Review Article

Circadian rhythms and sleep in bipolar disorder


Objective: Biological rhythm pathways are highlighted in a number of etiological models of bipolar disorder, and the management of circadian instability appears in consensus treatment guidelines. There are, however, significant conceptual and empirical limitations on our understanding of a hypothesised link between circadian, sleep, and emotion regulation processes in bipolar disorder. The aim of this article is to articulate the limits of scientific knowledge in relation to this hypothesis.

Methods: A critical evaluation of various literatures was undertaken. The basic science of circadian and sleep processes, their involvement in normal emotion regulation, and the types of evidence suggesting circadian/sleep involvement in bipolar disorder are reviewed.

Results: Multiple lines of evidence suggest that circadian and sleep-wake processes are causally involved in bipolar disorder. These processes demonstrably interact with other neurobiological pathways known to be important in bipolar disorder, but are unique in that they are open to behavioural manipulation.

Conclusion: Further research into biological rhythm pathways to bipolar disorder is warranted. Person-environment feedback loops are fundamental to circadian adaptation, and models of circadian pathogenesis (and treatment) should recognize this complexity.

Introduction and overview

Circadian rhythm hypotheses have been prominent in the explanation of bipolar disorder (BD) for more than 20 years (1, 2). Changes in sleep are part of diagnostic criteria (3), and stabilising daily rhythms is recognised as therapeutic in consensus treatment guidelines (4, 5). Biological rhythmicity is also a priority for patients, who report significant concern about their sleep (6) and readily appreciate the importance of rhythm stability (7). In short, there is consensus that biological rhythms play a critical role in the emotion dysregulation at the heart of BD. Biological rhythm approaches are compatible with other neurobiological explanations of BD, and this article includes numerous examples of overlap between circadian/sleep pathways and other targets of investigation.

The aim of this review article is to encourage further research into these important pathways by tracing the limits of scientific knowledge about biological rhythms in BD. We first outline the basics of circadian rhythms and sleep, highlighting the challenge of empirically separating these two factors. In the next section, literature on circadian and sleep moderation of emotion is reviewed, largely focusing on nonclinical populations. Evidence for an association between biological rhythms and BD is detailed next, and causal inferences considered. The penultimate section critically considers potential mechanisms of

1 The term biological rhythms is used to encompass both circadian and sleep-wake processes.

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biological rhythm action in BD, particularly the impact of clock genes and the putative role of rapid eye movement (REM) sleep in emotion regulation. Finally, we review clinical implications of the fact that biological rhythmicity is modified by behaviour.

**Circadian rhythms and sleep**

**Circadian system**

The endogenous circadian time-keeping system, strongly conserved across species, is adapted to optimise engagement with the earth’s cyclic environment by predicting critical environmental change (8). In mammals, the circadian pacemaker responsible for the temporal internal organisation and generation of endogenous rhythms of approximately 24 hours is located in the hypothalamic suprachiasmatic nucleus (SCN) (9). At the molecular level, intrinsically rhythmic cells of the SCN generate self-sustained rhythmicity via an autoregulatory transcription-translation feedback loop involving the genes: circadian locomotor output cycles kaput (Clock), Bmal1 (also known as Arntl), period homologue 1 (Per1), Per2, Cryptochrome 1 (Cry1), and Cry2 (10). The SCN output rhythm arises from nonlinear dynamic interaction between the cells in the SCN (11, 12).

The endogenous period generated in the SCN is close to but generally not equal to 24 hours. The process by which the pacemaker is both set to a 24-hour period and kept in appropriate phase with seasonally shifting astronomical day length is called entrainment. An important property of the circadian system, therefore, is its fundamentally open nature, and this open nature includes feedback to the pacemaker from clock-controlled activity of the organism (13, 14). Entrainment occurs via zeitgebers (environmental events that can affect phase and period of the clock), the most prominent of which is the daily alternation of light and dark due to the planet’s rotation (15). To a lesser degree, the SCN is also responsive to nonphotic cues, including arousal/locomotor activity, social cues, feeding, sleep deprivation, and temperature (16).

As shown in Figure 1, the circadian system is a network including multiple feedback loops (14). The peripheral clocks (extra-SCN oscillators in many organs and tissues) that the SCN orchestrates impact on the central clock. For example, redox potentials within cells are affected by circadian modulation of the mitochondrial oxidative phosphorylation pathway, but redox potential in turn affects the concentrations of oscillator components (including Clock, Mop3 and NPAS2) and thereby the rate of reactions in the SCN (17, 18).

The output rhythms themselves also affect the clock. For example, one of the major functional targets of SCN output is the pineal gland and its release of melatonin. There is a processing loop from the SCN to the pineal gland and back, supporting a process whereby when melatonin is synthesized (during the subjective night), it is detected by receptors in the SCN (MT1 and MT2), which moderate clock resetting at dusk and dawn (19). The SCN also appears to modify its own inputs (e.g., 20, 21). For example, lesion studies in rats suggest that retinal circadian rhythms in Per2 messenger RNA are dependent on SCN functioning (22).

Functionally, the most important clock feedback is behaviour itself. Behaviour influences the circadian clock directly (arousal is a zeitgeber) (16), but also indirectly via gating of light exposure. This is demonstrated clinically in the use of light treatment for seasonal affective disorder (23, 24) and the use of social rhythm stabilization to moderate relapse risk in BD (25, 26; see below). Given circadian involvement in the sleep-wake cycle, evidence for the effectiveness of cognitive-behavioural interventions for insomnia also speaks to this important feedback loop (27).

![Fig. 1. Schematic representation of the circadian system. SCN = suprachiasmatic nucleus.](image-url)
Sleep

Phylogenetically, sleep is a more recent and less ubiquitous adaptation than circadian rhythmicity (28). The specific adaptive function of sleep is unknown, but sleep is widely believed to perform a restorative function associated with the strengthening of immune function, somatic growth, and an anabolic metabolic state (29). Evidence is also accumulating for sleep’s role in particular types of cognition (30, 31), memory consolidation, and brain plasticity (32–35).

Based on characteristic physiological patterns, normal sleep can be divided into two distinct states: REM and non-REM (NREM). During REM (or paradoxical) sleep, the brain is highly activated, the muscles of the body are paralyzed, and dreaming occurs. In NREM, growth hormone is preferentially secreted and protein synthesis is increased, leading to the view that NREM may be critical for energy conservation and restoration. Characteristic electroencephalograph (EEG) patterns support NREM sleep being further categorized into substages: 1 (drowsiness, transition to sleep, lowest arousal thresholds), 2 (light sleep), and 3 and 4 (deep sleep, highest arousal thresholds). Together, stages 3 and 4 are often called delta or slow wave sleep (SWS) (36).

On a typical night, sleep of a young adult begins in stage 1 NREM and progresses through deeper NREM stages. The first episode of REM sleep occurs approximately 80–100 min after sleep onset. Thereafter, NREM sleep and REM sleep cycle with a period of approximately 90 min. NREM stages 3 and 4 concentrate in the early cycles and REM sleep episodes lengthen across the night. Therefore, in a normal night of sleep, SWS predominates in the early part of the sleep phase, while REM is more prevalent later in the night. Indeed, we are most likely to wake through the gate of REM sleep.

The relationship between circadian and sleep processes

The sleep-wake cycle is regulated by two processes, one of which is the clock-like circadian system described above (typically called Process C). The second factor is sleep’s (hourglass-like) homeostatic self-modulation [Process S (37)]. Process S is accumulated during wakefulness, dissipates during sleep, and regulates duration and structure of sleep on the basis of the history of sleep and wakefulness. The bidirectional interaction between Processes C and S predicts the propensity, timing, and internal structure of sleep (38–40).

For what follows, it is important to note that protocols for investigating the interaction between Processes C and S are unsuitable for people diagnosed with BD. Under normal conditions, Process C and Process S operate in synchrony (41), and in the field we can only observe the sleep-wake cycle, which is a complex endpoint of volition, SCN output, and the sleep homeostat (Fig. 2). Most of what we know about separate circadian and sleep processes, therefore, comes from laboratory studies. In the forced desynchrony (FD) protocol, a non-24-hour sleep-wake schedule (typically 28 hours) is enforced. Under these conditions, the circadian oscillator continues to cycle at approximately 24 hours and desynchronises from the sleep-wake cycle which adopts the enforced 28-hour period, thereby enabling separate estimate of circadian and sleep-homeostatic components (42). The sleep disruption and isolation of the multiday FD protocol make it unsuitable for individuals vulnerable to emotion dysregulation, and therefore fundamental questions about Process C and S involvement in BD cannot be directly tested.

The neurobiology of the C × S interaction is not fully understood. Arousal is mediated by neurons of the ascending reticular activating system which project to the thalamus and basal forebrain (43, 44). Research by Saper and others (45–47) suggests that the mechanism by which arousal is curtailed to produce sleep involves the ventrolateral preoptic nucleus (VLPO), a group of neurons in the hypothalamus which, via release of galanin and GABA, inhibits activity of the locus coeruleus, raphe nucleus, and the tuberomammillary nucleus. Mutual inhibition between arousal circuits and the VLPO ensures extended periods of wake undisturbed by sleep and vice versa. Stability in sleep or wake, and rapid switching between the two states, is achieved by a putative bistable switch (45).
switch is modulated by a circadian alerting signal deriving from the SCN, and, on the other side of the switch, the homeostatic sleep drive. The neural mechanisms of the sleep homeostat are unknown, but there is growing evidence that the wake-linked accumulation of the endogenous neuromodulator adenosine may be involved (48, 49).

Sleep, circadian function, and affect

As in the study of other psychiatric disorders, it is not uncommon to conceptualize BD as the extreme clinical manifestation of a neurobehavioral trait that is distributed throughout the population. Specifically, BD can be characterised as a pathologically elevated propensity to emotional dysregulation (50–52). Before reviewing the known associations between biological rhythms and BD, it is therefore useful to review findings linking biological rhythms to emotion regulation in normal populations.

Circadian interactions with emotion

The circadian system modulates current mood state, particularly positive affect (53–56), and challenges to the circadian system, such as shift work and jet lag, have negative consequences for mood (57–59). Under naturalistic conditions, emotional state also moderates circadian function via its influence on social rhythms, light exposure, arousal, and sleep (16, 60). Bidirectional influence can also be traced at the neurobiologic level: afferents from the SCN project via the paraventricular thalamic nucleus to the mesolimbic dopaminergic reward system (61), while emotion circuits impact circadian (and homeostatic) aspects of sleep regulation (62, 63).

Sleep disturbance and emotion regulation

Behavioural data support the popular assumption that sleep disturbance strongly increases negative mood, irritability, and affective volatility (e.g., 64–69). Sleep loss has been shown not only to increase negative emotional response to goal-thwarting events, but also to decrease positive emotional responses to goal-enhancing events (70). High levels of emotional arousal can, in turn, disturb sleep, raising the possibility of a vicious cycle between sleep disturbance and emotion dysregulation (71). At the neural-systems level, sleep deprivation has been linked to decreased medial-prefrontal cortical activity and increased amygdala activation, a distribution of activation consistent with impaired top-down regulation of emotional responses (72).

Particular importance of REM sleep in emotion regulation

The sleep state most strongly regulated by the SCN, REM sleep, may be particularly important in emotional processing and emotion regulation. Key findings include correlations between presleep mood and REM parameters, prospective associations between dream content and psychological outcomes, and REM-facilitated recall of emotional information (73, 74). There is also converging evidence concerning the role of REM in emotional processing (75–79).

The neurobiology of dreaming is an area of growing interdisciplinary interest. Stickgold and colleagues (33, 80) proposed that dreaming is the conscious awareness of critical ‘offline’ cortical generation functions occurring during sleep. In this model, dreaming is distinguished by the activation of neural networks supporting weak cortical associations in the absence of dorsolateral prefrontal cortex or hippocampal feedback, but in the presence of active error detection circuits (in the anterior cingulate cortex) and affective evaluation of errors by the amygdala and orbitofrontal cortex (81, 82). Potential implications of REM neurobiology for emotion regulation in BD are considered below in the subsection ‘Sleep-specific mechanisms’.

Neurotransmitters and the sleep – circadian – emotion interaction

At least two neurotransmitter circuits are critical in the link between biological rhythms and emotion. First, dopaminergic pathways, especially cells of the ventral tegmental area (VTA) and zona compacta of the substantia nigra (SNc), are strongly implicated in reward motivation and positive affects (83–85). Dopamine has been called a key substance in the regulation of sleep-wake (86), and dopaminergic neurons of the VTA and SNc are again implicated (87), particularly in REM sleep (88). Dopaminergic pathways also have multiple interactions with the SCN (e.g., 55, 61, 89, 90). Second, serotonergic pathways have pronounced (albeit complex) relationships with anxiety and stress responses (91). Serotonergic pathways are critical in circadian function (92) [and vice versa (93)], sleep per se (46, 94), and the interaction between stress and sleep (67, 95–98).

From normal populations to patients with BD

The above review presents strong behavioural evidence for the notion that emotion and emotion
regulation are associated with circadian function and sleep. Neuroanatomical pathways subserving these associations have been outlined, and the interacting role of two critical neurotransmitters (dopamine and serotonin) has been described. It seems reasonable to propose that the same relationships hold in patients with BD, and indeed to hypothesize that the symptoms of mood episodes in BD may be attributable, at least in part, to the pathways described here. It is particularly noteworthy that an independent literature argues for dopaminergic and serotonergic circuits as critical pathways in BD (e.g., 99–102).

Until recently, there was little integration between research into biological rhythm and neurotransmitter approaches to psychopathology. Early steps in this direction are captured in the hypothetical model of Figure 3 [adapted from Harvey et al. (102)], in which emotion regulation and sleep disturbance are proposed as the overt manifestation of interactions between dopaminergic, serotonergic, and circadian/sleep biology.

It is worth noting three caveats on generalizing from nonclinical to BD populations. First, the multiplicity of BD’s clinical manifestations is a challenge to generalization. For example, the sleep disturbance common in mania (decreased need for sleep) contrasts with that in bipolar depression (insomnia and hypersomnia) (103). Second, much of what we know about sleep and emotion regulation is based on sleep-deprivation studies, while hypersomnia is a common symptom of bipolar depression. Finally, some provocative disjunctions need to be recognized: (i) in nonclinical samples, sleep restriction may decrease reward sensitivity (70), while mania appears to involve positive feedback between sleep loss and reward seeking (104); and (ii) in nonclinical samples, REM sleep appears to support emotion regulation (72, 105), while in mood disorder samples, increased density and decreased latency of REM are associated with pathology (106; see below).

Sleep, circadian function, and mood symptoms in BD

A number of specific links have been demonstrated between BD and circadian and/or sleep function. Our aim here is to consider critically the nature and implications of these known associations, and it is useful to group findings as shown in Table 1.

The findings summarised in Table 1 indicate that most phases of BD (depressed, manic, episode prodrome, and interepisode periods) are cross-sectionally associated with sleep and/or circadian rhythm abnormalities. Clinical research shows that disturbed sleep affects quality of life in BD (107, 108), and, as reviewed above, sleep disturbance is detrimental to emotion regulation. Evidence that BD is associated with sleep disturbance therefore suggests that outcomes in BD can be improved by addressing sleep difficulties across phases of the disorder. Such interventions are briefly introduced below in the section ‘Psychosocial interventions targeting biological rhythms in BD’.

Beyond the immediate clinical implications of poor sleep, a range of evidence also suggests that biological rhythm disturbance is etiologically involved in BD. Not only is there prospective data linking sleep to mood in BD, but sleep changes reliably precede episodes (especially mania) and correlate with symptom load. Most strikingly, manipulation of sleep (sleep deprivation) improves bipolar depression and can induce hypomania/mania in some patients. This conclusion aligns with current clinical practice, in which sleep monitoring is a central relapse prevention strategy (109).

The literature cited in Table 1 also provides support for circadian dysfunction as a causal pathway to BD. First, relapse can be precipitated by zeitgeber challenge (particularly light manipulation), and effective treatments for acute episodes moderate circadian parameters. Second, a range of data suggests that ‘circadian instability’ may act as a traitlike vulnerability or diathesis to BD. For
Neurobiology shared between BD and biological rhythms

- Circadian and sleep function are subserved by the same brain regions (153) and neurotransmitters (e.g., 99, 100) are implicated in mood disorder.
- Polymorphisms in circadian genes have been associated with symptoms of BD in preclinical and human studies (129, 147, 162, 181).

Biological rhythms as diatheses to BD

- Sleep disturbance and instability of 24-hour rhythms continue when BD patients are not acutely ill (6, 182–185).
- Dysregulation of 24-hour activity rhythms has been reported in a familial high-risk sample (186) and in individuals at risk of hypomania (187).
- Neuroticism, the primary (albeit nonspecific) temperamental predisposition to BD, may be associated with circadian instability (119).
- Biological sensitivity to light, as measured in nighttime suppression of the pineal hormone melatonin, has been proposed as a trait marker of vulnerability to BD (188).
- Delayed circadian phase of melatonin secretion has been reported in euthymic BD patients (189), and BD patients self-report as more evening type (190).

Cross-sectional associations

- Some clinical features of BD are timed phenomena: diurnal variation in mood and early-morning wakening in depression, as well as seasonal and other cyclic variation in symptoms, are suggestive of circadian involvement (142).
- Circadian rhythms (including activity, body temperature, melatonin, cortisol and thyrotropin) are altered in episodes of BD (see 111, 191 for a review).
- Mania is strongly associated with decreased need for sleep, and insomnia and hypersomnia are both reliably found in bipolar depression (see 103 for a review).
- Within BD, short sleep duration is associated with more severe symptomatology, while both short and long sleep duration are associated with poorer function and quality of life (192).
- Episodes of BD have been associated with sleep polysomnographic changes (e.g., 193–195). The most consistent finding is abnormalities of rapid eye movement (REM) sleep in both mania and bipolar depression [typically shorter latency and increased density (see 103)].

Predictive relationships

- Episodes of BD can be precipitated by zeitgeber challenges, including seasonal change and time-zone travel (see 196 for a review).
- Sleep disturbance is the most common prodrome of mania and a significant prodromal symptom of bipolar depression (197). Altered sleep often precedes deterioration in clinical state and worsens further during an episode (197–199).
- Prospective evidence of a complex association between sleep length and mood change in BD has been found in a number of studies (198, 200–203).

Experimental and treatment effects

- Deliberate sleep deprivation is a same-day powerful treatment for bipolar (and unipolar) depression (203, 204). Maintenance of the therapeutic effect beyond the next sleep phase is a target of current research (171).
- In a recent study, combined sleep deprivation, sleep phase advance and timed light was an effective adjunctive intervention for bipolar depression (205).
- Bright light can induce symptoms of mania (171) and has significant effects on bipolar depression (206).
- Experimentally induced sleep deprivation induces hypomania or mania in a proportion of patients (199, 203).
- Bright light can induce symptoms of mania, and ‘dark therapy’ has been found to stabilize patients with rapid-cycling BD (171, 207).
- Effective treatments for BD (lithium, antidepressants, anxiolytics, electroconvulsive therapy) affect circadian function (208–210).
- Lithium and selective serotonin reuptake inhibitors impact genes involved in circadian function (92, 132, 211, 212).
- Future course in BD is predicted by sleep disruption and REM density (106).
- Effective psychosocial treatments for BD decrease REM density (213, 214).
- Improved social rhythmicity decreases relapse in BD (26).

Mechanisms underpinning biological rhythm involvement in BD

The mechanisms by which biological rhythms affect the development, course, and treatment of BD are not known. Early hypotheses emphasized gross abnormalities in circadian function, including short intrinsic period of the oscillator (114), phase advance (115), phase delay (116), and attenuated circadian amplitude (117–119). The relation between Processes C and S has also been implicated (120), and Process S itself has been
hypothesised to underpin the therapeutic effect of sleep deprivation (121). Coupling to external zeitgebers is critical in some models (26, 118, 122, 123). Physiological investigations of these broad hypotheses have been scarce over the past decade (2), and the methodological issues flagged above are a barrier to progress. Promising foci of contemporary research are circadian genes and the role of REM sleep in emotional processing, as discussed next.

Circadian genes

As research into broad circadian hypotheses has waned, the study of the genetics of circadian function in BD has expanded. Traditional candidate gene studies have found trends for an association between BD and the CLOCK gene (124, 125), but findings are inconsistent (126). A single nucleotide polymorphism in the 3' flanking region of CLOCK has also been associated with clinical features of BD, namely, patterns of more activity in the evening, delayed sleep onset and less sleep (127), higher rates of initial, middle and early insomnia (128), recurrence of illness episodes (128), and changes in neural response (129).

Several studies show that the mood stabilizer lithium affects circadian rhythms through the glycogen synthase kinase 3 beta gene (GSK-3β), which is a central regulator of the circadian clock (130–132). Valproic acid may act via the same intracellular signalling pathway (133, 134). Investigations of associations between BD, its clinical features, and GSK-3β have not been consistent (e.g., 135–137). Findings for an association with NR1D1 gene (regulation of which by GSK-3β is important for clock function) are also mixed (138, 139).

Other circadian genes for which some support exists include PER3 (140, 141), ARNTL (141, 142) and TIMELESS (142). In addition, Shi et al. (124) reported an interaction between CLOCK and two other genes of interest for their potential circadian function (BHLHB2, CSNK1E). In one genome-wide association study, the gene VGCNL1 (the mouse homolog of which regulates circadian function) had a significant association with caseness (143). Larger genome-wide studies have not identified circadian gene associations (144, 145).

Preclinical studies observing the effect of gene mutations have been a fruitful source of hypotheses. Mice with a mutation in the CLOCK gene show robust sensitization to cocaine and increases in the preference for cocaine (146, 147). These mice also have increased dopaminergic activity in the VTA which may be responsible for the increase in the reward value of cocaine (146). Notably, CLOCK mutant mice also show mania-like behaviour which is reversed by lithium treatment (147), and this reversal is mediated by altered regulation of dopamine release in the VTA (146).

Evidence for a BD-relevant pathway linking circadian genes to the dopaminergic reward system is consistent with the strong comorbidity between BD and substance abuse (148), the association between manic states and psychostimulant use (149), and the action of atypical antipsychotic medications for mania (134). A dopaminergic reward × clock gene circuit has been reliably demonstrated in nonhuman species (e.g., 150, 151) and is strongly implicated in human mood regulation (55, 152–156).

It is important to situate these clock gene findings within the broader genetics of BD. Like other psychiatric disorders, BD is probably inherited polygenetically, with numerous genes adding small effects to overall risk (143). Evidence from human studies suggests that these genetic effects are probabilistic, nonspecific, contingent on gene × gene × environment interactions, and causally remote from the phenotype (157). Given small genetic effects on risk, it is not surprising that failure to replicate associations is common, and that researchers have sought to refine the phenotype under investigation. In particular, endophenotypes [quantitative phenotypes intermediate between the genotype and the disorder (158)], are a major focus of contemporary study. Disturbance of circadian function is commonly forwarded as a candidate endophenotype for BD (e.g., 142, 159–163).

Sleep-specific mechanisms

The potential importance of REM sleep in normal emotion regulation was reviewed above. Recently, this hypothesis has been extended to make predictions about the role of REM in psychiatric disorders, including BD (105, 164). Walker and colleagues propose that the neurobiology of REM sleep is critical in processing episodic emotional memories, and describe three features of REM neurobiology that together support this role. First, emotional experiences of the preceding day are reactivated by increased arousal in limbic and paralimbic structures. Second, integration of the emotional experiences with other aspects of semantic memory are facilitated by dominant theta oscillations in subcortical and cortical nodes. Finally, REM occurs in the absence of noradrenergic arousal, suggesting a brain state that supports emotional processing unencumbered by high
anxiety. In parallel, the REM state is dominated by cholinergic neurochemistry, providing an ideal substrate for neocortical consolidation of memory information. Taken together, REM sleep seems adapted to progressively decouple emotions from the memory of emotional experiences, potentially improving next-day mood (164).

Under this model, the increased REM density seen in unipolar and bipolar depression (106) has two implications. First, it may represent a failed attempt to depotentiate negative emotional experiences across nights. Second, because emotional memories are preferentially encoded during REM sleep (34), increased REM density may pathologically reinforce negative self-narratives, maintaining negative moods postsleep (105). The translational implications of this ‘sleep to forget, sleep to remember’ model have not been teased out, and there are some contradictory data (e.g., 165), but the model raises the exciting possibility that manipulating sleep architecture may therapeutically regulate the balance of emotion and memory of past experiences. Important questions for future research include comparisons of the REM-emotion regulation association in healthy controls versus patients across the phases of BD.

**Psychosocial interventions targeting biological rhythms in BD**

Interactions between biology and psychosocial factors cannot be ignored in a biological rhythm approach to BD (166). The circadian system is adapted to be open to external cues, and environmental manipulations (particularly light exposure) have predictable effects on amplitude and phase of the endogenous oscillator (167, 168). Under naturalistic conditions, human exposure to zeitgebers is gated by behaviour, prominently the sleep-wake cycle (Circadian rhythms and sleep). The sleep-wake cycle is in turn moderated by volitional and social factors, and mediated partly through cognitive mechanisms (Sleep, circadian function, and affect). Biological rhythms therefore function as an open-loop system crossing multiple levels of persons and their environment (21). Psychosocial factors are integral to a biological rhythm explanation of BD, a fact which underpins the recent development of some novel adjunctive psychosocial interventions for BD.

The social zeitgeber hypothesis proposes that fundamental circadian instability in BD can be moderated by increased stabilization of daily rhythms and zeitgeber exposure [which could include light itself (112)]. This hypothesis takes clinical form in social rhythm therapy (169), which is a largely behavioural psychotherapy aimed at helping patients maintain stability in their social rhythms and so reduce the risk of relapse. In the treatment of BD, social rhythm therapy is typically integrated with principles from interpersonal psychotherapy in a treatment known as interpersonal and social rhythm therapy (IPSRT) (169). IPSRT has proven effective in two large studies (26, 170).

Interest in biological rhythm management is expanding alongside growing research into adjunctive psychosocial treatments for BD (112, 171–173). Rhythm stabilization is a core component in most adjunctive psychosocial treatments for BD (113), including cognitive behavioural therapy. Improving sleep quality is an important component of rhythm stabilization, and has functional benefits in its own right (102, 103). Interestingly, management of the sleep-wake cycle is a commonly reported well-being strategy amongst people with BD (174). Our qualitative investigations suggest that this strategy is appealing not only because it is judged effective, but also because it is empowering for patients to understand that a core element of BD biology is partly under their control (175).

Particularly interesting are treatments for bipolar depression [the most common and most resistant manifestation of BD (176)] using combinations of zeitgeber manipulation and pharmacotherapy. For example, Benedetti and colleagues (177) have shown that progressive sleep phase advance across three days can sustain the antidepressant effects of total sleep deprivation, and that the chronobiological mechanism is enhanced by lithium.

Chronotherapeutic interventions are therefore an important target for further study. Future research into these interventions should seek to identify moderators (e.g., light sensitivity, severity and diagnosis, temperament, gender) and mediators (e.g., light-dark cycle exposure, sleep quality, sleep architecture, circadian rhythmicity, daytime arousal) of treatment outcome. Our knowledge of possible interactions between behavioural and pharmacological treatments is also limited (171). Finally, the recent discovery that light’s neurobiological effects are blue-shifted (178, 179) encourages a more sophisticated investigation of light treatment for BD. One aspect of this investigation must be the potential toxicity of blue-enhanced light (see 180).

**Summary and conclusions**

Four main themes can be drawn from the present review. First, standard laboratory protocols for separating sleep and circadian function are not
feasible in vulnerable populations, so the biologically important distinction between these processes is difficult to investigate. Fundamental questions can instead be addressed by careful extrapolation from well populations, perhaps quantified by their degree of risk for BD. Second, biological rhythm pathways are interwoven with other pathways implicated in BD (e.g., monoamines, GSK-3β), and future research should actively address this complexity. Third, the wide variety of evidence demonstrating biological rhythm involvement in BD is a rich source of hypotheses for future work in this burgeoning area. Research in humans has yet to discover mechanisms of large effect, but preclinical studies suggest the reward–circadian interaction may be particularly fruitful. Finally, interventions built on chronobiological principles should be energetically investigated. These interventions are theoretically plausible, benign, economical, and attractive to patients.

In conclusion, research into sleep and circadian function in BD is an exciting, challenging and rewarding avenue for the future. It has the potential to significantly broaden understanding of a particularly serious mental illness and to improve the quality of life and functioning of patients.

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