# The Relationship Between Bipolar Disorder and Biological Rhythms

*Robert Gonzalez, MD*

**ABSTRACT**

***Background:*** Rhythm disruption is a core feature of bipolar disorder and it has been hypothesized that disturbances of the circadian timing system play a fundamental role in the etiology of the disorder.

***Objective:*** We sought to investigate (1) theoretical models for biological rhythm disruptions in bipolar disorder, (2) physiological disturbances of biological rhythms in bipolar disorder, (3) clinical and therapeutic implications of biological rhythm disturbances in bipolar disorder, and (4) associations between circadian gene variations and bipolar disorder.

***Data Sources:*** PubMed database was searched systematically for articles that were published on or before May 5, 2013, and were written in English using the terms *bipolar disorder, clock genes, endogenous clock, molecular clock, biological rhythms, circadian, suprachiasmatic nucleus, circadian rhythm, melatonin,* and *sleep*.

***Study Selection:*** Seventy-four articles highlighting the objectives were included in the review.

***Data Extraction:*** Data regarding exploring the association between bipolar disorder and circadian and chronobiological phenomena were reviewed and findings summarized.

***Results:*** The literature reviewed suggests that circadian rhythm disturbance may be a feature of bipolar disorder.

***Conclusions:*** In toto, the literature suggests that circadian rhythm disturbances may be a feature of bipolar disorder. This area of research has received theoretical consideration as playing a significant role in the pathophysiology of the illness but has been understudied to this point. Further research in the field is warranted.

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***Corresponding author:*** *Robert Gonzalez, MD, Department of Psychiatry, Texas Tech University Health Sciences Center at El Paso, El Paso, TX 79905 (Robert99.Gonzalez@ttuhsc.edu).*

All organisms exhibit rhythmic oscillations in a variety of physiological processes.[1,2] Central to this process is the circadian time-keeping system. The circadian timing system plays a major role in the regulation of important physiological processes such as hormone secretion,[3] sleep-wake cycles,[4] and the orchestration of circadian rhythmicity with respect to the light-dark cycle[5]—all systems that have been implicated in the pathophysiology of bipolar disorder. Disruptions in this timing system result in disturbances of biological rhythms[1] and may have clinical and pathophysiologic relevance to the bipolar disorder. Rhythm disruption is a core feature of bipolar disorder, and it has been hypothesized that disturbances of the circadian timing system play a fundamental role in the etiology of the disorder. The objectives of this study were to summarize (1) theoretical models for biological rhythm disruptions in bipolar disorder, (2) physiological disturbances of biological rhythms in bipolar disorder, (3) clinical and therapeutic implications of biological rhythm disturbances in bipolar disorder, and (4) associations between circadian gene variations and the illness.

## DATA SOURCES AND EXTRACTION

The PubMed database was searched systematically for articles that were published on or before May 5, 2013, and were written in English using the terms *bipolar disorder, clock genes, endogenous clock, molecular clock, biological rhythms, circadian, suprachiasmatic nucleus, circadian rhythm, melatonin,* and *sleep*. One hundred seventeen articles highlighting the objectives were included in the review. Data regarding exploring the association between bipolar disorder and circadian and chronobiological phenomena were reviewed and findings summarized.

## THEORIES OF CIRCADIAN RHYTHM DISRUPTION IN BIPOLAR DISORDER

Rhythm disruption is a core feature of bipolar disorder. Many have hypothesized that disturbances of the circadian timing system play a fundamental role in the etiology of the disorder. Multiple models have been proposed to explain the disruptions in rhythms associated with bipolar disorder. Some have hypothesized that there are intrinsic signatures in the biological rhythms of bipolar patients.[6,7] For example, although the findings were not universally demonstrated,[8] early temporal isolation studies noted that some bipolar disorder patients demonstrated an intrinsic period of rhythms that was shorter than the close to 24-hour period normally observed.[6,7] The opposing models of phase delays[9,10] and phase advances[11–15] of circadian rhythms have also been proposed as the primary circadian rhythm disturbances in the disorder.

While studies suggest that there are phase shifts or inherent differences in the period of biological rhythms, other research findings point to an inherent instability in the biological rhythms of those suffering from the illness. Wide variability in the phases of circadian rhythms have been reported in bipolar disorder.[16–20] In a similar phenomenon to that observed

**Clinical Points**

- Rhythm disturbances may be core pathophysiologic features of bipolar disorder.
- Disruption of biological rhythms may lead to worsening clinical symptoms and negatively impact course of illness in bipolar disorder.
- A greater understanding of the rhythm disturbances in bipolar disorder may lead to chronobiologically based interventions to treat the disorder.

in individuals intolerant to shift work,[21] patients with bipolar disorder may be more susceptible to the disruption of biological rhythms secondary to the blunting or weakening of biological rhythms.[22]

While no consensus has been reached regarding the exact nature of rhythm disruptions in bipolar disorder, all proposed models could potentially result in the internal desynchronization of physiological processes or external desynchronization of the organism with its environment. Unclear is whether a disturbance in the intrinsic time or phase of the biological rhythms, or a general instability of rhythms is responsible for the disturbances seen in bipolar disorder. Also uncertain is whether the rhythm disturbances are a primary pathophysiologic process or secondary to other pathophysiologic mechanisms of the illness.

## BIPOLAR DISORDER AND CHRONOTYPE

Recently, interest in the assessment of chronotype, or the diurnal preference for daily activities, in bipolar disorder has started to emerge. Chronotypes are associated with variations in physiological parameters[23,24] that may be important in the underlying pathophysiology of bipolar disorder. Physiological functions associated with chronotype include variations in catecholamine secretion,[23,25] sleep patterns,[23,26] subjective activation and arousal,[25] circadian rhythms of hormone secretion,[27] and circadian phase and phase relationships in the timing of various rhythms.[24,28,29] Although few in number, studies note that patients with bipolar disorder may have an evening preference for daily activities.[9,30] In the most extensive of these studies, which included 190 subjects with bipolar I and II disorder and controls, the authors reported that bipolar disorder was associated with an evening chronotype and hypothesized that this may reflect a phase delay of circadian rhythms.[9] In addition, the authors reported that chronotype remained stable in a subset of participants that were followed over a 2-year period. One report[31] also suggests that patients suffering from rapid mood swings may also have an evening preference for daily activities. As of yet, no studies have assessed the relationships between chronotype and underlying physiological markers in patients suffering from bipolar disorder. Unclear are the potential influences that imposed social schedules and medications may have on the assessment of chronotype and the expression of associated physiological parameters.

## BIPOLAR DISORDER AND SOCIAL RHYTHMS

Disruptions in the social rhythms of bipolar patients have been described. Literature suggests that bipolar patients demonstrate a lower degree of regularity in social rhythms when compared to controls.[32] The literature also suggests that in patients with bipolar disorder a disruption of social factors (ie, personal relationships, work, hobbies, daily routines, and life events) could destabilize overt biological rhythms and eventually lead to the exacerbation of mood episodes.[33] For example, association between life events that disrupt social rhythms and the onset of mania[33,34] has been reported. These observations have led some to hypothesize that stabilization of social rhythms could be a positive adjunct for the treatment of bipolar disorder. Interpersonal and social rhythms therapy (IPSRT),[35] for example, emphasizes the maintenance of daily rhythms and monitoring the influence that life events have on these routines. Patients receiving IPSRT in the acute phase of illness have demonstrated a longer time to the appearance of a new episode, an increase in regularity of social rhythms, and a more rapid improvement in occupational functioning.[36] An interesting finding of this research has demonstrated that altering treatment was related to increased recurrence risk.[37] These findings suggest that course of illness could be influenced by the stabilization or destabilization of social rhythms or daily routines and suggest possibilities for nonpharmacologic interventions for the illness.

## SEASONAL PATTERNS IN BIPOLAR DISORDER

While there are conflicting reports,[38] a subset of bipolar patients demonstrates a seasonal pattern to their mood episodes.[39–43] Depressive episodes have been reported to occur with greater frequency during the winter months, while manic episodes occur with greater frequency in the spring and summer.[39,40] The seasonal fluctuations in the types of mood episodes may be secondary to differences in photic stimuli. Variations in response to photic stimuli may have clinical as well as diagnostic implications. For example, it is hypothesized that the therapeutic effects of light therapy may work by shifting the phase of circadian rhythms.[44] Phototherapy has long been used for the treatment of seasonal affective disorder and has demonstrated efficacy in the treatment of both seasonal and nonseasonal depression[45] as well as for bipolar depression.[46–50] While phototherapy is considered to be well tolerated, there are several reports of serious adverse events being associated with bright light therapy, including suicidal ideation/suicide attempts,[51] mania,[49,52–54] and mood instability.[48,55] Difficulties arise when interpreting the results of these reports, especially when one considers the variability in the intensity, timing, and duration of administered light to which patients were exposed. While more rigorous randomized control trials are required to evaluate the efficacy of phototherapy[45] and the phenotypic and pathophysiologic implications of the response of light in bipolar disorder, both the reported

seasonality as well as the side effects associated with bright light therapy suggest that patients with bipolar disorder may demonstrate a hypersensitivity to photic stimuli.

## BIPOLAR DISORDER AND THE MELATONERGIC SYSTEM

The hormone melatonin is a fundamental component of the circadian timing system. Melatonin is produced and secreted by the pineal gland in a diurnal fashion.[56] The production of melatonin is significantly influenced by only endogenous circadian rhythms[57] and by ocular light exposure[56] that acts to inhibit melatonin production in a dose-dependent fashion. A dysfunction in the rhythmic secretion of melatonin may underlie some of the pathophysiology of bipolar disorder.[58] Even though melatonin has proven to be a reliable marker of circadian phase,[59] few studies have focused on this measure in bipolar disorder and have yielded contradictory findings. While some studies report phase disturbances[10,60] in the melatonin secretion in bipolar patients, others report no phase variations.[61] Bipolar patients have demonstrated significantly lower peak nocturnal melatonin levels[10] when compared to healthy controls. Both euthymic and acutely ill bipolar patients have also demonstrated a hypersensitive pineal response to ocular light exposure when compared to controls, as noted by a 2-fold greater drop in plasma melatonin after nocturnal light exposure.[62] Of interest, literature suggests that both valproic acid and lithium may exert some of their therapeutic effects by decreasing the sensitivity of melatonin secretion to nocturnal bright light administration[63,64]; however, these studies have yet to be conducted in patients with bipolar disorder. It remains unclear whether these findings indicate a primary dysfunction of the circadian timing system or other factors that modulate its expression (ie, hypersensitivity to light exposure) and the potential impact of light exposure on the phase of melatonin secretion.

Given its key function in the maintenance of circadian rhythms, melatonin has been hypothesized to be of potential therapeutic benefit. Two small open-label studies have examined the therapeutic effects of melatonin in bipolar disorder. One study[65] reported that melatonin administration was associated with increased sleep duration as well as a decrease in manic symptoms. The second study[66] reported that melatonin did not have a beneficial effect and that melatonin withdrawal was associated with both delayed sleep onset as well as mild mood elevation. Some of the most compelling evidence for manipulation of the melatonergic system in the treatment of bipolar disorder has emerged from studies of the novel antidepressant agomelatine, a potent melatonin receptor agonist.[67] Agomelatine has shown efficacy in the treatment of seasonal and nonseasonal depression.[67] One open-label study[68] of adjunctive agomelatine treatment in bipolar depression reported that 81% of subjects showed a greater than 50% improvement in depressive symptoms. It is a possibility that the clinical improvements noted may be secondary to agomelatine's effect on sleep and circadian rhythms. Agomelatine administration has been reported to increase rapid eye movement (REM) and result in a phase advance of circadian rhythms[67] in healthy individuals. Agomelatine administration has also been shown to result in improvements in sleep quality and sleep efficiency as well as a possible normalization of non-REM sleep[67] in depressed patients. Given the dosing schedule, it is unclear whether the noted therapeutic effects of melatonin agonist are produced via manipulation of the circadian timing system (ie, entrainment), secondary to somnolence, effects on the circadian clock, or whether other mechanisms were involved. While timed melatonin administration has demonstrated efficacy in the treatment of circadian rhythm and sleep disorders, these protocols have yet to be studied in bipolar disorder using melatonin or melatonin agonists.

## BIPOLAR DISORDER AND SLEEP-WAKE CYCLES

The biological timing system plays a major role in the regulation of sleep,[2] including sleep propensity and sleep structure.[4,69] It is therefore no surprise that disturbances of the biological timing system are associated with disturbances in sleep-wake cycles.[70] Sleep disturbance is a hallmark of bipolar disorder. Sleep disruptions have been associated with a worse course of illness,[71,72] increased symptom severity,[71–73] and impairments in functioning and quality of life,[71–73] and they may be initial prodromes[74–76] and trait markers[73] for the illness. Somnographic findings in both manic and depressed bipolar subjects include a disruption in sleep continuity, increased time spent in stage 1 sleep, shortened REM latency, and an increase in the density of REM sleep.[77] Even though many of these findings point to the detrimental effects of sleep disturbances in bipolar disorder, these observations have led some to hypothesize that manipulation of the sleep-wake cycle may yield potential clinical benefits. While the antidepressant effects of sleep deprivation are transient, significant data have accumulated that indicate that sleep deprivation is an effective treatment for both unipolar and bipolar depression,[78] with some reports suggesting that patients with bipolar depression may respond preferentially to this treatment.[78] The antidepressant effects of sleep deprivation are robust and occur rapidly usually within the course of 24 hours.[79,80] Both lithium[81,82] and sleep phase advancement[81] have been shown to sustain the antidepressant effects of sleep deprivation. Some have hypothesized that sleep deprivation owes its antidepressant effects to the resetting of abnormalities in endogenous molecular clocks.[80] Even though reports of therapeutic benefits of sleep deprivation are encouraging, it should be noted that sleep deprivation has been reported to precipitate manic or hypomanic episodes.[83] While these studies suggest a causal relationship between sleep deprivation and the switch to mania, some studies have reported that the decreased sleep time and insomnia present prior to the switch,[84,85] suggesting that decreased sleep may be a naturally occurring characteristic of the switch process. Although not yet fully explored in bipolar disorder, sleep deprivation may impact the functioning of various physiological systems implicated in the pathophysiology of the illness, such as the hypothalamic-

**Table 1. Summary of Chronobiological Findings Associated With Bipolar Disorder**

| Chronotype Topic | Study |
|---|---|
| Proposed circadian disturbances in bipolar disorder | Inherent less than 24-hour rhythm |
| | Bipolar disorder subjects free run with circadian rhythms shorter than near 24-hour rhythm usually noted[6,7] |
| | Lithium slowed and lengthened this rhythm[7] |
| | Phase delay |
| | Later time to melatonin secretion in bipolar disorder compared to controls[10] |
| | Greater preference for evening activities in bipolar disorder subjects as compared to controls[9] |
| | Phase advance |
| | Phase advance in urinary 3-methoxy-4-hydroxyphenylglycol in bipolar disorder subjects as compared to controls[11] |
| | Phase advance in temperature in bipolar disorder subjects as compared to controls[11] |
| | Early timing of the nadir of adrenocorticotropic hormone and cortisol secretion in bipolar disorder subjects as compared to controls[13–15] |
| | Phase advancement of activity rhythms in manic and mixed patient compared to controls and euthymic patients[12] |
| | Phase advancement of activity rhythm in euthymic bipolar disorder patient compared to controls[12] |
| | Instability/variability |
| | Significant variation and fluctuation in body temperature in mania[16,17] |
| | Significant variation and fluctuation in body temperature in depression[16–19] |
| | Less stable and more variable circadian activity patterns in bipolar disorder subjects as compared to controls[20] |
| Chronotype | Association with bipolar disorder |
| | Evening chronotype in bipolar disorder as compared with controls[9,30] |
| | Rapid mood swings in patients associated with lower composite scores[31] |
| Social rhythms | Association with bipolar disorder |
| | Life events associated with social rhythm disturbances were associated with the onset of mania[33,34] |
| | Lower social rhythm metric scores in rapid-cycling bipolar disorder compared to controls[32] |
| | Phase delays noted in depression as compared to hypomania and euthymia[32] |
| | Treatment (interpersonal and social rhythms therapy [IPSRT]) |
| | No difference between IPSRT and intensive clinical management in adjunctive treatment after 2 years[36] |
| | More rapid initial improvement[36] |
| | Greater improvement in occupational functioning[36] |
| | Altering treatment was related to increased recurrence risk[37] |
| Seasonality and photic | Association with bipolar disorder |
| | Mania with peak in early spring and nadir in late fall[39] |
| | Mixed mania peaked in late summer and nadir in November[39] |
| | No seasonal pattern of mania[40] |
| | Preponderance of depression in autumn[40] |
| | Greater degree of seasonality in bipolar disorder subjects as compared to controls and unipolar depression subjects[41] |
| | Bipolar disorder subjects exhibit intermediate seasonality between controls and seasonal affective disorder patients[42] |
| | Bipolar disorder twins demonstrate greater seasonality and seasonal changes in sleep and mood as compared to control twins[43] |
| | Treatment |
| | Efficacy in the treatment of nonseasonal bipolar depression[47] |
| | Phototherapy enhanced the efficacy of sleep deprivation in treating bipolar depression[46] |
| | Light therapy showed some benefits and side effects in adjunctive treatment in rapid cycling bipolar patients[48] |
| | Midday exposure indicated some improvement[48,49] |
| | Morning sunlight decreased hospital stay in bipolar depression[50] |
| | Adverse effects |
| | Manic symptoms associated with phototherapy[52–54] |
| | Mixed states associated with morning administration of phototherapy[49] |
| | Mood instability associated with morning administration of phototherapy[48] |
| | Mood swings associated with uncontrolled light exposure[55] |
| | Phototherapy associated with suicidality[51] |
| Melatonin | Association with bipolar disorder |
| | Bipolar disorder patients had significantly lower melatonin levels compared to unipolar and control groups with nocturnal light exposure[10] |
| | Later peak time for melatonin on dark night[10] |
| | Phase delay of melatonin secretion[60] |
| | Lower levels of melatonin or urinary 6-sulfatoxymelatonin in bipolar disorder compared to controls[61] |
| | No differences in melatonin secretion between mood state[61] |
| | Twofold greater decrease in euthymic unmedicated bipolar disorder patients compared to controls after nocturnal light exposure[62] |
| | Treatment |
| | Adjunctive melatonin treatment for insomnia in bipolar disorder increased sleep time and decreased mania[65] |
| | Adjunctive treatment with melatonin in rapid-cycling bipolar disorder showed no improvement in mood or sleep[66] |
| | Agomelatine adjunctive therapy for bipolar disorder depression demonstrated efficacy (80% met response [50% decrease in 17-item Hamilton Depression Rating Scale score])[68] |
| | Decreased sensitivity of melatonin secretion to nocturnal light exposure in healthy controls after treatment with lithium[63] and valproic acid[64] |
| | Adverse effects |
| | Melatonin withdrawal was associated with delayed sleep onset and possible mood elevation[66] |

*(continued)*

**Table 1 (continued). Summary of Chronobiological Findings Associated With Bipolar Disorder**

| Chronotype Topic | Study |
|---|---|
| Sleep | Association with bipolar disorder |
| | Manic and depressed bipolar disorder patients exhibit disturbed sleep continuity, increased stage 1 sleep, shortened rapid eye movement (REM) latency, and increased REM density when compared to controls[77] |
| | Lower and more variable sleep efficiency associated with more lifetime depressive episodes[71] |
| | Variability in falling asleep time associated with concurrent depressive symptoms[71] |
| | Decreased sleep efficiency associated with manic symptoms[71] |
| | Greater REM density in bipolar disorder patients compared to controls[72] |
| | Duration of REM and slow-wave sleep were positively correlated with manic symptoms[72] |
| | Short sleep duration associated with more severe symptoms[73] |
| | Short and long sleep duration associated with poor functioning and quality of life[73] |
| | Higher rates of sleep disturbance in high-risk offspring of parents with bipolar disorder[74] |
| | Sleep disturbances noted as prodromes of the illness[75,76] |
| | Decreased sleep prior to manic switch[85] |
| | Treatment |
| | Efficacy of sleep deprivation in bipolar disorder patients[78] |
| | Efficacy of sleep deprivation greater in bipolar disorder when compared to unipolar depressive subjects[78,83] |
| | Lithium sustains the antidepressant effects of sleep deprivation[81,82] |
| | Sleep phase advance sustains the antidepressant effects of sleep deprivation[81] |
| | Adverse effects |
| | Manic switch secondary to sleep deprivation[83,84] |

pituitary-adrenal axis,[86] the serotonergic[87] and dopaminergic systems,[87,88] and may result in the activation of specific brain regions (eg, hippocampus[89] and prefrontal cortex[90]).

A summary of the chronobiological findings associated with bipolar disorder is summarized in Table 1.

## RELATIONSHIP BETWEEN BIPOLAR DISORDER AND CIRCADIAN GENES

The precision of the circadian timing system is, in large part, dictated by the expression of circadian genes and the interactions of their protein products.[1,5] Alterations in these core circadian genes can change the expressed circadian period and phase[91] and disrupt normal circadian rhythmicity.[92] Given the social, behavioral, and physiological rhythm disturbances that characterize bipolar disorder, genes that encode the components of endogenous clocks or systems that modulate them would suggest them to be good candidate genes.

Studies in bipolar disorder suggest that variations in circadian genes could potentially impact the expression of the disease, may be associated with specific clinical aspects of the illness, and may serve as markers for treatment response. Recent studies suggest an association between variations in circadian genes and bipolar disorder as well as specific clinical characteristics of the illness.[93–110] These findings are summarized in Table 2. Preliminary studies categorizing functioning of molecular clocks in bipolar patients also seem to indicate that less robust molecular clocks may be associated with the illness.[111]

Emerging literature suggests that certain pharmacologic treatments for the illness may exert some of their therapeutic action via their influence on endogenous molecular clocks. Both lithium[112] and valproic acid[113] have been shown to influence the rhythmic expression of circadian genes and the rhythmic properties of molecular clocks. Lithium[114] and valproic acid[115] may exert some of these actions via inhibition of glycogen synthase kinase-3β (GSK3-β). Inhibition of GSK3-β results in modification of phosphorylation patterns in circadian proteins with subsequent lengthening of circadian period. Interestingly, a single nucleotide polymorphism located in the GSK3-β promoter region has been associated with response to total sleep deprivation during depressive episodes[94] and long-term response to lithium treatment[95] in bipolar patients.

Perhaps the most compelling evidence implicating circadian genes in the pathophysiology of bipolar disorder comes from a unique animal model. Roybal and colleagues[116] have mice with a point mutation in the gene *CLOCK* that yields an inactive protein. The behavioral profile of the *CLOCK* mutant mice is strikingly similar to manic symptomatology. These mice demonstrate decreased time spent in all sleep stages, decreased anxiety-like behavior, and an increased sensitivity to the rewarding effects of cocaine. From a physiological perspective, the ventral tegmental area (VTA) dopaminergic neurons in the *CLOCK* mutants show increased firing rates, an increase in the expression of tyrosine hydroxylase activity, and a decreased expression of other clock genes, such as *PER1*, *PER2*, *CRY*, and *CK1ε*. Interestingly, both the delivery of a functional *CLOCK* gene to the VTA dopamine neurons via viral gene transfer and lithium treatment returned many behaviors of *CLOCK* mutants to near wild-type levels. Taken together, these results suggest an important role for circadian genes in regulating complex behavior and may represent an animal model for mania.

## FUTURE DIRECTIONS

Even though there is compelling evidence to suggest biological rhythm disruption in bipolar disorder, as of yet no consensus has been reached as to the exact nature of these disturbances. Small sample sizes, lack of control or comparator groups, research in mixed-diagnosis populations, and a lack of accounting for potential masking effects impacting the accurate assessment of outcome variables in

**Table 2. Summary of Reported Associations Noted Between Circadian Gene Variations, Bipolar Disorder, and Clinical Characteristics of the Illness**

| Circadian Gene OMIM Nomenclature (chromosomal location) | Genetic Association |
|---|---|
| *BHLHB2 (DEC1)* Basic helix-loop-helix domain containing, class B, 2 (3p26.1) | SNP associated with bipolar disorder[96] |
| *BHLHB3 (DEC2)* Basic helix-loop-helix domain containing, class B, 3 (12p12.1) | SNP associated with bipolar disorder[99] |
| *ARNTL1 (BMAL1)* Aryl hydrocarbon receptor nuclear translocator-like 1 (11p15) | SNPs associated with bipolar disorder[97–99]<br>Haplotype associated with bipolar disorder[100]<br>SNPs and haplotypes associated with rapid cycling[96] |
| *ARNTL2 (BMAL2)* Aryl hydrocarbon receptor nuclear translocator-like 2 (12p12.2-p11.2) | SNP associated with bipolar disorder[99]<br>SNP associated with diurnal mood worse in the evening[96] |
| *CK1ε* Casein kinase 1 epsilon (22q13.1) | Haplotype associated with rapid cycling[96]<br>SNP associated with bipolar disorder [98,99]<br>SNPs associated with morningness[101] |
| *CSK1δ* Casein kinase 1 delta (17q25) | SNP associated with bipolar disorder[101] |
| *CLOCK* Circadian locomotor output cycles kaput (4q12) | SNP associated with increased recurrence rates[110]<br>SNPs associated with insomnia[96,102]<br>Haplotypes associated with insomnia[96]<br>SNP associated with greater insomnia with selective serotonin reuptake inhibitor treatment for depression[103]<br>SNPs associated with bipolar disorder[101]<br>SNPs and haplotypes associated with rapid cycling[96]<br>SNP associated with bipolar disorder[99]<br>SNP associated with diurnal preference of daily activities[104] |
| *CRY1* Cryptochrome 1 (12q23-q24.1) | SNP nominally associated with bipolar disorder[99] |
| *CRY2* Cryptochrome 2 (11p11.1) | SNP associated with bipolar disorder[98] |
| *DBP* D site of albumin promotor-binding protein (19q13.3) | SNP associated with diurnal mood worse in the evening[96] |
| *GSK3-β* Glycogen synthase kinase 3 β (3q13.3) | SNP associated with later age at onset[94]<br>SNP associated with greater response to total sleep deprivation[94]<br>SNP associated with response to lithium[95]<br>SNP associated with female gender in bipolar II disorder[105] |
| *NPAS2* Neuronal PAS domain protein 2 (2q11.2) | SNPs associated with bipolar disorder[98,99,101] |
| *NPAS3* Neuronal PAS domain protein 3 (14q12-13) | SNPs and haplotypes associated with bipolar disorder [106]<br>Haplotypes associated with increased risk and protective attributes[106] |
| *NR1D1* Nuclear receptor subfamily 1, group D, member 1 (17q11.2) | SNP associated with female bipolar disorder patients[107]<br>SNPs associated with bipolar disorder [101]<br>Haplotype associated with bipolar disorder [108]<br>Haplotype associated with age at illness onset[108] |
| *PER1* Period homolog 1 (drosophila) (17p13.1) | SNP associated with bipolar disorder [101] |
| *PER2* Period homolog 2 (drosophila) (2q37.3) | SNPs associated with bipolar disorder [101] |
| *PER3* Period homolog 3 (drosophila) (1p36.23) | SNPs associated with bipolar disorder [97,99]<br>Haplotype associated with bipolar disorder [100]<br>SNP associated with eveningness[101] |
| *RORα* RAR-related orphan nuclear receptor α (15q22.2) | SNP nominally associated with bipolar disorder [99] |
| *RORβ* RAR-related orphan nuclear receptor β (9q22) | SNPs associated with bipolar disorder [98]<br>SNPs and haplotype associated with bipolar disorder in a pediatric population[109] |
| *TIM* Timeless homolog (drosophila) (12q13.3) | SNPs associated with bipolar disorder [97]<br>SNP associated with insomnia in mania[96]<br>Haplotype associated with rapid cycling[96] |

Abbreviations: OMIM = Online Mendelian Inheritance in Man, SNP = single nucleotide polymorphism.

early studies may contribute to contradictory findings and the difficulties in the interpretation of studies conducted to this point. The expression of endogenous circadian rhythms is influenced by exogenous factors (eg, daily activities, lifestyle choices, environmental factors).[117] These exogenous factors can cause alterations in the expression of endogenous circadian rhythms.[117] These factors must be accounted for in order to accurately characterize and measure endogenous rhythms.[117] In addition, it should be noted that many of these studies used different methodologies and focused on testing different physiological parameters (eg, various hormones, peptides, temperature), thus making comparisons between studies difficult.

A broadening of our conceptual and theoretical approaches to studying biological rhythms in bipolar disorder is required. For example, many of the studies conducted to this point in bipolar disorder have focused on circadian or diurnal rhythms. It is well known that biological rhythms fluctuate at multiple different lengths. Not only must circadian (~24 hours) rhythms be considered but also ultradian (cycles occurring with periods shorter than 24 hours) and infradian (cycles occurring with periods longer than 24 hours) rhythms. A broader range of study designs that sample markers of rhythm at multiple sampling densities and time durations is therefore required to fully characterize the rhythm disturbances in bipolar disorder. Specific protocols have been developed in order to control for the environmental factors that can mask biological rhythms. These protocols are challenging for both researchers and subjects and require the control of multiple variables (eg, constant dim lighting, subjects being required to remain supine, isocaloric meals). In addition, many of these protocols involve sleep deprivation or disturbances of the normal 24-hour sleep-wake cycle. Even though masking is reduced in these protocols, it presents some clinical challenges when considering conducting these experiments in bipolar subjects.

While both clinical and preclinical research point to a disruption of the biological timing system in bipolar disorder, the possibility that rhythm disturbances are an epiphenomenon exists. The circadian timing system is heavily intertwined with other physiological systems and is influenced by both internal and external environmental factors. Perhaps other physiological or environmental processes act to destabilize biological rhythms rather than there being a primary dysfunction in the biological timing system itself. One of the challenges of future research in the field will be to define the relationships between rhythm disturbances and other physiological processes noted in bipolar disorder.

In toto, the literature suggests that circadian rhythm disturbance may be a feature of bipolar disorder. This biological rhythm disruption is an area that has received theoretical consideration as playing a significant role in the pathophysiology of the illness but has been grossly understudied. An improved understanding of biological rhythm disturbances may enhance our understanding of bipolar disorder on multiple pathophysiologic levels. The development of intermediate phenotypes based on chronobiology may provide a directed approach to examining the possible pathophysiologic mechanisms of the disorder. Further research of rhythm disturbances in bipolar disorder could provide clues to the mechanisms underlying variations in clinical symptoms and course of illness,[9,41,110] factors leading to illness decompensation,[39,83] and the mechanisms of action of pharmacologic treatment for the disorder.[63,64,114] The development of chronobiologically based pharmacologic[68] and nonpharmacologic[35,44,78] treatments for the illness may also be a consequence of research in this area.

***Drug names:*** lithium (Lithobid and others), valproic acid (Depakene and others).

***Author affiliation:*** Department of Psychiatry, University of Texas Health Sciences Center, San Antonio. Dr Gonzalez is currently at the Department of Psychiatry, Texas Tech University Health Sciences Center at El Paso.

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