

Temporal organization as a therapeutic target

Anna Wirz-Justice, PhD

Abstract

Biological functions occur at many different frequencies, and each has its healthy and pathological ranges, patterns, and properties. Physiology, biochemistry, and behavior are not only organized at the morphological level in cells and organs, but separated or coordinated in time for minimal interference and optimal function. One of the most important temporal frameworks is that of the 24-hour day-night cycle, and its change in day length with season. Robust circadian rhythms are important for mental and physical well-being. Though rhythms have been long neglected as irrelevant (in spite of the high prevalence of sleep disorders in nearly every psychiatric illness), we now have tools to document rhythm disruption and, through better understanding of underlying molecular and physiological mechanisms, to develop therapeutic applications. Light as the major synchronizing agent of the biological clock is becoming a treatment option not only for winter depression but other, nonseasonal forms, as well as an adjunct in optimizing sleep-wake cycles, daytime alertness, cognition, and mood in many neuropsychiatric illnesses. Melatonin is the signal of darkness and promotes sleep onset. Manipulation of sleep (wake therapy, phase advance) has yielded the most rapid, nonpharmacological antidepressant effect known, and combinations (with light, medication) provide long-lasting response. Thus, by analogy, new molecules to augment synchronization or mimic changes occurring during night-time wakefulness may yield novel treatments. This issue on biological rhythms contains articles on a variety of different frequencies not included in the usual definition of chronobiology, but which open up interesting approaches to time and illness.

Time in biology ticks at all frequencies: from the milliseconds of neuronal firing and seconds of the heartbeat to hours of the day, seasonal change, and years, encompassing the human life cycle. Time-related information provides a different approach to understanding pathology. Psychiatrists in the nineteenth century were fascinated by these levels of temporal organization, intuiting a deep connection with many of the symptoms manifested by their severely disturbed patients. In the pre-psychopharmacological era, such rhythms in psychopathology were documented over months and years in an attempt to correlate them with physiology or biochemistry (eg, thyroid hormone and periodic catatonia). With the advent of long-term ambulatory monitoring, better tools became available to measure physiological rhythms and their links with clinical states.

The major cyclic phenomena that appear relevant to psychiatric illness are 24-hour (circadian) rhythms. The circadian clock interacts with a homeostatic drive of sleep pressure increasing during wakefulness and dissipating during sleep. These two processes are primarily responsible for the architecture of the sleep-wake cycle, cognitive and motor performance, sleepiness, and mood throughout the day. Thus, great attention needs to be paid to the correct alignment of the circadian system with the day-night cycle to obtain restorative sleep coupled with daytime alertness and well-being. Under naturalistic conditions, the dawn-dusk signal would act as a *Zeitgeber* to synchronize all rhythms to function at the right time, and we would receive adequate light during the day and real darkness during the night. Modern society, with the invention of artificial light, has achieved apparent independence from the solar day, but at what cost? Chronobiologists consider our 24/7 lifestyle and lack of clear light-dark exposure to be the downside of temporal freedom, and that it contributes to the increasing incidence of depressive and sleep disorders. The only way of countering a lack of temporal order is to re-establish regular synchronizing signals, the most

Guest editorial

prominent of these being light. A great deal of research shows how the timing, intensity, and spectral composition of light affects human behavior separately from vision, providing not only a new treatment, but in addition, a conceptual development in architectural lighting. The more we know about the importance of light (in particular blue wavelengths) for these “nonvisual” photic functions related to the biological clock, the more we can apply it to general and mental health. An exciting fast-moving field incorporates this aspect in the design of buildings with optimum daylight exposure and adequate artificial light, ranging from work and school environments to retirement homes or neonatal units and emergency rooms in hospitals.

What does this mean for everyday clinical work?

First, the long-established backbone of psychiatric practice has been to develop and maintain regular patterns of sleep, mealtimes, work, and exercise in patients in order to structure the day. This can be interpreted in chronobiological terms as increasing the strength of different zeitgebers to enhance good synchronization of rhythms. Indeed, “social zeitgeber” therapy has been developed on these principles and successfully applied. Second, more attention should be paid to the environment in which patients spend their days. If the ward or rooms are poorly lit, with small windows and facing West or North, the amount of “biologically active” light will be too little for improving mood, cognition, and sleep. For example, depressed patients who lived on the sunny East side of a ward stayed 3 days less in hospital than those in dim rooms without morning light; in a prospective study, depressed patients also stayed 3 days less in hospital after lighting in bedroom, dining area, corridors and dayroom was augmented, than before the renovation. This indicates, as do investigations of the effect of light on many psychological and behavioral indices in healthy subjects, that good environmental lighting acts as a passive adjunct therapy. Specific treatment with a light box (an active, higher dose taken regularly at an optimal time in the morning) is, however, indicated in many depres-

sive states, including bipolar patients; the poor sleep patterns found in a high proportion of psychiatric patients, eg, with schizophrenia or borderline personality disorder, can also be improved with light. Regular sleep-wake timing is correlated with better mood, cognitive function, and alertness. Thus, light has a much broader application than just for its original use in seasonal affective disorder—it is the most important zeitgeber for our internal clock and can be applied (in combination with usual treatment) to many different syndromes. Good response to light has been found in antepartum depression, geriatric depression and Alzheimer’s disease, bulimia, and attention deficit-hyperactivity disorder, to select but a few recent findings. Applications have even broadened beyond psychiatry, to Parkinson’s disease in neurology and sleep-wake cycle disturbances in internal medicine, eg, kidney transplant recipients or patients with liver cirrhosis. The extent of potential application is far from having been defined; it is important that studies with light follow the same stringent randomized design and analyses as trials of a new drug, to attain acceptance as a valid treatment option.

In major affective disorder, light therapy is slowly gaining acceptance beyond only winter depression, though it still remains for the official committees developing treatment guidelines to include it under main strategies and not in the last section of “alternative possibilities.” The same applies to the still little-used treatment of sleep deprivation (“wake therapy”), for which a 40-year body of evidence demonstrates rapid efficacy. More recently, it has been shown that combination with light or medication can prevent relapse after recovery sleep. Shifting sleep earlier (phase advance) has a slower, but longer-lasting antidepressant effect. This field, designated chronotherapeutics, has accumulated data documenting good response in difficult-to-treat conditions such as bipolar, chronic, or therapy-resistant depression. Moreover, it appears that a short chronotherapeutics combination over only a few days can yield long-lasting improvement and diminish relapse rates months thereafter.

Guest editorial

The pineal hormone melatonin is also part of the chronotherapeutics armamentarium. Parallel to the dual effects of light to shift the clock and promote alertness, melatonin—as a signal of darkness—shifts the clock and induces sleepiness. Melatonin agonists have similar properties. Darkness itself (in the form of an enforced long night, or by means of blue-blocking glasses) has remarkable effects on rapid-cycling in bipolar patients, or as antimanic treatment. Even though most research has been done on light, we should not forget the importance of darkness, particularly in hospital environments, to strengthen the zeitgeber signal at night.

As described by Benedetti in this issue (p 401), it is time that the neglected or “orphan” chronotherapeutics is recognized as a powerful clinical instru-

ment in everyday psychiatric practice. It is also astonishing how few pharmaceutical companies have utilized the approach of developing drugs that act on the biological clock, or of finding out the molecular correlates of the switch out of depression during a night awake.

For more information about light therapy, see the multilingual nonprofit Web site www.cet.org, where questionnaires are available for downloading, and join the discussion forum at:

www.chronotherapeutics.org.

Address for correspondence: Anna Wirz-Justice, PhD, Professor Emeritus, Centre for Chronobiology, Psychiatric Hospitals, University of Basel, Wilhelm Klein Strasse 27, CH-4012 Basel, Switzerland (e-mail: anna.wirz-justice@unibas.ch)

FURTHER READING

1. Wirz-Justice A, Benedetti F, Terman M. Chronotherapeutics for Affective Disorders. *A Clinician's Manual for Light and Wake Therapy*. Basel, Switzerland: S. Karger AG; 2009 (2nd edition 2013 in press).
2. Wirz-Justice A, Bromundt V, Cajochen C. Circadian disruption and psychiatric disorders: the importance of entrainment. *Sleep Med Clin*. 2009;4:273-284.
3. Wirz-Justice A, Terman M. Chronotherapeutics (light and wake therapy) as a class of interventions for affective disorders. *Handb Clin Neurol*. 2012;106:697-713.
4. Wulff K, Gatti S, Wettstein JG, Foster RG. Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease. *Nat Rev Neurosci*. 2010;11:589-99.
5. Terman M, McMahan I. *Chronotherapy. Resetting your Inner Clock to boost Mood, Alertness, and Quality Sleep*. New York, NY: Avery; 2012. (www.chronotherapy.us)
6. Münch M, Bromundt V. Light and chronobiology: implications for health and disease. *Dialogues Clin Neurosci*. 2012;14:448-453.
7. Benedetti F. Antidepressant chronotherapeutics for bipolar depression. *Dialogues Clin Neurosci*. 2012;14:401-411.