

# Circadian rhythms: Their role and dysfunction in affective disorder

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All humans are synchronised to the rhythmic light-dark changes that occur on a daily basis. Rhythms in physiological and biochemical processes and behavioural patterns persist in the absence of all external 24-hour signals from the physical environment, with a period that is close to 24 hours.

These rhythms are referred to as 'circadian', from the Latin 'circa diem' ('about a day'), and are attributable to internal biological clocks, driven by a major circadian pacemaker in the brain. The circadian pacemaker is entrained each day to the 24-hour solar cycle, which is the major 'zeitgeber' (literally time-giver). Other zeitgebers are food intake, activity, or social cues, e.g. the alarm clock. Good temporal entrainment allows for optimal performance at the right time of the day, because being able to anticipate future tasks allows the appropriate physiological and psychological preparation. However, our modern society often imposes deviations from the regular work-rest-scheme, as in shift work, which results in problems with entrainment.

Failure to adapt to environmental and societal time cues leads to misalignment of internal biological clocks. This 'dysentrainment' comes with enhanced risk of errors and accidents, loss of productivity, and health risks such as increased propensity for cancer, depression, sleep disturbances, gastrointestinal, metabolic and cardiovascular disorders, decreased immune responses and even [life span](#). Hence, people with circadian rhythm disruption caused by shift work often develop glucose intolerance, diabetes and hypertension, and maybe cancer. The recent

discovery of the core molecular circadian clock machinery has dramatically increased interest in the impact of circadian dysregulation on mental and physical health.

## **Molecular basis of circadian rhythms**

Circadian rhythms are directed by a master [biological clock](#) in a specific [brain structure](#) of the hypothalamus called the suprachiasmatic nuclei (SCN). Apart from the SCN, the body has circadian oscillators in all brain regions and peripheral tissues, for example the liver (Schulz & Steimer, 2009, Bechtold et al., 2010). The SCN is synchronised daily by environmental signals - mainly light (Wirz-Justice, 2006). Receiving information on lighting conditions directly from the retina, the SCN drives secretion of the pineal gland hormone melatonin as well as and many peripheral clocks, and their outputs modulate the SCN through feedback or feed-forward effects. Thus, in the body there is a hierarchy of interacting clocks (Schulz, 2007).

In all cells, the expression of many genes changes rhythmically over 24 hours. Specific circadian genes such as CLOCK, BMAL1, and PER are responsible for the main SCN clockworking machinery as well as subsidiary clocks in other parts of the body. In mice with mutations in time-keeping genes, deviant circadian sleep-wake and other rhythms can be observed. In addition, new interest in the role of circadian dysregulation in psychiatric disorders has arisen from the finding that a mutation in a core circadian clock gene induces hyperactivity, decreased sleep, and mania-like behaviour in mice (Turek, 2008).

Animal studies were the key development that brought the field to its present exciting position, because their findings suggested that 'clock genes' are directing the circadian rhythms in all physiological processes.

## **Circadian disturbances: clinical impact on affective disorders**

In healthy individuals, physiological and biochemical variables such as body temperature, cortisol and melatonin, thyroid stimulating hormone (TSH), noradrenaline and serotonin exhibit a circadian rhythm.

However, in patients with affective disorders, many of these circadian rhythms are disturbed in phase and amplitude (Schulz & Steimer, 2009; McClung, 2007).

For instance, women with depression have a greater degree of variability in the timing of physiological and endocrine rhythms. Dysregulation of circadian rhythms and sleep disturbances are also core elements of bipolar disorder, and might be involved in its pathogenesis (Dallaspesza & Benedetti, 2009). Clinicians have learned the enormous importance of synchronising agents (‘zeitgebers’) to entrain rhythms in patients with mood disorders, and how useful they are as novel treatments (e.g. light, melatonin).

With regard to major depressive disorder, almost all patients present with sleep disturbances and altered circadian rhythms including hormonal secretion, cardiac function, and body temperature. Sleep disruption is a major symptom in depression, with over 90% of patients showing sleep complaints that affect daytime functioning (Thase, 1999). Insomnia often appears before the onset of mood disorder symptoms and may persist into clinical remission: sleep disturbances are known to be a frequent residual symptom of depression, and the presence of insomnia marks an increased risk of relapse or recurrence. Sleep difficulties often are the key factor that causes depressed patients to seek medical help, and relief of sleep disturbances is important to encourage compliance with antidepressant medication. Associated with chronic depression, sleep disturbance can have as great an impact on health-related quality of

life as the mental illness itself (Katz & McHorney, 2002).

It is well known that changes in clinical state are accompanied by shifts in timing of the sleep-wake cycle. The switch out of depression is often associated with a spontaneous sleep deprivation. Conversely, a prescribed sleep deprivation can rapidly show antidepressive activity. Even more strikingly, a phase advance of sleep timing can induce longer-lasting antidepressant effects, suggesting an intimate functional relationship between sleep, its timing, and the depressive state.

In healthy individuals and in patients with affective disorders, there is a close link between circadian rhythms, the stability of mood, and sleep regulation.

## **How to reset the human biological clock in affective disorders**

In clinical practice, sleep disturbances in depression generally can be improved with effective antidepressant medication. However, commonly used modern antidepressants may be sleep-disturbing, particularly early in treatment, often to the extent that a sedative or hypnotic compound has to be prescribed concomitantly (Mayers & Baldwin, 2005). The search for novel antidepressants has focused primarily on drug development, with the role of psychotherapy and cognitive behavioural therapy to help depressive patients being well accepted. Surprisingly though, clinical application of chronobiological research, so called chronotherapeutics, appears not to fit into any conventional category, and is mostly neglected as putative treatment.

## **Chronotherapeutics**

Chronotherapeutics is defined as controlled exposure to environmental

stimuli that act on biological rhythms (e.g. light) or direct manipulations of sleep in order to achieve therapeutic effects in the treatment of psychiatric disorders. One major aim of chronotherapeutics is to synchronise impaired circadian rhythms. Today the range of chronotherapeutic indications not only comprises affective disorders such as major depression (seasonal and non-seasonal), bipolar disorder, and premenstrual dysphoric disorder and depression during pregnancy, but also bulimia nervosa, attention-deficit/hyperactivity disorder (ADHD), dementia, Parkinson's disease, and shift work and jet-lag disturbances (Wirz-Justice et al., 2009). Chronotherapeutic elements include light therapy, dark therapy or blue-blocking sunglasses, wake therapy (total or partial sleep deprivation in the second half of the night), phase advance of the sleep-wake cycle, and exogenously administered melatonin.

Light therapy as a zeitgeber has been used to resynchronise disturbed sleep schedules back to a more normal pattern. Light is also an effective antidepressant, acting on many of the same neurotransmitter systems and brain structures as antidepressant drugs. What is fascinating about light therapy is that it is the first treatment in psychiatry that developed directly out of basic neurobiology research related to seasonal hibernation and reproduction in rodents. Light therapy is effective for all groups of major depression - not only for the seasonal subtype (SAD), for which it is well recognized as the treatment of choice. As an adjuvant to antidepressants in unipolar depressive patients, or lithium in bipolar patients, morning light hastens and potentiates the antidepressant response. Light therapy shows benefit even for patients with chronic depression of 2 years or more, and provides a viable alternative for patients who refuse, resist or cannot tolerate medication, or for whom drugs may be contraindicated, as in antepartum depression (Wirz-Justice et al., 2005). In addition, light therapy has been successfully used in other psychiatric or neurological illnesses, including bulimia nervosa and Alzheimer's disease.

Dark therapy has yielded positive results to control symptoms in acute mania and to calm 'rapid-cycling' bipolar patients in the manic phase - a group with one of the highest suicide rates among the mentally ill. By keeping patients in the dark and extending rest-sleep for periods of 10 to 14 hours, the mania episode could be ended.

Dark therapy is theoretically interesting for its rapid effects, but is not very practical. One alternative at present being investigated is the use of blue-blocking sunglasses. Blue is the wavelength to which the circadian system is particularly sensitive, thus by blocking this range in the light spectrum we can induce "circadian darkness" while not impairing the patient's vision.

Melatonin is a hormone secreted by the pineal gland only at night, and is suppressed by light. Cued by darkness, melatonin is especially important for the onset of sleep, but is also involved in many other systems - cardiovascular, immune, endocrine, and metabolic. If rhythms are out of sync, as in depression, then melatonin rhythms also occur at the wrong time thus accentuating the sleep disturbance. Exogenously administered, melatonin acts as a zeitgeber to synchronise circadian rhythms. In addition, its thermoregulatory action is important to induce a rapid onset of sleep, though it is not a sedative agent per se.

Wake therapy (a single night's sleep deprivation) is the most rapid antidepressant available today: approximately 60% of patients, independent of diagnostic subtype, respond with marked improvement within hours. A single night's sleep deprivation induces similar brain changes as many weeks of antidepressant drugs (Benedetti and Smeraldi, 2009). Relapse after recovery sleep can be prevented by daily light therapy, concomitant administration of antidepressants (SSRIs), lithium (for bipolar patients), or a short phase advance of sleep over 3 days. Combinations of these interventions show great promise (Wirz-Justice et al., 2005, 2009).

Despite the growing evidence for the efficacy of the available chronotherapeutic methods, it is surprising how limited the use of these treatments still is. Given the rapid action of chronotherapeutics, lack of side effects, and easy combination possibilities, how can sleep physicians and psychiatrists be educated about their use? Perhaps it is the patients that need to be educated, who are much more interested in non-pharmaceutical approaches? Obviously, treatments that are not patentable do not make profits for industry, thus denying the commercial marketing model used for drugs. Because they do not go through official clinical trial registration at federal regulatory agencies, chronotherapeutic treatments are not on the list for insurance reimbursement. On account of their simplicity, chronotherapeutics contrast with high-tech medicine, and for this reason are often not taken seriously.

## **Clinical implications**

In clinical practice there is still rather widespread ignorance about circadian [sleep disturbances](#) and chronotherapeutics in spite of the significant evidence base. How can wider dissemination of chronotherapeutics be achieved?

First, enterprising doctors should try them out. Only with first-hand experience does the reality of efficacy and response emerge.

Second, the techniques should be taught in medical school and during residency - since it is the younger generation that is most open to change and use of cogent alternatives to medication. The nonprofit, multilingual patients' website [www.cet.org](http://www.cet.org) and clinicians' website [www.chronotherapeutics.org](http://www.chronotherapeutics.org) of the Center for Environmental Therapeutics (CET) illustrate some first attempts to meet this Phase 3 educational challenge.

Third, through its societies, the field of chronotherapeutics needs to

advocate recognition for reimbursement.

In the treatment of affective disorders, chronotherapeutics offer a new synthesis of non-pharmacologic interventions designed to accelerate remission in patients with depression and bipolar disorder. Combining chronotherapeutics with concomitant or follow-up medication shows great promise.

Given the urgent need for new strategies to treat patients with residual depressive symptoms, clinical trials of wake therapy and/or adjuvant light therapy, coupled with follow-up studies of long-term recurrence, are of high priority.

## **Conclusion**

Circadian dysfunction can have drastic consequences on brain functions. Increasing evidence suggests that disrupted temporal organisation impairs behaviour, cognition, and affect (Benca et al., 2009).

Disruption of circadian clock genes impairs sleep-wake cycle and behavioural rhythms, which may be implicated in mental disorders. Several different psychiatric disorders, including depression, bipolar disorder, seasonal affective disorder (SAD), schizophrenia, and borderline-related disorders are commonly associated with abnormalities in circadian rhythms.

In particular, biological clocks play a major role in the pathophysiology of affective disorders. Synchronising impaired circadian rhythms, improving sleep, or paradoxically staying awake most of the night can be extremely helpful to treat patients with depression and bipolar disorder.

Chronotherapeutic combinations of light and wake therapy achieve fast results and, by reducing residual symptoms, also minimise relapse over



many months. In addition, chronotherapeutics seem to be a major facilitator of drug response, and, in combination with antidepressants, a promising method to stabilise patients over the long term.

Researchers are working on extending our knowledge concerning pharmaceutical and non-pharmaceutical ways to alter circadian rhythms. Recent discoveries of molecular clocks responsible for the generation of [circadian rhythms](#) provide novel insights into temporal disruption, offering new therapeutic avenues for the treatment of affective disorders.

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