

Circadian abnormalities as markers of susceptibility in bipolar disorders

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1. ABSTRACT

Chronobiological models have contributed to a better understanding of the pathophysiology of bipolar disorders. Circadian functions dysregulations are associated with bipolar disorders, including biochemical (melatonin and cortisol profiles), actigraphic (sleep/wake patterns), and dimensional (chronotypes) circadian markers. These associations are observed not only during acute episodes but also during euthymic periods. Most markers that are associated with bipolar disorders are also found in the healthy relatives of patients, suggesting a strong degree of heritability. As such, they may serve as trait markers of the disorder. Several circadian genes have been found to be associated with bipolar disorders: at least three studies have reported positive associations for each of *CLOCK*, *NPAS2*, *ARNTL1*, *NR1D1*, *PER3*, *RORB* and *CSNK1epsilon*. Thus the clock machinery may contribute to the genetic

susceptibility to bipolar disorders. The circadian model theory has also led to the development of novel therapeutic strategies such as InterPersonal and Social Rhythms Therapy and chronotherapeutics. Additionally, the circadian model theory may help explain how mood stabilizers (in particular lithium carbonate) bring about their therapeutic effects.

2. INTRODUCTION

The etiology of bipolar disorders (BD) etiology is highly complex and involves interplay between psychological, physiological, genetic, and environmental factors. There has been an increasing amount of work investigating changes to the rhythmicity of circadian functions during periods of mania and depression. These

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include changes in mood, appetite, sleep, and energy, which also manifest during periods of remission. Thus circadian abnormalities may be involved in the pathogenesis of BD and may serve as biomarkers of the disorder. Indeed, instability of circadian rhythms may be one of the major candidate endophenotypes in BD (1). Mood regulation is also closely connected to circadian variables in theoretical models. According to the “Social Zeitgeber theory”, life events may trigger disruptions to circadian rhythms, leading to affective episodes in vulnerable individuals such as patients with BD (2). Murray and Harvey proposed a model to explain the spectrum of mood disorders (3). This model integrates a multitude of factors, including genetic susceptibility, sleep patterns, circadian functioning, the activity of neurotransmitters, and deregulation to mood. The authors suggest a genetic component to the disturbance of circadian rhythm: particular variants of candidate genes (mainly genes involved in circadian functions) may affect the speed and ease with which circadian rhythms can adapt to changing environmental conditions. Hence, such variants can predispose an individual to instability in circadian function and leave them prone to sleep disturbances.

In this review, we summarize current knowledge of circadian phenotypic and physiological disturbances in BD during periods of remission. We also review genetic association studies that suggest circadian genes are involved in susceptibility to BD. Finally we discuss the treatment of BD using chronotherapeutic strategies. The effectiveness of such strategies underlines the clinical relevance the circadian clock machinery in the management of BD, and further reinforces the idea that perturbation to this machinery plays a role in disease pathology.

For this purpose, we conducted an extensive review of the literature on circadian/sleep issues in BD. The publications were obtained from the PubMed electronic database in June 2013. The literature search was performed using four different combinations of the Mesh heading: 1) “Bipolar Disorder” AND (“circadian gene” OR “clock gene” OR “melatonergic gene”), 2) “Bipolar Disorder” AND (“chronotype” OR “circadian typology” OR “regularity”), 3) “Bipolar Disorder” AND (“hormone” OR “cortisol” OR “melatonin”) 3) “Bipolar Disorder” AND (“sleep” OR “actigraphy” OR “actimetry” or “polysomnography”), 4) “Bipolar Disorder” AND “circadian” AND (“chronotherapeutics” OR “agomelatine” OR “melatonin” OR “ramelteon” OR “lithium” OR “valproate” OR “carbamazepine” OR “lamotrigine” OR “atypical antipsychotic” OR “light therapy” OR “psychoeducation” OR “interpersonal and social rhythm therapy”). We also used the ‘related articles’ function of the PubMed database and the reference lists of the studies identified, and we searched Google Scholar to identify additional articles. We included only data in articles published in English.

3. NEUROBIOLOGY OF THE CIRCADIAN SYSTEM

3.1. The molecular clock

Circadian rhythm is the term used for all physiological processes (biological and behavioral) displaying a periodicity of 24 hours (“*circa diem*”- “about a

day”). Anatomically “the master circadian pacemaker” is located in the suprachiasmatic nuclei (SCN), a paired cluster of about 10,000 neurons in the anterior hypothalamus. Clock mechanisms of the SCN comprise a complex network of transcriptional-translational feedback loops that result in the rhythmic expression of clock genes (on a time scale of just over 24 hours) (4). In the primary feed-back loop, CLOCK and BMAL1 (also known as ARNTL1) heterodimerize and initiate the transcription of genes containing E-box *cis*-regulatory enhancer sequences, including *PER* and *CRY* (figure 1). *PER* and *CRY* proteins heterodimerize and translocate to the nucleus and inhibit the CLOCK-BMAL1 complex, thereby creating a negative feedback loop that represses their own transcription. Another regulatory loop involves CLOCK-BMAL1 heterodimers, which activate the transcription of retinoic acid-related orphan nuclear receptors, *REV-ERBalpha* (or *NR1D1*) and *RORA*. Through ROREs (retinoic acid-related orphan receptor response elements) in the *BMAL1* promoter, RORs and REV-ERBs regulate *BMAL1*: RORs activate, whereas REV-ERBs repress, transcription (4). TIMELESS dimerizes with *PER* and is thought to inhibit the CLOCK-BMAL1 transcription complex (5). CNSK1 family kinases phosphorylate *PER* and *CRY* and regulate the turnover of *PER* and *CRY*. GSK3beta phosphorylates TIMELESS and REV-ERB (6, 7). The physiology of the circadian system is common to all organisms, and there is a particularly high degree of conservation of core clock genes in very diverse species (8).

An intrinsic circadian rhythm is slightly longer than 24 hours and does not depend on any external time cues (referred to as a ‘free-running rhythm’). However, endogenous oscillations (without changing their periodicity) can synchronize with environmental time signals in a process called ‘entrainment’ (see for review (4)). The light-dark cycle is likely to be the most potent entraining time signal. Specialized retinal ganglion cells project through the retino-hypothalamic tract and are the main afferent input to the SCN. These cells use a photopigment called melanopsin, which is highly sensitive to blue light. The principal oscillator in the SCN sends information through various output pathways to regulate the rhythmic expression of Clock-Controlled Gene (CCGs). The expression of these genes controls rhythmic functions including sleep-wake cycle, feeding behavior, core body temperature, release of hormones, and metabolic regulation (4, 9). The expression and rhythmic regulation of clock genes is widely distributed among many peripheral cells (liver, endocrine tissues, heart, skeletal muscles...) (10, 11).

3.2. The melatonergic system

A second major actor of the circadian system is the pineal gland, which synthesizes melatonin. Melatonin secretion is regulated by the environmental light/dark cycle via the SCN (12). Melatonin secretion is high during the dark phase of the light/dark cycle and decreases in response to light (13, 14), and also responds to seasonal changes in light. Hence, melatonin acts as an internal calendar and clock, or ‘zeitgeber’, (literally ‘time giver’) Melatonin can be assayed in blood, saliva, and urine (in the latter case by

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measuring the melatonin urinary metabolite, 6-sulfatoxymelatonin). The most widely used circadian melatonin phase marker is the Dim Light Melatonin Onset (DLMO) (15). The DLMO is defined as the time at which the concentration of melatonin in the plasma rises above 10 pg/ml; this is normally between two or three hours before bedtime (16). The circulating melatonin concentration increases before bedtime, remains high during nocturnal sleep, and decreases rapidly around the time of awakening and is near or below the threshold of detection during the daytime. Body temperature and circulating cortisol concentrations follow inverse circadian variations (high during the daytime and low at night) (17).

3.3. The influence of circadian systems on neurotransmitter systems involved in regulating mood

Circadian systems and neurotransmitters systems are thought to be highly interconnected. Rhythmic deregulation of certain neurotransmission pathways may be involved in the pathophysiology of BD. Several neurotransmitters are implicated in mood regulation and these neurotransmitters shows circadian variation. Similarly, the enzymes responsible for the synthesis and catabolism of these neurotransmitters, along with the receptors to which these neurotransmitters bind, show circadian variations in their transcription and translation. This is particularly the case for serotonergic (18-21), dopaminergic (22-25) and noradrenergic (26, 27) neurotransmission.

One of the most densely populated serotonergic plexuses in the brain is located in SCN (28). This plexus is formed mainly of neurons from the median raphe nuclei (29). Lesion of the raphe nucleus or chemical blockade of serotonergic neurons leads to impairment of serotonergic function in the brain. Although this does not disrupt circadian rhythms, it does lead to a decrease in their amplitude and an alteration of their periodicity (30). Serotonin signaling via efferent pathways from median raphe nuclei increases the stability of circadian rhythms (31). Indeed, the serotonergic projection from the median raphe nuclei to the SCN may be the anatomical interface between circadian functions and mood disorders (32). Serotonin has also been implicated in the regulation of the SCN by photic (33-35) and non-photoc zeitgebers (31, 36). Moreover, serotonergic activity is influenced by light exposure and time of year (37). Yan *et al.* identified molecular connections between serotonergic signaling and the regulation of TIMELESS in *Drosophila*: serotonergic signaling increased the phosphorylation of SHAGGY (homolog of human GSK3beta), resulting in a decrease of its activity and the light-induced degradation of TIMELESS (38). Connections between the metabolism of serotonin and melatonin are observed in the pineal gland. Melatonin is synthesized from serotonin and the SCN modulates the catabolism of serotonin into melatonin (39). Tryptophan is a common precursor of both serotonin and melatonin. Hence, the availability of this essential amino acid is crucial to the synthesis of these molecules, the production of both of which is cyclic with peaks at night time (40).

Dopamine signaling in the tegmental ventral area and substantia nigra is a key component of the wake/sleep cycle and is mostly involved in paradoxal sleep (41, 42). Dopaminergic signals, which are relayed via D2 receptors, regulate the activity of the CLOCK-BMAL1 complex (43). Dopamine is also a major chemical agent in the retina and seems to play an important role in the adaptation to light (44).

Few data are available on the interactions between circadian functions and noradrenergic neurotransmission. Noradrenalin is implicated in the metabolic activity of the pineal gland and therefore also in the regulation of the melatonin synthesis (45).

There may be a relationship between perturbation of biological circadian rhythms and dysfunction of monoaminergic neurotransmission in patients with BD. Indeed, the disruption of circadian rhythms and emotional imbalance may both be consequences of complex interactions between serotonergic, dopaminergic systems, and the circadian clock (3).

4. CIRCADIEN DISTURBANCES AS TRAIT MARKERS IN BIPOLAR DISORDERS

Patients with BD display persistent disturbances of circadian rhythms during both physiological and behavioral euthymic periods; it is possible that these circadian abnormalities could serve as trait biomarkers of BD. A 'biomarker' is a characteristic that can be objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention (46). Measures or variables with any of following characteristics may be considered to be biomarkers of BD: (i) being detectable during normothymic periods and having a distinguishable characteristic or value associated with the presence of the disorder, (ii) being heritable among patients with BD and/or in the general population, (iii) being detectable among healthy first-degree relatives of patients or populations at high-risk for the disorder (47). A biomarker can be qualified as an intermediate phenotype if it is a mechanism-based manifestation of a complex phenotype, and as an endophenotype if it is a heritable intermediate phenotype associated with a disease (48). In the following paragraphs, we will describe circadian biomarkers that fulfill some of these criteria.

4.1. Lifestyle regularity

Lifestyle regularity can be assessed using several approaches. For example, patients with mood disorders may be asked to keep a diary; one of the most frequently used is the Social Rhythm Metric (SRM) (49, 50). The SRM assesses the effect of daily routine - social and occupational rhythms - on sleep quantity and quality. High regularity of lifestyle is associated to fewer sleep problems (51) and to a preference for being active in the morning (52), indicating that the regularity of social rhythms, diurnal preference, and sleep quality are highly interconnected.

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Sylvia *et al.* showed that patients with BD exhibited less regularity of lifestyle than healthy controls (53). This was confirmed by another study using the BRIAN (Biological Rhythms Interview of Assessment in Neuropsychiatry) (54). People with a 'hypomanic personality' - at risk of BD - showed a lower regularity of daily activities than controls, with more variation in the duration of sleep (55). Irregular social rhythms were also observed in a sample of 414 undergraduate students diagnosed with bipolar spectrum disorders (cyclothymia or BD type 2), and appeared to be a significant predictor of the onset of major depressive, hypomanic, and manic episodes in the following three years (56).

These reports are consistent with the theory that bipolar spectrum patients have irregular social daily routines. These social rhythms can be considered as 'social zeitgebers' - synchronizers that help set the circadian clock. Irregularity in an individual's social zeitgebers may precipitate or contribute to mood relapse (57).

4.2. Morningness-eveningness typology

Questionnaires, such as the Horne-Östberg morningness-eveningness questionnaire, the Composite Scale of Morningness (CSM) (58), or the Munich ChronoType Questionnaire (59) are used to categorize quantitatively individuals as 'morning types' or 'evening types', or in the case of extreme circadian tendencies, as 'larks' or 'owls'. These questionnaires assess diurnal preference (chronotype) for times of activity/sleep, i.e. the rhythm that an individual would like to adopt as opposed to the rhythm an individual is forced to adopt due to life constraints. Diurnal preference is a highly informative measure because morningness-eveningness correlates strongly with other endogenous phase markers of the circadian clock, such as body temperature (60, 61), the amount and timing of salivary melatonin secretion (62), and the cortisol awakening response (63). Morningness/eveningness is stable over time, as confirmed in various populations with different cultural habits (64, 65).

Five studies in populations with different cultures showed that patients with BD were more likely to be of an 'evening type' than were control individuals (66-69) or patients with recurrent major depressive disorder (70). Wood *et al.* showed that age-corrected CSM scores did not differ significantly between BD type 1 and BD type 2, suggesting CSM score is a useful biomarker for a large spectrum of BD (66). Wood *et al.* noted also a significant correlation between CSM scores measured two years apart in patients with BD, implying that diurnal preference in patients has temporal stability (66). Some manifestations of severe forms of bipolar disorders are correlated to eveningness. These manifestations include severe depressive mood ratings, anxiety, substance abuse, childhood disruptive behavioral disorders (66), early age-of-onset, and rapid cycling course (68). The finding that patients with more severe depressive mood symptoms are more likely to be evening types (66) is consistent with the findings showing that depression is correlated with eveningness in general population (71).

Boudebesse *et al.* used the CSM and also the Circadian Type Inventory (CTI) - a self-assessment questionnaire reflecting rhythm stability and amplitude - in their assessment of diurnal preference in patients with BD (72). They found that patients with BD had higher scores of eveningness and were also significantly more languid than controls. Patients also reported a higher sensitivity to sleep reduction and were more lethargic following a reduction in the time of sleep. This result is consistent with a reduction in the peak of the melatonin abundance at night in patients with BD (see 4.5.2) and the high irregularity of their activity rhythms as measured by actigraphy (see 4.3).

Four, large independent studies in the general population suggest that diurnal preference is a heritable trait (73-76). Consistent with this view, diurnal preference is similar between patients with BD and their healthy monozygotic or dizygotic twins (77).

Thus, diurnal preference or chronotype may be a robust biomarker of BD, because it is associated with the disorder, is stable over time, and is heritable. Studies involving the unaffected relatives of patients with BD are needed to demonstrate whether or not diurnal preference is an endophenotype of BD. Nonetheless, we can conclude that it is at least an intermediate marker of the disorder.

4.3. Sleep-wake cycle

Sleep-wake cycles can be measured by polysomnography (PSG) and actigraphy. PSG is the gold standard in sleep research and assesses sleep architecture, continuity and quality of sleep in a laboratory setting. An actigraph is a wristwatch-like tool that consists of an accelerometer that detects, scores, and stores information about the intensity and the timing of motion over several, consecutive 24-hour intervals. In comparison with PSG, actigraphy has the advantage of providing an ambulatory assessment of both sleep and circadian rhythms over time in the subject's home setting (78). In addition actigraphy is a valid tool for estimating sleep duration and fragmentation in BD; indeed, these estimates match closely those obtained using PSG and sleep diaries (79).

The sleep-wake cycle, as assessed by PSG, is altered in patients with BD during manic or depressive episodes, but also during periods of remission. Indeed, during periods of remission, patients with BD had a high density of rapid eye movement (REM) during the first REM period of sleep. Additionally, these patients were highly sensitive to the cholinergic receptor agonist arecoline, and showed a higher percentage of REM sleep after administration of this drug (80). Nocturnal arousals were observed more frequently in patients undergoing periods of remission than in normal controls (81).

Eight studies characterized circadian rhythms using actigraphy in euthymic patients with BD as compared to healthy controls, "good sleepers" or patients with insomnia (82-89). On the whole, these studies suggest that euthymic patients with BD have a greater variability in their sleep/wake patterns, longer sleep duration, longer sleep latency, higher WASO (Wake After Sleep Onset),

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and lower sleep efficiency than insomniacs or controls. Two of these studies also reported that the daily activity of patients with BD undergoing periods of remission was lower than that of control participants (83, 88).

Using actigraphy, Ankers and Johns showed that individuals at high-risk of developing bipolar spectrum disorders exhibited greater variability in the duration, fragmentation, and efficiency of sleep, shorter sleep duration, later and more variable bedtimes, and lower relative amplitude of activity patterns than controls (90). A greater variability in sleep fragmentation and shorter sleep latency were observed in the children of patients with BD than in the children of parents without a psychiatric condition (91).

Twin- and family-based studies show that sleep length is heritable ($h^2 = 0.44$). In one study, the contribution of genetics to variance in sleep quality and to sleep disturbance was 33%, and to variance in sleep pattern 40% (92). Work based on using sleep questionnaires and PSG also provides evidence for a genetic contribution to pathological sleep patterns (93).

4.5. Neuroendocrine and other physiological parameters

4.5.1. Hypothalamic-pituitary-adrenal axis: cortisol

Cortisol secretion follows a 24 h cycle. In healthy individuals, cortisol secretion has a morning peak. In a given individual from the general population, the cortisol awakening response is highly regular across extended periods (94).

Cortisol is one of the most studied circadian markers of BD. Cortisol secretion over 24 hours is significantly higher in patients with BD than in controls, irrespective of the phase of BD (manic, depressive, or euthymic). (95). Patients with BD type I, who were kept euthymic for a long period of time using lithium prophylaxis, had significantly higher salivary cortisol concentrations upon awakening, than both control subjects in the study and than the large numbers of healthy subjects for who the relevant data has been published (96). The abundance of glucocorticoid mRNA in the hippocampi and amygdala nuclei was lower in patients with BD than in healthy controls (97). Hence, hypercortisolemia in BD may be related to a low abundance of glucocorticoid mRNA.

In healthy monozygotic and dizygotic twins, the heritability of cortisol secretion has been estimated to be 62% (98). The cortisol awakening response may be the most heritable circadian measure (99, 100), however it is not the most useful biomarker for affective disorders. Instead, high secretion of cortisol in the evening may be associated with a high risk of developing affective disorders, particularly in specific high-risk affective disorders population (101).

In one study, the salivary cortisol concentration in the afternoon was higher in the offspring of parents with BD than in the offspring of parents with no mental disorder (102). This difference was stable over a follow-up period of

two years. A difference in the secretion of afternoon cortisol was also observed between bipolar twins and their healthy twins (101). However, this endophenotypic characteristic of cortisol secretion has not been consistently replicated (103).

Hence, dysfunction of the hypothalamic-pituitary-adrenal axis that results in alterations to cortisol secretion may be a trait (rather than state) marker of BD.

4.5.2. Pineal function: melatonin

Abnormalities of melatonin secretion, in particular hypersensitivity to light, may be a trait marker of BD. Two studies report that the reduction of nocturnal plasma melatonin concentrations in response to light was two-fold greater in acutely ill and euthymic drug-free patients than in healthy controls (104, 105). However, this finding was not replicated elsewhere (106, 107). In euthymic BD type I patients who were exposed to light during the night time, melatonin secretion was low following exposure to light (108). In addition, melatonin secretion prior to light exposure was low and also showed a late peak time of secretion during the night time in these patients. Circulating melatonin concentrations during the night are similar in patients with BD irrespective of illness state (i.e. manic, depressive and euthymic phases), but lower than in healthy controls. These studies suggest that low serum melatonin levels is a trait but not a state marker in BD (109).

No difference in the total pineal volume between patients with BD and healthy subjects was observed using a voxel-based volumetric measurement method (110). Hence, the putative dysfunction of the pineal gland in BD is not correlated with the parenchymatous volume, but presumably with some other functional aspects of the gland.

By studying monozygotic and dizygotic twins with no history of psychiatric disorders, Hallam *et al.* found that nocturnal melatonin secretion and sensitivity to light have a genetic component (111).

The healthy offspring of bipolar parents are more likely to show supersensitivity in the melatonin response to light exposure during the night than age-matched controls (45% more sensitive than controls). Furthermore, this supersensitivity was more pronounced in the healthy offspring of couples who were both affected by major affective disorder than in children with only one parent affected by major affective disorder (72% increase in sensitivity versus controls and 57% of increase versus controls respectively) (112).

The total amount of melatonin in the plasma is similar between patients with BD and healthy individuals. However, in patients with BD, melatonin secretion shows abnormal changes in amplitude and periodicity, suggesting that abnormalities in melatonin secretion are a marker of BD.

4.5.3. Other hormones

The secretion profiles of many circadian hormones have been studied in patients with BD in various mood states. There is little evidence to suggest that

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Table 1. Circadian parameters as potential trait markers and endophenotypes in bipolar disorders: studies demonstrating positive correlation

Circadian parameter	Association with bipolar disorders	Presence during remission	Heritability	Over-represented among high risk subjects for bipolar disorders
Lifestyle irregularity	Yes	Yes	?	Yes
Evening-type	Yes	Yes	Yes	?
Higher sleep-wake cycle variability	Yes	Yes	Yes	Yes
Higher cortisol secretion	Yes	Yes	Yes (awaking)	Yes (afternoon)
Supersensitivity of nocturnal plasma melatonin in response to light	Yes	Yes	Yes	Yes
Lower overnight serum melatonin	Yes	Yes	Yes	?

abnormalities in the secretion of these hormones are trait markers in BD (113). Nonetheless, there are some arguments that favor such a notion, including perturbation of luteinising hormone during mania (114), thyroid stimulating hormone during depressive states (115, 116). Studies that have examined perturbation of the secretion of circadian hormones in patients in remission periods are scarce. The secretion profiles of other neuroendocrine hormones, such as prolactin or growth hormone are not clearly different between patients with BD and controls (117, 118).

4.5.4. Body temperature

Variations in body temperature follow a 24-hour cycle, and can be considered as a circadian marker. In general populations, body temperature decreases during the night-time and increases during the day-time. Body temperature is also tightly associated with other circadian variables such as sleep (119). One study found that body temperature was deregulated in patients with BD during mood episodes (116), although this finding has not since been replicated. Again, studies examining this relationship in patients during remission periods are lacking.

In conclusion, several circadian functions seem to fulfill criteria for being (endo)phenotypes in BD. These include secretion profiles for the circadian hormones cortisol and melatonin, and diurnal preference as assessed by actimetry or validated questionnaires (Table 1).

5. CIRCADIEN GENES AND BIPOLAR DISORDERS

Patients with BD display major disruptions of circadian rhythms and at least some of these characteristics appear to be heritable. These observations suggest the existence of susceptibility genes encoding proteins involved in these chronobiological processes, and thus putative candidate genes for BD and its clinical expression. Various studies favor this hypothesis, including classical genetic association studies, copy number variation analysis (CNV), genome-wide association studies (GWAS), animal models, transcriptomics/proteomics, and Convergent Functional Genomics (CFG).

5.1. Candidate genes: association studies

Genetic association studies suggest associations between single nucleotide polymorphism (SNP) in circadian genes and the occurrence of BD. The results of these studies are summarized in Table 2. Several circadian genes have been found to be associated with BD, with at

least three studies implicating *CLOCK*, *NPAS2*, *ARNTL1*, *NR1D1*, *PER3*, *RORB* and *CSNK3epsilon*. Appropriate meta-analyses would undoubtedly add further support to these associations. Lachman *et al.* reported that the frequency of a CNV in the *GSK3beta* locus was higher in patients with BD than in controls (120). This association between *GSK3beta* and BD was not suggested by association studies using single nucleotide polymorphisms (121-123).

5.2. Other molecular approaches

Besides classical genetic association studies using candidate genes, other molecular approaches have implicated several circadian genes in the pathophysiology of BD. One approach involves the analysis of circadian rhythms in cultured cells derived from human skin biopsies, blood samples (124), or hair follicles cells (125). This approach allows the measurement of circadian rhythmicity without the influence of external zeitgebers and has the obvious advantage that the subject under study need not spend prolonged periods of time in the laboratory. Remarkably, circadian functions, including the amplitude and phase-resetting responses, in human fibroblasts in culture correlated with chronotypes of subjects from which the cells were derived (126). Using a transcriptomic approach, Yang *et al.* demonstrated that the amplitude of rhythmic expression of *BMALI*, *REV-ERBalpha* and *DBP*, was lower in fibroblasts derived from patients with BD than in those from controls (127). The overall mRNA expression level for *DEC2* and *DBP* and the level of *GSK3beta* phosphorylation were also reduced. Hence, susceptibility to BD involving circadian genes involves both genetic variations (SNPs, mutations or CNV) but also differences in their transcriptional output.

Circadian genes have also been implicated in “bipolar-like” behaviors in animal models. The most cited example is the behavior of mice carrying a deletion of exon 19 in the *CLOCK* gene, which represents a valuable model of mania (128). *Clock* mutant mice show a craving for rewarding stimuli similar to patients with BD in the manic state. These mice also display other behavioral responses associated with mania including less depression-like behavior and lowered anxiety. The manic-like behavior of the *Clock* mutant mice can be reversed by lithium treatment or the restoration of a functional *CLOCK* gene in the Ventral Tegmental Area (129). Other examples of mouse models involving circadian genes include transgenic mice overexpressing *GSK3beta* which show a manic-like

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Table 2. Studies supporting associations between circadian genes and bipolar disorders

Gene	OMIM nomenclature	Positive studies
<i>CLOCK</i>	Circadian Locomotor Output Cycles Kaput	(123, 141, 142, 187)
<i>NPAS2</i>	Neuronal PAS Domain Protein 2	(123, 187, 188)
<i>ARNTL1</i> (or <i>BMAL1</i>)	Aryl Hydrocarbon Receptor Nuclear Translocator-like 1 (or Brain and muscle ARNT like 1)	(122, 187-190)
<i>ARNTL2</i> (or <i>BMAL2</i>)	Aryl Hydrocarbon Receptor Nuclear Translocator-like 2 (or Brain and muscle ARNT like 2)	(187)
<i>PER1</i>	Periodhomolog 1 (Drosophila)	(123)
<i>PER2</i>	Periodhomolog 2 (Drosophila)	(123)
<i>PER3</i>	Periodhomolog 3 (Drosophila)	(122, 187, 189)
<i>CRY1</i>	Cryptochrome 1	(187)
<i>CRY2</i>	Cryptochrome 2	(188)
<i>TIMELESS</i>	Timeless homolog (Drosophila)	(189)
<i>NR1D1</i> (or <i>REV-ERBalpha</i>)	Nuclear receptor subfamily 1, group D, member 1 (or orphan nuclear receptor REV-ERBalpha)	(123, 138)(191) ¹
<i>RORA</i>	Retinoid-related orphan receptor A	(187)
<i>RORB</i>	Retinoid-related orphan receptor B	(188, 190)(192) ²
<i>CSNK1delta</i>	Casein kinase 1 delta	(123, 193)
<i>CSNK1epsilon</i>	Casein kinase 1 epsilon	(141, 187, 188, 193)
<i>GSK3beta</i>	Glycogen synthase kinase 3 beta	(194) ¹
<i>BHLHB2</i>	Basic Helix-Loop-Helix domain containing, class B, 2	(141)
<i>BHLHB3</i> (or <i>DEC2</i>)	Basic Helix-Loop-Helix domain containing, class B, 3	(187)
<i>PPARGC1B</i>	Peroxisome proliferator-activated receptor-gamma, coactivator 1 beta	(123)
<i>DECI</i>	Deleted in esophageal cancer 1	(190)
<i>MTNRIA</i>	Melatonin receptor 1A	
<i>MTNR1B</i>	Melatonin receptor 1B	
<i>ASMT</i>	Acetylserotonin methyltransferase	(195)
<i>AANAT</i>	Arylalkylamine N-acetyltransferase	

¹association observed only for females with bipolar disorders (191, 194), ²association for pediatric bipolar disorder (192)

phenotype (130), *DBP* knockout mice which exhibit a short duration of sleep and sleep EEG abnormalities, and *Cry1* knockout mice that have a poorly synchronized circadian rhythmicity (131).

These data coming from different experimental approaches in different organism contexts have proven difficult to unify. In this respect, the results obtained using Convergent Functional Genomics (CFG) are particularly useful. This approach integrates data from gene expression studies in animal models with data from human genetic linkage/association studies, as well as data obtained from human tissue (blood, postmortem brain). Findings from CFG suggest that some top candidate genes for BD (such as *ARNTL1*, *GSK3beta*, *RORA* and *RORB*) are implicated in the regulation of circadian rhythms (132, 133).

5.3. Phenotypic expression associated with circadian genes and pharmacogenetics

It remains unclear whether genetic variants of circadian genes are implicated in the genetic susceptibility to BD, or whether they act as disease modifiers, being associated not with the disorder *per se* but with its clinical

expression. In BD, several circadian genes have been associated with an early age of onset (*PER3*, *REV-ERBalpha*, *GSK3beta*) (134-138) and/or with a high recurrence of illness (*GSK3beta*, *CLOCK*) (139). Some circadian genes are associated to rapid cycling of BD: *CRY2* (140), *CLOCK*, *ARNTL2*, *TIMELESS* and *CSNK1epsilon* (141). Therefore, particular circadian genes may be important in a certain subgroup of BD (early onset subgroup), or they may be important in modulating the pattern of recurrences. In either case, these genes are associated with problems in the synchronization of circadian rhythms and a high sensitivity to external cues, both of which could facilitate disease onset or relapses.

Studies that have examined the relationship between circadian gene variants and chronotypes in patients with BD are rare, despite a strong interest to understand genetic susceptibility to BD and its possible links to circadian genes. To date, only two studies have been published: the *3111T/C* variant in *CLOCK* was associated with an extreme evening type in a Korean bipolar population (142), and a non-synonymous coding SNP in *PER3* and two intronic SNPs in *CSNK1epsilon* were associated with eveningness (as assessed with the Basic Language Morningness score) among patients with BD (123). Further studies are required to correlate genotype to phenotypes in BD. Such studies will identify intermediate phenotypes in BD that may serve as clinical markers (such as eveningness) and their genetic underpinnings.

Finally, some circadian genes may also be implicated in pharmacogenetics. The mechanisms responsible for the therapeutic effects of lithium are far from understood. Nonetheless, one of the major effects of lithium is the inhibition of *GSK3beta* (143), which is believed to play a central role in mood regulation (144). Patient responses to lithium salts may be partly determined by inter-individual differences in biological clocks. In patients with BD, a polymorphism (-50T/C) in the proximal promoter region of *GSK3beta* is associated with patient response to lithium therapy, with a TT genotype being associated with a poor response (137). This genotype is also associated with an early age of onset of BD (134), consistent with the observation that early-onset patients with BD respond poorly to lithium (145). Evidence linking variants in the *NR1D1* gene and poor response to lithium has also been reported (146), although this was not replicated (147). Some circadian genes may be markers of therapeutic response rather than markers of the disorder itself.

To date, the role of circadian gene in the genetic susceptibility to BD remains to be clarified because it is unclear if these genes are risk factors for the disorder itself or if they are clinical modulators or markers of a therapeutic response.

6. CHRONOTHERAPEUTIC ASPECTS IN BIPOLAR DISORDERS

Understanding the role of circadian disturbances in BD will be useful for a better understanding of the

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disease pathology, but will also help to direct strategies of pharmacological and psychotherapeutic interventions.

6.1. Manipulating circadian rhythms using photic input

Chronotherapeutics relies on the controlled exposure to environmental stimuli, in particular controlled photic input, with the aim of influencing biological rhythms to achieve therapeutic effects. Several techniques have been proposed as useful in the management of patients with BD, mainly during acute phases of the disease. These techniques include light therapy and sleep deprivation, and less frequently dark therapy and extended bed rest. However, it is not known if such measures are effective, because randomized controlled *versus* placebo clinical trials are lacking. Therefore, these treatments are not standardized clinical interventions that should be currently used for the routine management of patients with BD, although various practices may be beneficial for some patients. Patients with BD may respond more quickly to antidepressants or mood stabilizers if these treatments are given in combination with sleep deprivation (148-150). Additionally, light therapy may be effective for the treatment of bipolar depression (151, 152). Forty-nine patients with BD who received medication (mood stabilizer and antidepressant) in combination with three established circadian-related treatments (sleep deprivation, bright light, sleep phase advance) showed a more rapid and sustained decrease in depression scores than a medication-only group (153). Some reports suggest that manic symptoms or rapid cycling can be reduced by dark therapy (154, 155) or by amber lenses that block blue light (156).

Chronotherapeutics are believed to target the same neurotransmitter systems and the same brain areas as psychotropic drugs. The effects of chronotherapeutics are rapid and transient. However, a more enduring therapeutic effect could be obtained by combining chronotherapeutic techniques with each other or with common drug treatments. Chronotherapeutics may be useful during the acute phases of BD, but their relevance during the remission periods is unclear.

6.2. Inter-Personal and Social Rhythm Therapy and psychoeducation

Evidence from clinical practice and sleep log studies suggest that psychosocial stressors and low regularity in social rhythm are associated with a high risk of mood relapses in BD (see 4.1.). Some psychological interventions that are used in patients with BD aim to target the disruption of circadian rhythms, particularly the disruption of sleep-wakes cycles. Frank *et al.* developed the Inter-Personal and Social Rhythm Therapy (IPSRT), which combines a modified form of interpersonal therapy and a social rhythm therapy. BD type I patients who received this therapy showed a greater improvement in the stability of routines (sleep, meal, exercise) than BD type I patients treated only with medication. In acute phase patients treated with IPSRT, an increase in the regularity of social rhythms was associated with a positive long-term response to treatment, resulting in longer survival times between episodes in a two-year preventive maintenance program (157). The efficacy of IPSRT therapy was confirmed in two

controlled studies and extended to BD type 2 (158). Psychoeducation showed efficacy in preventing relapses in patients with BD. This treatment involves sessions that stress the importance of life-style regularity, even if this variable is not the main target (159).

The effectiveness of psychotherapies that aim to improve the regularity of daily social rhythms is further evidence that external triggers (e.g., environmental zeitgebers) that influence circadian rhythms can affect mood in patients with BD. Accordingly, these treatments and their effects also suggest that circadian functions are vulnerable to disruption in patients with BD.

6.3. Non-focused circadian pharmacological treatments

Most patients with BD have circadian rhythms that run faster than one cycle per 24 hours (160, 161). Mood-stabilizers, and in particular the gold standard for mood stabilizers, lithium, may work in part via a chronobiological mechanism. Lithium has phase-delaying properties because it causes a lengthening of the circadian period in a variety of organisms, including humans (162, 163). Lithium also enhances the amplitude of PER2 protein cycling in the central and peripheral circadian clockwork (164). Transgenic mice carrying a mutation in the *Clock* gene display a human mania-like behavior, which reverts to a near normal state following the chronic administration of lithium (129). Some circadian genes (*GSK3beta*, *NR1D1*) have also been implicated in pharmacogenetics, because they are associated with differential responses to mood stabilizers, and in particular to lithium (see 5.3).

Low doses of lithium carbonate reduce melatonin secretion in response to light in healthy volunteers, suggesting that lithium also acts on the melatonergic system (165). This property is shared with sodium valproate, another mood stabilizer (166). Valproic acid also increases the amount of melatonin receptors in C6 glioma cells (167) and influences the expression of several circadian genes in the amygdala (168).

There are currently no relevant data available for other mood stabilizers that are frequently prescribed in maintenance phases in BD (carbamazepine, lamotrigine, atypical antipsychotics).

6.4. Focused circadian pharmacological treatments

Focused treatments are those that directly act on the circadian or melatonergic systems. These include exogenous melatonin and melatonin receptor agonists that have the potential to synchronize the sleep/wake cycle. The efficacy of these treatments is unclear because they have rarely been specifically studied. There has been only a handful of case reports describing patients in manic, depressive or rapid-cycling phases of BD given focused treatments in combination with various regimens of mood stabilizers (169-172). These reports suggest that melatonin – as an adjunctive treatment – can be effective in improving sleep quality. However, these studies are insufficient to support the routine use of melatonin in the treatment of BD.

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Ramelteon is a melatonin receptor agonist that is used for insomniacs and people who have difficulty falling asleep. Euthymic patients with BD, who took ramelteon during a treatment period of 24-weeks, were more stable in the maintenance phase and showed a longer time before relapse than patients taking a placebo (173).

Agomelatin is a melatonin receptor agonist and a serotonin 5-HT(2C) receptor antagonist. Agomelatin was found to synchronize circadian rhythms involving body temperature, cortisol and other hormones in animal models and in humans, which may underlie some of its therapeutic effects (174). Three studies have reported the efficacy of agomelatin as an adjunctive treatment in bipolar depression (175-177).

In conclusion, direct manipulation of circadian rhythms using photic stimuli or rhythms therapy appears to be most effective in the depressive acute phases of BD. The utility of chronotherapeutics in acute manic phases requires further investigation. For the maintenance phase of the disorder, the strongest evidence that circadian functions may be targeted to achieve a therapeutic effect comes from IPSRT (focused on rhythms) and lithium (non-focused on rhythms) therapies. Concerning lithium carbonate, it would be useful to explore what circadian characteristics are predictive of good clinical responses, to help define the circadian profile of subjects who are more likely to be good responders.

7. PERSPECTIVES

Several lines of evidence (clinical, physiological, biological, genetic and therapeutic) suggest that disruption to circadian rhythms may be involved in the pathophysiology of BD. Clinical data regarding evening preference and actigraphic variables are relatively consistent across studies. Physiological data regarding cortisol and melatonin secretion profiles may also be informative for the understanding and diagnosis of BD, although their fidelity as biomarkers seems less certain and questions still remain regarding the relevant measure to use (cortisol awakening response, dim light melatonin onset). Genetic association studies implicate several circadian genes - *CLOCK*, *ARNTL2*, *GSK3beta*, *PER3* and *NR1D1* - in the susceptibility to BD and/or its phenotypic expression. However, in these studies the level of significance was sometimes low due to small sample sizes and/or corrections for the large numbers of variants being tested. The use of chronotherapeutics (both pharmaceutical and non-pharmaceutical) in patients with BD reinforces the hypothesis that major disruptions in circadian regulation are an underlying cause of BD. Focused-circadian behavioral therapy including IPSRT has been successful in treating patients with BD. Finally, details of the mechanisms of the therapeutic effects of mood stabilizers are emerging: it may be that they act by regulating circadian rhythms.

Studies among healthy first-degree relatives of patients with BD are required to elucidate more details about the endophenotypic aspects of most circadian markers. Cortisol and melatonin profile or actimetric features may constitute endophenotypes, according to

studies in first-degree relatives of patients with BD. However, little is known about the heritability of chronotypes and more research is necessary to test the hypothesis of evening type as endophenotype.

A second major issue is the specificity of such markers to BD. Ideally a marker should help to delineate or to discriminate nosographical entities. This is probably not the case for circadian markers, as several of them are also associated with other psychiatric conditions. Several examples of this lack of specificity have been reported in the literature. Harvey and colleagues have discussed the specific *versus* transnosographic aspects of some sleep-related markers (178). For example, eveningness has been found to be associated with other mood spectrum disorders such as depressive states (179-182) and seasonal affective disorder (183), and also with Attention Deficit Hyperactivity Disorder (184, 185) and some personality traits (186). Therefore, vulnerability of the time keeping system and a misalignment between endogenous and exogenous synchronizers may be common to a number of disorders including BD.

Concerning the involvement of circadian genes in BD, various questions remain unsolved: the number and nature of the associated genes, the specificity of these associations to BD, and the role of these genes in the genetic susceptibility to BD and/or in the phenotypic modulation of the disorders. Indeed, it remains unclear whether circadian genes predispose to BD *per se* or to a more severe form of BD characterized by an early age at onset, a higher sensibility to relapses, and a poor response to lithium. The identification and better understanding of phenotype/genotype correlations would greatly facilitate exploration of the relationship between these genes, circadian markers, and the clinical manifestation of the disorders.

Circadian markers can be considered as the readout of stable, trait-like, deregulation to circadian functions in individuals with BD. Circadian genes may also play a role in the genetic susceptibility to BD. The number of investigations of the relationship between BD and circadian genes, chronotypes, and circadian physiological processes is growing, and their findings strongly suggest that chronobiology may help to clarify the underlying mechanisms of mood disorders. Furthermore, chronotherapeutics may add new weapons to the current arsenal of treatments for BD. Light therapy, sleep deprivation and specific behavioral therapy, including IPSRT, have shown efficiency in the management of BD. Lithium salts may also act by affecting circadian rhythmicity. The study of circadian phenotypes and circadian genes in bipolar disorders constitutes a major field of both clinical and fundamental research that may reveal the pathophysiological determinants of the disorder; this may in turn lead to the development of personalized psychosocial and psychotropic treatments for patients.

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Abbreviations: BD: bipolar disorders; BD1: bipolar disorder type 1; BD2: bipolar disorder type 2; SCN: suprachiasmatic nuclei; CLOCK: circadian locomotor output cycles kaput; ARNTL1 (or BMAL1): aryl hydrocarbon receptor nuclear translocator-like 1 (or brain and muscle ARNT like 1); ARNTL2 (or BMAL2): aryl hydrocarbon receptor nuclear translocator-like 2 (or brain and muscle ARNT like 2); PER1: period homolog 1; PER2: period homolog 2; PER3: period homolog 3; CRY1: cryptochrome 1; CRY2: cryptochrome 2; NR1D1 (or REV-ERBalpha): nuclear receptor subfamily1, groupe D, member1 (orphan nuclear receptor REV-ERBalpha) ; RORA: retinoid-related orphan receptor A; RORB: retinoid-related orphan receptor B; TIMELESS: timeless homolog; CSNK1delta: casein kinase 1 delta; CSNK1epsilon : casein kinase 1 epsilon; GSK3beta: glycogen synthase kinase 3 beta; CSM: composite scale of morningness; PSG: polysomnography; REM: rapid eye movement; CNV: copy number variation; SNP: single nucleotide polymorphism; DBP: D site of albumin promoter; DEC2 (or BHLHB3): differentially expressed in chondrocytes 2 (or basic helix-loop-helix domain containing, class B, 3); IPSRT: interpersonal and social rhythm therapy; OMIM: online mendelian inheritance in man

Keys Words: Bipolar disorders, Circadian rhythms, Chronotype, Clock genes, Trait marker, Melatonin, Review

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