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REVIEW

# Clinical parameters of circadian rhythms in affective disorders

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**Abstract**

Many affective disorders show episode cycling and the classic symptoms of these disorders show rhythmicity, such as diurnal variation in mood. There are several plausible stress–vulnerability models that suggest links between these observed phenomena and the circadian system. For example, an individual with increased sensitivity to social rhythm disruption may be more at risk of circadian rhythm (CR) dysregulation. Furthermore, there are hypothesized neurobiological mechanisms that may explain how CR dysregulation might lead to sleep, activation, and mood changes in unipolar and bipolar disorders. There are gaps in our understanding, but this paper highlights that clinical measures of sleep and activation are increasingly useful for monitoring the onset and course of affective disorders. Also, evidence suggests that CR disruptions may represent core elements not simply epiphenomena of affective disorders.


There is evidence of periodicity, including the seasonality of some depressions (seasonal affective disorder; SAD) and cyclicity of some bipolar sub-types (rapid cycling disorder; RCD), and of rhythmic fluctuations in episode symptoms such as diurnal variation in mood and activation levels. These features have led to hypotheses that dysregulation of circadian rhythms (CRs) may represent an important phenotype for major affective disorders.

This paper briefly describes the circadian system and then explores clinical parameters representing direct or proxy measures of disturbed CR. A small set of studies from the literature was selected to demonstrate how researchers have examined whether these variables (i) differentiate 'at-risk' phenotypes for affective disorders from healthy controls, (ii) differentiate euthymic affective disorder patients from healthy controls, (iii) contribute to relapse prodromes, and/or (iv) whether early symptoms of relapse are directly or indirectly linked to CR disruptions. As there are a number of reviews that focus on CR disruption in unipolar depressions, this paper will focus on some examples of recent research on bipolar disorders (BP).

## 1. The circadian system

The circadian system is an endogenous, self-sustaining program that provides temporal ordering to a variety of physiological and behavioral events (Wirz-Justice, 1995). There are clear patterns of brain wave activity, hormone production, cell regeneration, and other biological activities linked to this daily cycle (Schibler et al., 2003). In humans, the

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CR period is about (though not exactly) 24 h, but phase differences can exist within this, e.g., advanced or delayed sleep timing. Periodicity is more strongly determined genetically than phases, while phases are more open to other influences than periodicity (Emilien and Maloteaux, 1999).

Wehr et al. (1983) and others describe that the process of aligning endogenously generated rhythms with the phase of regular environment oscillations is called entrainment and environmental cues that each day reset the CR are called zeitgebers (from the German, meaning 'time givers'). The most potent zeitgeber is the daily alternation of light and dark, which entrains CR by resetting the central pacemaker (or master clock) in the suprachiasmatic nucleus (SCN) of the hypothalamus (Ehler et al., 1988; Klien et al., 1991). The SCN is probably required for the coordination, but not for maintenance of peripheral circadian clocks, e.g., in the liver, gastrointestinal tract, and other tissues (Goodwin and Jamison, 2007).

Research demonstrates that there are a range of non-photic zeitgebers (e.g., exercise). Although less well understood, these zeitgebers probably have weaker effects on phase or amplitude (Dijk and Czeisler, 1995). Also, some of these zeitgebers, e.g., feeding (or the absence of food intake), act on peripheral oscillators. Social zeitgebers are social and occupational routines, demands, tasks and interpersonal relationships that can entrain the master clock. They may act directly or indirectly on the SCN, since they determine the timing of meals, sleep, physical exercise, and outdoor light exposure (Schibler et al., 2003).

## 2. Circadian rhythm dysregulation

In healthy adults, the circadian system usually adjusts to small or gradual changes in input signals (e.g., seasonal change in daylight hours), but takes time to adapt to sudden or large changes (Benca et al., 2009). For example, jet lag is characterized by about 2–5 days of fatigue, disorientation, and insomnia, while shift work may lead to more prolonged disturbances of sleep, often accompanied by irritability, apathy, reduced physical activity, impaired cognitive functioning, or poor appetite, or a combination of these (Boivin, 2000; Frese and Semmer, 1986). However, in individuals at risk of affective disorders, loss of entrainment resulting from changes in photic and non-photic zeitgebers may precipitate manic or depressive relapses (Malkoff-Schwatz et al., 1998). These adverse outcomes may be explained if some individuals have a greater predisposition to adapt poorly to environmental challenges (Goodwin and Jamison, 2007).

Stress–diathesis models hypothesize that biological factors increase individual risk for the development of a fragile circadian system (see Hallonquist et al., 1986 and Wirz-Justice, 1995). Psychological vulnerabilities are also implicated, such as an altered intensity of cognitive, affective, and behavioral responses to environmental cues because of hypersensitivity to certain types of stimuli (and/or reduced sensitivity to other cues). For example, Havermans et al. (2010) demonstrated that 'daily hassles' were rated as more stressful and produced a greater negative affective response in those with subsyndromal depressive symptoms.

Table 1 highlights several potential clinical markers of CR sensitivity, many of which can be assessed by questionnaire assessment of personality style, such as premorbid neuroticism (e.g., Murray et al., 2002), or of behavioral dispositions, such as defined by the learned helplessness models (e.g., Healey and Williams, 1988).

## 3. Indicators of dysregulation

Several well-established direct or indirect indicators of CR functioning are described in the research literature (see Table 2). In depression, there is robust evidence for daily changes in the amplitude of core body temperature rhythms and of endocrine abnormalities such as altered 24-hour secretion patterns for cortisol, prolactin, TSH, and melatonin. Observed changes in sleep pattern in affective disorders include diminished amplitudes, shorter latencies for rapid eye movement (REM) sleep and other sleep phase advances or delays. It is not yet established whether these changes are a

**Table 1** Biological and psychosocial factors that may predispose to or precipitate circadian dysregulation in affective illness. Adapted from Hallonquist et al., 1986 and Wirz-Justice, 1995.

| Factors | Biological | Psychological |
|---|---|---|
| Proximal (precipitating factors) | Season<br>Maturation/aging hormonal status<br>Internal dysregulation associated with physical illness or primary sleep disorder | Changes in temporal order:<br>Trans-meridian air travel (jet lag)<br>Shift work<br>Social Rhythm Disrupting (SRD) Events: e.g.,<br>Family, social, work, meal disruption<br>Breakdown/loss of social interactions<br>Major life events involving separation or death |
| Distal (predisposing factors) | Genetic<br>Perinatal factors<br>CR pacemaker characteristics: e.g.,<br>Abnormal period<br>Abnormal entrainment<br>Altered sensitivity and/or<br>Response to zeitgebers | Developmental: e.g.,<br>Repetitive early life stress<br>Negative and/or chaotic emotional environment<br>Increased sensitization to negative life events and/or personality style, e.g.,<br>High premorbid neuroticism,<br>Learned helplessness |