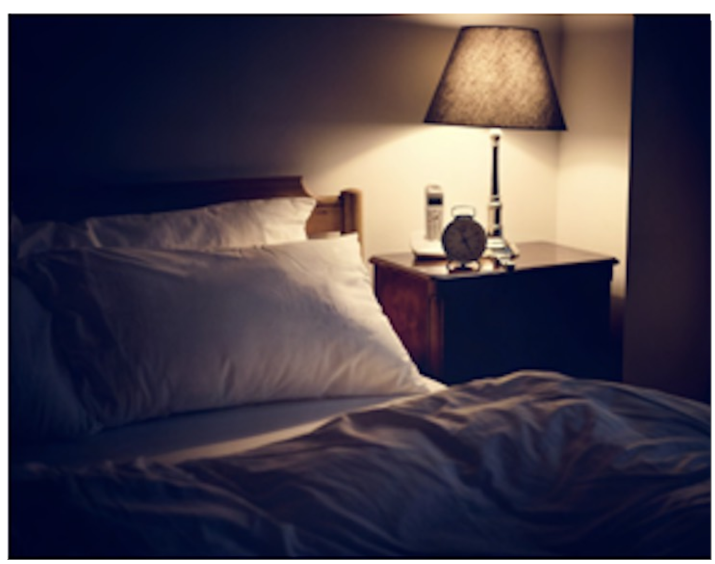
In most people, the circadian clock tends to run at a period slightly longer than 24 hours. This may explain the weekend drift later. It also means the clock needs to be synchronized to 24 hours every day, and the most important synchronizing agent (zeitgeber) is light. Other zeitgebers are exercise, mealtimes, alarm clocks, social cues.

There is a range of free-running periods in different people (colored vertical lines), and this is one of the determinants of an individual’s phase of entrainment (the preferred sleep timing on free days [colored horizontal lines]). Bedtime can range from the extremes of 7 p.m. to 5 a.m. If you have a fast clock, you are an early bird in everyday life; if your clock is slow, you are a late riser.



This is the basis of chronotype, a term describing each individual’s natural sleep time without alarm clocks and duties — mostly determined by clock genes — though it shifts across the life span. The large majority of the population are neither early (“lark”) nor late (“owl”) chronotypes, but rather, “intermediates.”

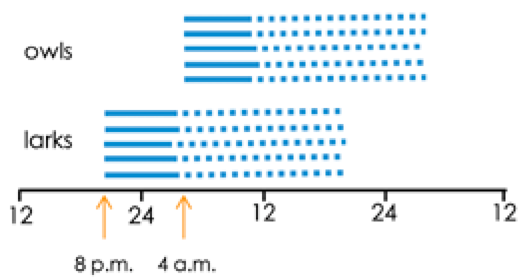




Owls go to bed later and wake up later (causing problems with work or school times), which we call “phase delayed”. This is a characteristic of teenagers.

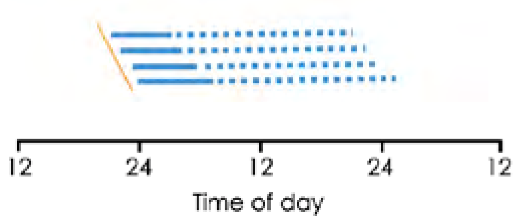
Larks are phase advanced, and usually don’t have problems, since “the early bird catches the worm.” Larks fit in nicely with social values that attribute virtue to getting up early (and alas, laziness to getting up late), though they do mostly miss out on parties… Often, sleep-wake cycles drift earlier as we age, causing unwanted early morning awakening. Extreme owls and larks could actually share a bed without being in it at the same time!

Larks and owls suffer from what is called social jet lag. They live — as it were — in the wrong time zone and can’t adapt to daily life. It is important to realize that this behavior is biology, not a psychological choice, and we should not be judgmental about it.



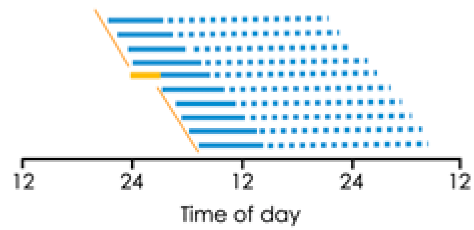
LIGHT SHIFTS CIRCADIAN RHYTHMS

These rhythms can be — and are — shifted earlier or later every day, depending on when the biological clock sees light (usually high intensity outdoors). We are not always so stable in our bedtimes from day to day, as our diagrams imply, and the alarm clock usually masks what would be our natural wake-up time (on weekends and holidays). We know what this pattern of shifts following light exposure looks like — it has been formalized as a phase response curve to light (PRC). When studied in the lab, the technique is established. The subject is permitted to free run for a few days in near darkness to establish period (orange line).

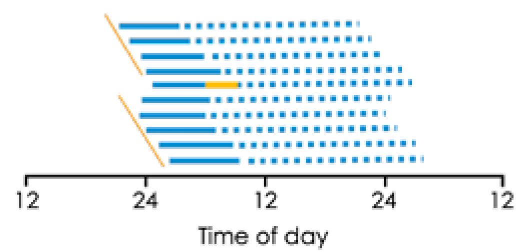


Then a pulse of bright light (orange bar) is administered at different times of the day, and the free running rhythm allowed to continue so as to be able to see what shift has been induced (lower orange line.

Light that closely precedes sleep onset induces a phase delay in the free running period.

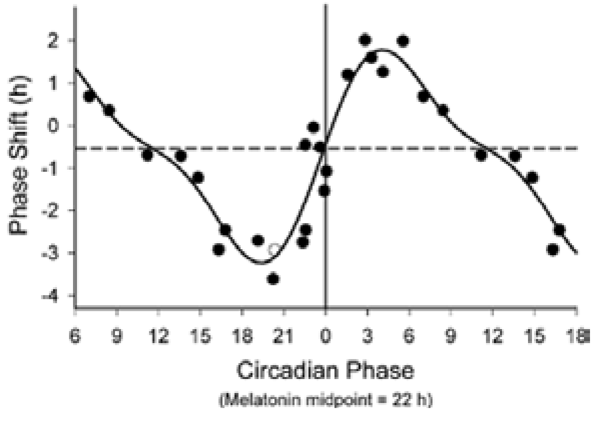


Light in the second half of the night (or early morning) induces a phase advance of the free running period. It takes a few days for an advance to be completed; the adjustment is less swift than for phase delays.



Plotting the shifts that occur at different times of day yields a phase response curve. The graph displays the most detailed information we have for humans (PRCs have been done for all kinds of creatures), and it is remarkable how light at nearly every time of day has an effect. (In animals there is usually a “dead zone” during the day when no shifts occur.) Exposure to bright light from about 2 p.m. to 11 p.m. results in delays (negative values in the graph), the largest shift being 3 to 4 hours. Light from midnight to about 11 a.m. induces phase advances of 1 to 2 hours (positive values in the graph).

If this seems too theoretical, consider that evening light shifts the clock later (phase delay), and morning light shifts the clock earlier (phase advance). Since most of us have a clock longer than 24 hours, morning light is absolutely necessary to shift rhythms earlier in order to entrain to the solar day. Evening light potentiates the clock’s natural drift later, and here we must be careful or we will have problems falling asleep.



Khalsa SB, et al. A phase response curve to single bright light pulses in human subjects. J Physiol 2003;549:945-952

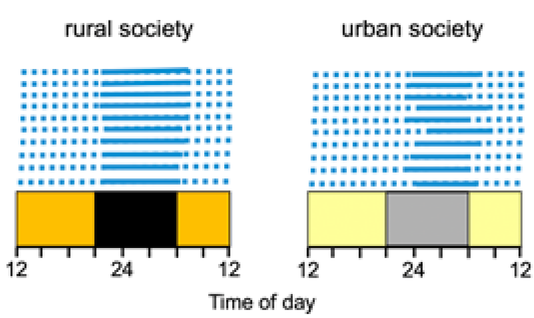
HOW MUCH LIGHT DO WE NEED?

What is sufficient light for good entrainment in terms of intensity, spectrum, time of day and duration of exposure? A key question that is the focus of much present research is, What is the sensitivity to light for different functions? It seems that high intensities (5000 to 10,000 lux, as used for therapeutic purposes) are necessary for mood improvement and maybe also required for the following night's sleep quality. Alertness can be induced at lower intensities from ~100 lux, and entrainment requires about half an hour of 1000 lux every morning. These are rough estimates and depend on the color temperature of the lamps used (the more blue, the less intensity required, since this is the wavelength range of maximal ipRGC sensitivity). Here we have a basic set of tools to use light to manage rhythms, sleep, and mood when these are disturbed.

MODERN LIFE HAS CHANGED NATURAL LIGHT EXPOSURE

A last thought. When we compare pre-industrialized or rural societies with today's industrialized urban environment, there is a clear change in light-oriented behavior. We no longer rise with dawn and go to sleep after dusk.

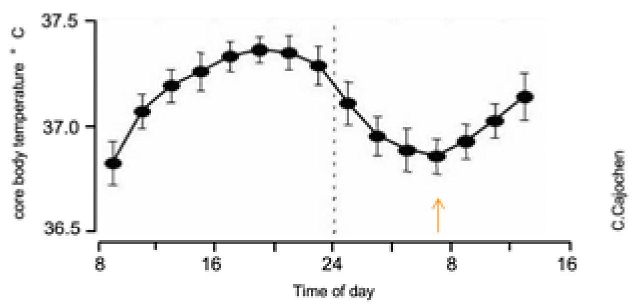
Our 24/7 society has artificial light around the clock. Lacking a clear dawn signal, sleep in modern life is later, shorter, and more variable than that of our forebears. There is less exposure to daylight, and the nights are no longer dark.



Indeed, there are multiple factors determining our sleep and wake timing, duration, and quality, as well as our mood and alertness during the day. Some of them are given (our clock genes, age, sex), though we do have control over our light-oriented behavior and should be careful to get enough morning light every day.

HOW CAN CIRCADIAN RHYTHMS GO WRONG?

In introducing the topic, we have emphasized the sleep-wake cycle as an output of the biological clock to describe how rhythms function. Now, in order to look properly at the circadian system, we need a better output. The reason is that even though under good conditions rhythms are all nicely synchronized, the sleep-wake cycle is much more variable and unreliable than internal functions such as core body temperature (CBT).

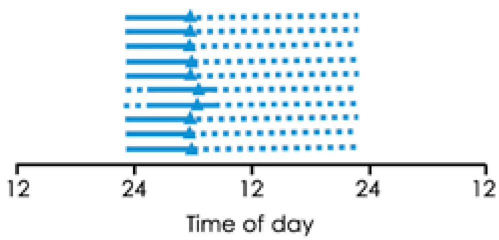


Let us look at the circadian rhythm of CBT under controlled conditions in the laboratory. Temperature rises throughout the morning to a maximum in the late afternoon and a minimum at the end of sleep around 6 a.m. (orange arrow). We have used this CBT minimum (▲) as a phase marker together with the sleep-wake cycle to illustrate how circadian rhythms can get out of sync. By showing them in this schematic manner, we hope the reader will better understand the various disturbances.

The diagrams that follow on the next page illustrate these circadian rhythm disorders. All use the same structure: a full line denoting sleep, a dotted line for the duration of wakefulness, and the triangle showing the minimum of the core body temperature rhythm as a marker of internal time. In each case, 10 successive days are shown one below the other.

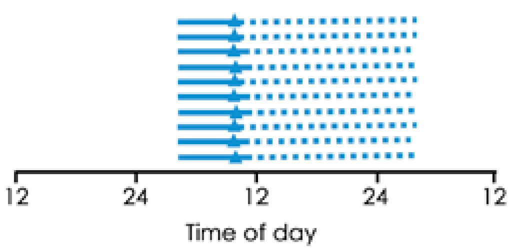
Let's begin with healthy synchronization: bedtime before midnight, with the core body temperature minimum at the end of sleep. Often, there is a small delay on weekends. This is as it should be.

We've all heard about chronotype, which is a term for each individual's natural sleep timing. The example below represents the large majority of the population who are neither early ("lark") or late ("owl") chronotypes, but "intermediates."



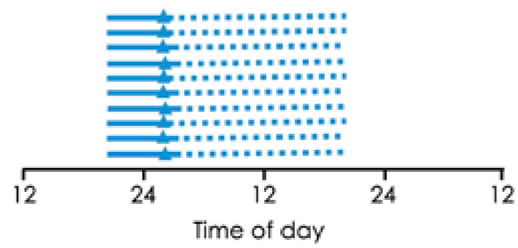
An owl who goes to bed later and wakes up later ("phase delayed") is not suffering from an illness, though it can be a problem. The pattern is common between the ages of 12 and 20, as adolescents tend to shift their rhythms later and later, a hormonal consequence of puberty. However, extreme cases are diagnosed as Delayed Sleep-Wake Phase Disorder (DSPD), which is very resistant to any treatment and causes serious problems (for example, missing out morning school).

Owls have their internal clock (temperature minimum) at the end of sleep, as is normal, so their problem is not with internal, but external desynchronization — all their rhythms are shifted many hours later relative to clock /solar time.



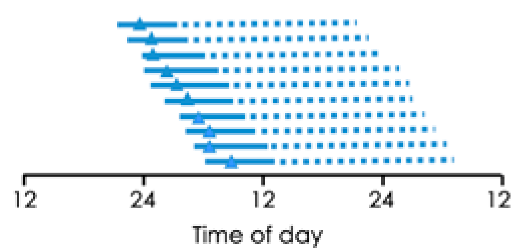
A lark who goes to bed earlier and wakes up earlier ("phase advanced") is also not suffering an illness. Larks are the lucky ones who don't have to be dragged out of bed with an alarm clock. Their temperature minimum is at the end of sleep, as normal.

However, the extreme case of Advanced Sleep-Wake Phase Disorder (ASPD), although much less common than DSPD, is a sleep disorder that affects all aspects of daily life. These individuals fall asleep in the early evening and forgo many social or family events and are then wide awake in the wee hours of the night before dawn.



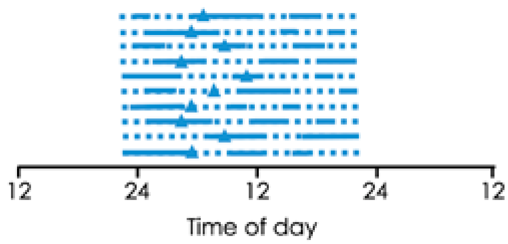
Although we don't classify larks and owls as ill, they do experience "social jet lag", which muddles their ability to be on time and function with the rest of their environment, and show abnormal entrainment to the day-night cycle.

However, there is a third group that doesn't entrain at all. Their sleep-wake cycles "free run" with a periodicity determined by their clock genes, usually longer than 24h. This is classified as Non-24-Hour Sleep-Wake Rhythm Disorder. In this case, the internal rhythms shift earlier (the temperature minimum lies at the beginning instead of the end of sleep). What leads to such an extreme condition? Most often it is lack of light input necessary to synchronize the clock, as in the visually impaired or blind. Social cues are not strong enough to keep these people in sync with the rest of the world.



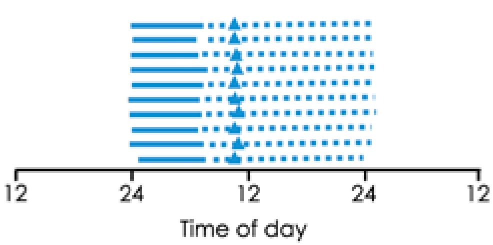
A rare disorder of arrhythmic and irregular sleep is characterized by numerous naps throughout the 24-hour day, without a main nighttime sleep episode.

There is no discernible sleep-wake pattern, sleep is of poor quality, and wakefulness is marked by sleepiness (Irregular Sleep-Wake Rhythm Disorder). The temperature rhythm is very variable and shifts back and forth from day to day. Such patterns have been seen as symptomatic of some neurological disease, including Alzheimer's disease.

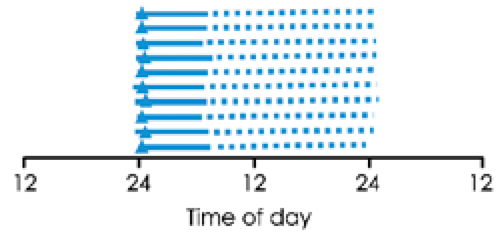


Next, we focus on disturbances characterized by internal desynchronization. The sleep-wake cycle is more or less normally entrained to the solar day, but the internal clock is not.

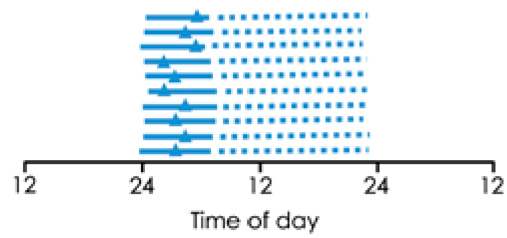
One manifestation is a phase delay of the biological clock, where the core body temperature (CBT) minimum occurs long after waking. This results in poor functioning in the morning, since the temperature minimum corresponds to the low points of performance, mood, and alertness.



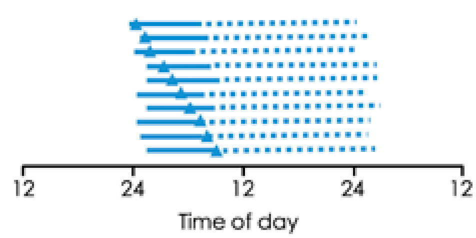
In a second variation, there is a phase advance where the CBT minimum occurs at the start of sleep. This pattern is often found in clinical depression.



Additionally there is the condition of unstable phase, where the core body temperature minimum shifts from day to day. Clinically, this can be seen in many insomnia patients. Often, they also show unstable sleep timing that shifts from day to day as well.



Our last group shows a sleep-wake cycle that is more or less entrained (by external cues and alarm clocks), while the internal clock free runs. Core body temperature is not entrained and shifts through sleep and wake at its own endogenous period. Such a difficult situation cannot persist very long, and often the sleep-wake cycle begins to free run as well. This pattern is found in visually impaired and blind patients who strive with difficulty to maintain and entrain their sleep-wake cycle even though their inner clock is free running.



In these circadian sleep disturbances, carefully timed light exposure is a therapeutic option, often combined with other interventions. Obviously, this is not an option for patients with visual impairment or blindness. In such cases, however, a regular schedule of low dose melatonin before sleep can serve as a zeitgeber to establish 24-hour regularity and improved quality of life.

We complete our survey by pointing to two obvious externally induced circadian sleep disorders —

JET LAG over multiple time zones, where the internal clock and sleep don't catch up with the external light-dark cycle on landing (usually requiring 1 day per time zone to readapt, with greater difficulty following eastward [advanced] flight than westward [delayed] flight).

SHIFT WORK, in all its variants — just bad news for the circadian system. Some shifts are less disturbing than others, but all result in desynchronization between the time of day required for being awake at work and internal clock time, which is slow to adapt.

Of course, this summary doesn't cover all the 83 different sleep disorders in the International Classification of Sleep Disorders (3rd edition, 2014), of which only 7 are related to the circadian system. These all require diagnosis and treatment in an accredited sleep medicine clinic.

Circadian-Rhythm Sleep Disorders

Time Zone Change (Jet Lag) Syndrome
Shift Work Sleep Disorder
Delayed Sleep-Wake Phase Disorder
Advanced Sleep-Wake Phase Disorder
Irregular Sleep-Wake Rhythm Disorder
Non-24-Hour Sleep-Wake Rhythm Disorder
Circadian Rhythm Sleep Disorder Not Otherwise Specified

The lack of regular daylight or bright light exposure is common to many of the sleep-wake cycle disorders in our survey. We are realizing that the consequences of poor lighting are both short-term and long-term. This knowledge needs to be incorporated into general medical practice.

Circadian rhythm sleep disorders respond to chronotherapy, whether administered exclusively or in combination with other established treatments. We should begin thinking in terms of a new Chrono-ecology, where our relationship to daylight is enhanced.

Get outdoors to synchronize your rhythms and improve your mood! And make your nights darker . . . at least in the bedroom!

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About us

The Center for Environmental Therapeutics is a 501(c)(3) nonprofit based in New York, founded in 1994 in response to international interest in new environmental therapies – drug-free ways to improve mood sleep, and energy. We are leaders in the research and development of light therapies as counterparts to conventional medications. Our program serves health care providers, the consumer public, and industry. CET is made up of a multidisciplinary team of eminent researchers and clinicians committed to pooling their efforts toward the development of effective environmental therapies. We host a popular website, cet.org, with educational material for the general public and clinicians; online, personalized self-assessments of depressive disorders, symptom severity, and circadian rhythm status; and an extensive question library based on inquiries from the public, which offers guidance from academic and clinical experts.

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