Sleep Medicine Reviews 41 (2018) 133–140

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

THEORETICAL REVIEW

Delayed sleep phase syndrome and bipolar disorder: Pathogenesis and available common biomarkers

Farid Talih [a, b, *], Nour Y. Gebara [a, **], Farah S. Andary [a], Stefania Mondello [c, d], Firas Kobeissy [a], Raffaele Ferri [d]

[a] Faculty of Medicine, American University of Beirut Medical Center, Beirut, Lebanon
[b] Department of Psychiatry, American University of Beirut Medical Center, Beirut, Lebanon
[c] Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Messina, Italy
[d] Sleep Research Centre, Oasi Research Institute IRCCS, Troina, Italy

A R T I C L E I N F O

Article history:
Received 19 October 2016
Received in revised form
3 February 2018
Accepted 7 February 2018
Available online 13 February 2018

Keywords:
Circadian rhythm sleep-wake disorders
Bipolar disorder
Delayed sleep wake phase disorder
Biomarkers
Mood disorder
Sleep disorders
Melatonin

S U M M A R Y

Circadian rhythm disturbances are common in bipolar affective disorder (BD). Delayed sleep-wake phase syndrome (DSWPD) is the most prevalent circadian rhythm sleep-wake disorder (CRSWDs) and is frequently observed in BD. It is unclear whether DSWPD in BD is an independent process or is a consequence of BD. In this hypothetical review, we discuss the overlap between BD and DSWPD and potential common biomarkers for DSWPD and BD. The review will include a discussion of the genetics of DSWPD and BD. Biomarkers elucidating the pathophysiological processes occurring in these two disorders may offer insight into the etiology and prognosis of both conditions.

Introduction

Circadian rhythm sleep-wake disorders (CRSWD) are due to abnormalities in the circadian time-keeping system characterized by a misalignment between the endogenous circadian rhythm and the environment. CRSWDs are associated with difficulties in initiating sleep, excessive daytime sleepiness, and functional or cognitive impairment [1]. Delayed sleep-wake phase syndrome (DSWPD) is the most studied CRSWD. It has a typical onset during the second decade of life and is associated with abnormalities in sleep initiation [2,3]. Individuals with DSWPD exhibit delayed sleep/wake times by at least 2 h from socially desired times [4]. DSWPD has been identified as a possible risk factor for bipolar affective disorder (BD), a psychiatric condition characterized by cyclical fluctuations in mood [5–7]. BD has a prevalence of approximately 2% and is a major cause of psychiatric disability [3,6].

There is significant evidence linking BD and DSWPD and both disorders exhibit similar pathophysiological and clinical characteristics [8,9]. This could be due to shared biological pathways and overlapping genetic profiles. We hypothesize that biomarkers for DSWPD such as melatonin levels or circadian rhythm genes may be associated with BD. Examining these biomarkers and genes can represent a novel approach to better understand the evolution and progression of BD. Biomarkers can provide insight into the underlying mechanisms of these disorders and may assist in the development of treatment modalities [10]. In this manuscript, we will examine candidate biomarkers for DSWPD and BD, and focus on the role of circadian genes and their expression profiles that may represent common denominators for both conditions.

Methods

When the review was conceptualized, we opted for a systematic review approach as per the Cochrane guidelines for systematic reviews. MEDLINE, PubMed, and Google Scholar were queried

* Corresponding author. Building 56, 3rd Floor, Department of Psychiatry, American University of Beirut Medical Center, PO Box 110236, Cairo Street, 1107 2020, Beirut, Lebanon. Fax: +961 1 749209
** Co-corresponding author.
E-mail addresses: ft10@aub.edu.lb (F. Talih), nyg00@mail.aub.edu (N.Y. Gebara).

https://doi.org/10.1016/j.smrv.2018.02.002
1087-0792/

Abbreviation list

AA-NAT	Arylalkylamine N-acetyltransferase
BB	blue blocking
BD	bipolar disorder
BDNF	brain Derived Neutrophic Factor
BMAL1	Aryl hydrocarbon receptor nuclear translocator-like protein 1
CBT	core body temperature
CRSWD	circadian rhythm sleep-wake disorders
cry1 and cry2	cryptochromes genes
CSNK1D	casein kinase 1 delta
DLMO	dim light melatonin onset
DSM-5	Diagnostic and Statistical Manual of Mental Disorders
DSWPD	delayed sleep wake phase disorder
EDS	excessive daytime sleepiness
GSK3β	glycogen synthase kinase 3-beta,
HPA	hypothalamic-pituitary-adrenal
hper3	human period 3
Li	Lithium
MMP-9	metalloproteinase-9
MT1	melatonin receptor 1
MT2	melatonin receptor 2
NLR	neutrophil-lymphocyte ratio
per1 per2 and per3	period genes
PLR	platelet-lymphocyte ratio
PRC	phase response curve
PTM	post-translational modification
REM	rapid eye movement
ROR	retinoic acid-orphan receptor
RREs	retinoic acid-orphan receptor response elements
SCN	suprachiasmatic nucleus
sIL-2R	soluble Interleukin 2 receptor
SNPs	single nucleotide polymorphisms
sTNFR1	soluble tumor necrosis factor receptor type 1
TNF- α	tumor necrosis factor- α
VNTR	variable-number tandem-repeat
YMRS	Young Mania Rating Scale

using standardized terms related to BD and DSWPD. Non-peer reviewed studies were excluded to ensure methodological integrity [11]. All articles evaluating biomarker for DSWPD in individuals with BD up to March 2017 were selected for review. Additionally, articles examining links between BD and DSWPD were also included for screening. Despite the relatively large number of studies identified, there was considerable variability in terms of biomarkers evaluated and study design and quality. Due to the heterogeneity of the literature and the paucity of studies that address our hypothetical question, the authors concluded that a systematic review was not feasible and subsequently opted for a theoretical review. The literature review was conducted by three of the authors (NG, FA, and FT). Two reviewers screened abstracts of potentially relevant publications; if the article was deemed relevant to our topic the full manuscript was reviewed. Discrepancies were resolved by consensus with a third author.

Delayed sleep-wake phase syndrome

The suprachiasmatic nucleus (SCN) maintains the endogenous circadian rhythm [12]. The SCN receives and processes information from the retina via the retinohypothalamic pathway and modulates the secretion of the hormone melatonin from the pineal gland via the autonomic nervous system [6]. Many physiologic functions exhibit circadian rhythmicity, these include: endocrine functions, core body temperature (CBT), and alertness [6]. Synchronization or entrainment of the endogenous circadian rhythm with the environment is achieved through environmental cues known as zeitgebers. Zeitgebers include temperature, feeding and light. Light is the most effective zeitgeber [13]. Entrainment ensures that the circadian clock remains in phase with the solar 24 h day (Fig. 1) [14].

The exact pathophysiology of DSWPD remains unclear [12], proposed theories include: abnormalities in the circadian system

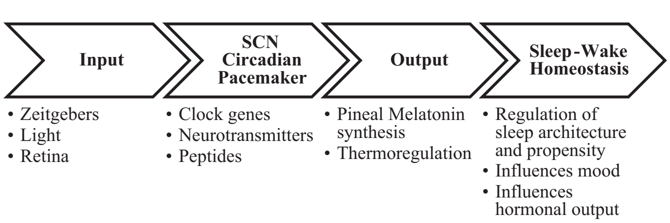

Fig. 1. Entrainment of the circadian rhythm with zeitgebers.

and sleep homeostasis, behavioral and neuropsychiatric factors, and genetic predisposition [2]. Behavioral patterns appear to play a role in perpetuating DSWPD [15]. The major factors implicated in DSWPD will be discussed in the following section.

Factors implicated in DSWPD

Behavioral factors

Behavioral factors have been shown to contribute to the pathogenesis of DSWPD [16,17]. Circadian phase delayed individuals were found to have an evening chronotype and when forced to rise earlier than their preferred times they were irritable, lethargic, and dysphoric [15]. Individuals with DSWPD frequently engage in activities such as late night socializing, using electronic devices at bedtime, and increased stimulant use (nicotine and caffeine) that perpetuate the disorder. Delayed bedtimes and compensatory behaviors exacerbate DSWPD [15]. Shirayama et al. [17] observed impulsivity, decreased motivation, and emotional dysregulation when assessing the psychological profiles of individuals with DSWPD. Regestein et al. [18] proposed that loss of external timing related information and social cues explains this psychological profile. Takashi et al. [19] detected depression in 64% of their DSWPD sample and symptoms were reported to be worse in the morning [19]. It is also important to note the significant association between depressive symptoms and an evening chronotype. Additionally, those with an evening chronotype tend to report more attention problems, emotional lability, and substance abuse [19].

Melatonin

The hormone melatonin is secreted by the pineal gland into the cerebral capillary system and the cerebrospinal fluid (CSF). Melatonin secretion begins in the evening, peaks around midnight, and then decreases gradually until levels become undetectable in the morning. Melatonin influences the secretion patterns of the endocrine system, CBT fluctuations, and modulates the immune system. Due to its circa annual variation melatonin was found to influence seasonal changes in sleep and appetite [12]. At the molecular level, melatonin functions in two ways. One function effects the expression of the clock genes in the pars tuberalis of the pituitary and influences the SCN directly by binding to its melatonin receptors (MT1 and MT2) [6]. Another function of melatonin is to modulate the electrical and metabolic activities of SCN neurons which alters the phase and amplitude of the circadian cycle [20]. Serial sampling of salivary or plasma melatonin levels or 6-sulfatoxymelatonin (melatonin metabolite) can be used to measure the phase of melatonin secretion. Changes in melatonin levels collected under controlled posture and dim light conditions, are optimal markers of the circadian phase in humans [14]. CBT fluctuations are a manifestation of the SCN rhythmic activity and can be used as a biomarker to measure the circadian rhythm. CBT decreases in the evening and reaches its nadir during the second half of the sleep cycle [21]. Chang et al. [4] showed that CBT rhythms are phase delayed in DSWPD. Micic et al. [22] supported these findings by demonstrating that the temperature rhythm of a DSWPD group delayed faster than a control group [23–25]. In normal sleepers CBT demonstrated phase shifts in response to light exposure [26–28], in DSWPD individuals phase shifts did not occur with exposure to light [4].

Genes and genetics

The circadian clock involves an autonomous transcription–translation feedback loop composed of a core set of genes that are highly conserved in mammals. These include the “locomotor output cycles kaput” gene [29]; and its paralogue “neuronal PAS domain protein 2” (Npas2), and the brain and muscle aryl hydrocarbon receptor nuclear translocator-like (ARNT-like) gene-1 (Bmal1) that translates the CLOCK and BMAL1 proteins. During the day, the heterodimer formed by these proteins promotes the transcription of period genes (per1, per2 and per3) and cryptochromes genes (cry1 and cry2). The resulting PER and CRY proteins heterodimerize, move to the nucleus and interact with the CLOCK-BMAL1 complex to inhibit gene transcription. After a constant time period, the PER-CRY receptor complex is degraded allowing the CLOCK–BMAL1 to activate another cycle of transcription [6,30]. The time period of this perpetual loop ultimately determines an organism's circadian rhythm.

Post-translational modification (PTM) and degradation of circadian CLOCK proteins are also crucial in determining circadian rhythmicity. For example, post translation, the PER and CRY proteins are subjected to phosphorylation PTM by key kinases like casein kinase 1 delta (CSNK1D), CSNK1D and the glycogen synthase kinase 3-beta (GSK3β). This phosphorylation occurs rhythmically in synchronization with daylight. Given that the main role for the phosphorylation of CLOCK proteins is to prepare them for polyubiquitination and degradation by the 26S proteosomal pathway, the PER/CRY phosphorylated complex will be degraded during darkness (night); removing the inhibition of CLOCK-BMAL1 and allowing the further transcription of Per and Cry genes. A 24 h-long negative feedback loop is formed as a result of the above cycle [6,30].

A secondary self-regulating feedback loop also exists. It is composed of Rev-erbA, which is targeted by the CLOCK-BMAL1 transcription complex. Rev-erbA suppresses the transcription of Bmal1 via an inhibitory pathway. It also competes with a retinoic acid-orphan receptor (ROR) to bind ROR response elements (RREs) in the Bmal1 promoter. This secondary feedback loop regulates the main feedback loop [6,30]. Associations between structural polymorphisms in circadian rhythm genes and circadian disorders [31] have been reported; these include the H4 haplotype of the human period 3 (hper3) clock gene, variable-number tandem-repeat (VNTR) polymorphism present in the PER3 gene [32,33], and a variation of the CRY1 gene in familial DSWPD [34].

A significant association was found by Hohjoh et al. [35] between the arylalkylamine N-acetyltransferase (AA-NAT) gene and DSWPD. The AA-NAT gene codes for a rate-limiting enzyme in melatonin synthesis and is responsible for the cyclical changes in melatonin levels. Four single nucleotide polymorphism (SNP) sites were observed for the gene; only one (619SNP) was implicated in DSWPD. The allele positivity of 619A (129Thr) was found to be significantly higher in DSWPD cases (16%) when compared to controls (3%). The 619 SNP is involved in an amino acid substitution (alanine to threonine). Therefore, the AA-NAT gene can be implicated in the development of DSWPD and is potentially a susceptibility gene [35].

The impact of genetics in DSWPD is highlighted by the presence of familial cases [36,37] and by twin studies [38–41]. Fukuda et al. reported that monozygotic twins had less variations in sleep patterns than dizygotic twins [42].

DSWPD and BD: common factors and pathways

The circadian timing system plays an important role in many physiologic functions. In BD it is unclear whether the rhythm disturbances are a primary pathological process or secondary to the disorder itself [43]. Sleep disturbances appear to be present during all stages of BD [44]. Yoshikazu et al. [45] demonstrated that DSWPD appears to be more prevalent among BD patients (32.4%) than the general population. Dagan et al. [12], showed that those with personality disorders and BD had high rates of DSWPD. There is increasing evidence that individuals with BD and DSWPD share common clinical and biological/biomarker profiles, which we will discuss in the following sections.

Clinical features and profiles

Circadian rhythm abnormalities are observed in all phases of BD [46–48]. For example, patients with acute BD depression present with insomnia, early awakening and hypersomnia; while manic/euphoric patients show a decreased need for sleep and hyper vigilance. Circadian abnormalities are considered to be a trait of BD since they are also observed in euthymic BD patients. Euthymic patients exhibit an evening chronotype, hypersensitivity to fluctuations in light, and abnormal melatonin secretion [48,49].

Wood et al. showed that individuals with DSWPD and BD share several clinical symptoms and an evening chronotype. [50]. Family history of suicide and psychiatric disorders were more common in individuals with DSWPD and a younger age of onset for BD was detected among those with DSWPD [45]. Since BD and DSWPD share many clinical characteristics these symptom clusters might help identify at risk individuals who may develop either DSWPD or BD. Circadian disturbances tend to precede relapse in BD patients, therefore assessing sleep patterns of at risk patients may help mitigate the risk of relapse [51].

Melatonin profiles

Wyatt et al. [52] studied volunteers with DSWPD and controls and determined that the salivary dim light melatonin onset (DLMO) occurred significantly later in those with DSWPD. There was no significant difference between both groups in the length of the circadian phase [52]. Chang et al. [4] confirmed these findings and the source of the melatonin sample (plasma or saliva), did not appear to effect the results [4]. Shibui et al. [16] showed that sleep duration was significantly longer in DSWPD subjects, and that sleep initiation relative to melatonin onset was found to be significantly delayed in DSWPD [16,53]. To explain this delay in sleep initiation, Hoban et al. [16,54] suggested that individuals might sleep through the phase advancing portion of the phase response curve (PRC) and therefore do not benefit from the phase re-setting effects of daylight. However, a recent study [4] showed no significant difference in the phase relationship between DLMO and sleep time in DSWPD.

Micic et al. [23] measured melatonin secretion in DSWPD and normal sleepers. DLMO in normal chronotypes was followed by an initial surge of melatonin, which was much less pronounced in the DSWPD group. Alvarez et al. [16] showed normal melatonin rhythm in subjects with DSWPD, however the study was not performed in dim light conditions.

Melatonin's role in cyclical mood disorders like BD, cyclothymia, and seasonal affective disorder (SAD) is still being evaluated [55,56]. Research using DLMO as a phase marker has mainly focused on SAD [55,57–59]; and shows phase advancement in the circadian rhythm of SAD patients.

Some researchers hypothesize that fluctuating melatonin levels are an intrinsic feature of BD rather than being state dependent [6]. Novakova et al. [53] demonstrated a melatonin profile similar to DSWPD in BD patients in the euthymic and depressed states. In this study manic states were associated with an increase in melatonin and an advance in its peak levels during episodes of mania [53]. However, results obtained in the manic state were not consistent; and some studies detected a decrease in the levels of melatonin [16,53]. Other studies confirmed lower levels of melatonin in all phases of BD (euthymic, depressed, and manic) when compared to healthy subjects [60]. Interestingly, melatonin secretion abnormalities were found in other psychiatric disorders [60–62]. Bumb et al. [63] showed that CSF melatonin levels were decreased in BD but not in major depressive disorder (MDD); while serum levels were lower in MDD. These findings suggest the existence of body fluid specific melatonin levels in different mood disorders.

Another common feature of BD and DSWPD is increased melatonin sensitivity to light. Lewy et al. [64] showed a two fold reduction in nocturnal plasma melatonin levels following exposure to light in a group of acutely ill BD patients. Increased sensitivity to light may act as a possible putative trait marker for BD [65]. In another study, remitted BD subjects did not exhibit the observed hypersensitivity to light [66].

The significance of the melatonergic pathway in BD and DSWPD is highlighted by the clinical improvement in DSWPD and BD with interventions that target the melatonergic pathway. In a double-blind placebo-controlled study involving DSWPD patients, administration of melatonin 5 h before the individual DLMO was found to significantly advance the onset of the nocturnal melatonin profile by approximately 1.5 h [67]. Sleep onset and sleep latency were also improved and participants reported feeling refreshed in the morning. Rahman et al. [68], showed that melatonin administration improved depressive symptoms and sleep continuity in depressed subjects [68]. The improvement in both depression and DSWPD as a result of melatonin's phase advancing effect on the circadian rhythm demonstrates the potential role of melatonin in both disorders.

Agomelatine, a melatonin receptor agonist and an antagonist of the serotonin 5-HT (2C) receptor, is effective in the treatment of depressed BD patients when co-administered with lithium (Li) or valproic acid (VA) [69,70]. Agomelatine improved mood, increased rapid eye movement (REM) sleep, and advanced the sleep phase in BD [71]. Agomelatine also improved sleep efficiency in MDD [71].

The resynchronizing effect of agomelatine on the circadian rhythm was observed in animal models of DSWPD [72–77]. Armstrong et al. [72] showed that keeping rats in darkness for several months and then re-exposing them to a normal light/dark cycles resulted in a delay of activity onset by 3–4 h. This effect was reversed by the daily administration of agomelatine [77]. The researchers concluded that agomelatine could influence resynchronization by affecting melatonergic receptors [78,79]. Although the effectiveness of agomelatine in treating depression is limited, its effect in modulating the melatonergic pathways in BD depression deserve further investigation [80]. The loss of agomelatine's synchronizing properties in rats with SCN lesions but not in pinealectomized rats suggests that the melatonergic receptors are involved in circadian rhythm modulation via the SCN [78,81]. The phase advancing effect of agomelatine has also been demonstrated in humans [82].

The relationship between BD and DSWPD can be further examined by observing the pharmacological effects of mood stabilizers like Li and VA. Both mood stabilizers can decrease the sensitivity of melatonin to light in healthy controls [65,83,84]. It is still unclear how Li decreases melatonin sensitivity to light without affecting overall melatonin synthesis; however, these findings suggest a chrono-biological mechanism of action [71].

Following the discovery of the blue light sensitive retinal photoreceptors that inhibit melatonin production, *Henriksen* et al. [85] assessed the effectiveness of “blue blocking” [86] (orange tinted) eyeglasses in reducing bipolar mania. Using “blue blocking” eyeglasses significantly reduced mania as per the Young mania rating scale (YMRS). These findings underscore the relationship between mood, melatonin and environmental factors.

Melatonin profiles appear to vary in the different phases of BD and patients seem to benefit from targeting the melatonergic pathway. These findings propose a role for the melatonergic pathway in developing BD in the context of DSWPD; which suggests a common etiology between BD and DSWPD.

This line of research can have implications on the diagnosis, management, and prognosis of BD. For example, DLMO can be used to identify the optimal time for administering treatments such as melatonin or phototherapy. Another significant finding was a correlation between the magnitude of DLMO phase advance after morning phototherapy and a reduction in depressive symptoms. Terman et al. recommended scheduling phototherapy 8.5 h after DLMO (rather than using clock time) for optimal results [55]. In a recent report continuous observation of sleep patterns in BD helped prevent relapse by detecting early changes in sleep patterns. More data is needed to determine if sleep patterns can act as markers for imminent relapse in BD [87].

Genes involved in the circadian system

It has been proposed that DSWPD and BD may share a genetic basis. A number of genes involved in the circadian rhythm are also implicated in BD. Some of these genes are CLOCK, GSK3β, NPAS2, ARNTL1, PER3, NR1D1, and ASMT [88]. Nievergelt et al. [89] assessed the association and linkage of ten circadian clock genes with BD. Applying haplotype analysis using single gene permutation tests, haplotypes in ARNTL and PER3 were found to be associated with BD. These results, however, were not confirmed in subsequent analyses.

Ramanujam et al. examined the existence of PER3 polymorphisms in BD and schizophrenia. The 18 amino acids encoded by this gene are variable-number tandem repeat (VNTR) and can repeat either four times (PER3-4 allele) or five times (PER3-5 allele). The occurrence of the five repeat allele of Per3 may be a risk factor for BD but not for schizophrenia [90].

The PER3 gene VNTR appears to influence the age of onset of BD. Homozygote carriers of the PER3-5 variant exhibited an earlier age of onset and heterozygote carriers exhibited an intermediate age of onset. Homozygote carriers of PER3-4 showed a later age of onset [29]. The investigators propose that the VNTRs of CLOCK genes are potential biomarkers for BD. Replicating the result has been difficult since BD is influenced by multiple susceptibility factors. Additionally, gene–gene interactions cannot be dismissed, since most of the circadian proteins heterodimerize into larger complexes and share common functions [89]. Of note, in Japanese individuals with DSWPD a higher frequency of the shorter VNTR allele was observed [32].

Jones et al. [33] examined the frequency of the 4 and 5 VNTRs of PER3 in separate age groups. The 4 repeat allele was found to be significantly more frequent in evening chronotypes types and this association decreased with age [33]. It is still unclear if DSWPD is an over-expression of an eveningness preference or a distinct disorder [91]. Pereira et al. [92] found that homozygosity for the shorter PER3 repeat allele in an English sample was strongly associated with DSWPD; however, this could not be replicated in a Brazilian sample. The authors proposed that factors such as temperature, length of day and solar intensity at different latitudes influence PER3 polymorphisms in DSWPD. Therefore gene–environmental interactions in circadian disorders are potentially possible.

Benedetti et al. [93] attempted to demonstrate that circadian genes could predict the prognosis of BD by assessing the role of Clock genes polymorphism in the regulation of diurnal mood fluctuations during a depressive episode of BD. They were able to show that Clock gene polymorphisms influenced relapse rates in their sample of BD [93]. In participants who were homozygote for the C variant of the Clock gene the relapse rate was double that of controls.

An association was observed between BD genes and melatonin synthesis genes. A common polymorphism associated with BD is located in the ASMT promoter rs446909, and is associated with lower enzymatic activity that causes diminished conversion of N-acetylserotonin to melatonin [94]. This finding is of interest since N-acetylserotonin has been shown to stimulate TKRB receptors, which in turn potentiate the action of TRKB and BDNF, the latter being a key factor in BD. These findings are not confirmatory, and only a few studies have shown a significant association between an SNP (rs11077820) in AANAT and mood disorders [95].

Geoffroy et al. conducted gene analysis based on 349 SNPs spanning 21 circadian genes and three melatonin pathway genes [96]. Of the 14 SNPs identified in the circadian genes the NPAS2, CRY2, ARNTL, ARNTL2, RORA and RORB genes were found to be associated with cyclical mood patterns. Only 5 SNPs in NPAS2 were shown to have significant associations with BD. Circadian genes can potentially help predict the phenotype of BD; this finding may be of relevance in the clinical setting since different phenotypes require different treatments strategies [96].

Li, an established treatment for BD, is effective in the manic and depressed phases and can prevent relapse. Li can serve as a tool to investigate the mechanisms and genetics of BD [97–100]. Li affects multiple steps in the cellular signaling of brain pathways, these include: GSK3, CREB and $Na+/K+$ ATPase.

We will focus on circadian genes (specifically GSK3) when assessing Li's mechanism of action in BD. At the molecular level Li regulates CLOCK gene expression and protein synthesis patterns in the SCN [47]. Li inhibits GSK3β expression and activates CLOCK transcription. In mice transgenic for GSK3β and Clock, Li was shown to reduce mania like behaviors [101,102]. Li possibly influences circadian rhythms through its effect on Rev-Erbα, a protein product of the NR1D1 gene [98]. Li mainly prevents the degradation of Rev-Erbα a phosphorylation target of GSK3, by inhibiting GSK3 [98]. Therefore, Li possibly stabilizes circadian rhythms in BD and prevents desynchronization [51]. This finding is supported by several studies where Li was found to delay the phase of behavioral and physiological rhythms (e.g., CBT rhythms and physical activity) [46,103].

Circadian biomarkers can potentially be used to predict response to Li. Based on multiple linkage studies [104–106], chromosome 18 was found to be of interest when assessing the response to Li [107]. Morissette et al. [108] performed a genome-wide scan for susceptibility loci for BD in a homogenous population in Quebec. Results showed that the chromosome 12q23-q24 region predicted a good clinical response to Li. These results were later replicated [109]. Evidence for linkage of loci on chromosome 15q14 and 7q11.2 was demonstrated in a study examining bipolar families that responded well to Li [110]. In a recent study, initial linkage analysis followed by mapping and gene expression analysis was performed; response to Li in BD was associated with the 3p25, 3p14, and 14q11 regions [111].

The data presented above describes the interaction of circadian and melatonin synthesis genes with BD and DSPWD. Since genes such as PER3, CLOCK, and AANAT, are involved in both disorders, the existence of a relationship between DSPWD and BD cannot be dismissed. However, not all of these findings could be replicated and ethnicity as well as geographic location appeared to influence some of the results. Epigenetic and environmental factors such as temperature, length of day, and solar intensity may influence circadian genes.

Li appears well positioned to examine the underlying mechanisms of BD and DSPWD. For example, it maybe feasible to predict response to Li by examining circadian gene expression in peripheral white blood cells [112].

Conclusion

Genetic, behavioral, and environmental factors have been implicated in the development of BD and DSWPD. A phase delay in melatonin rhythms was observed in both disorders and melatonergic drugs were found to be effective in treating both conditions. Circadian genes have been implicated in the pathogenesis of both BD and DSWPD. Haplotypes of the ARNTL and PER3 circadian genes were found to be significantly associated with BD. Circadian genes were shown to be potential biomarkers for the development of BD.

Despite several shared biomarkers, some biomarkers remain unique for each disorder. BDNF and the immune system appeared to be implicated in pathogenesis of BD but not of DSWPD. The similarities in clinical profiles and biomarkers in BD and DSWPD strongly suggest an underlying common etiology. The exact pathophysiological link cannot be definitely identified. However, disruptions in the melatonergic pathway and/or circadian genes appear to be the most likely candidates. Because circadian disturbances are present in all phases of BD and they influence its course and prognosis; we hypothesize that DSWPD leads to disruptions in circadian rhythms that are implicated in the pathogenesis of BD. In our opinion, there exists a complex multifactorial relationship between circadian rhythm sleep disorders and mood disorders. Further research may lead to novel therapeutic modalities that can address pathways common to both disorders.

Practice points

- Genetic, behavioral, and environmental, factors have been implicated in the etiology of DSWPD and BD.
- A number of shared biomarkers, namely melatonin profiles and circadian genes, and clinical features co-exist in both disorders
- Circadian disturbances are variably present during all stages of BD and appear to influence the prognosis and treatment outcomes of BD.
- Individuals with DSWPD are at risk of developing BD at an earlier age and may have a more severe course.
- Targeting the circadian system might help treat BD.

Research agenda

- Further research on melatonin profiles in BD should be considered.
- Careful examination of the prevalence of DSWPDs in BD is needed.
- The roles of ARNTL and PER3 gene alterations in BD and DSWPD require further investigation.

Conflicts of interest

Disclosure: Dr. Ferri has consulted for Fidia Farmaceutici (Italy). Remaining authors declare no conflict of interest.

References

[1] International classification of sleep disorders. 3rd ed. Darien, IL USA: American Academy of Sleep Medicine; 2014.
[2] Crowley SJ, Acebo C, Carskadon MA. Sleep, circadian rhythms, and delayed phase in adolescence. Sleep Med 2007;8:602–12.
[3] Mahowald MW, Schenck CH. Insights from studying human sleep disorders. Nature 2005;437:1279–85.
[4] Chang AM, Reid KJ, Gourineni R, Zee PC. Sleep timing and circadian phase in delayed sleep phase syndrome. J Biol Rhythm 2009;24:313–21.
[5] Martinez-Rodriguez JE, Santamaria J. CSF markers in sleep neurobiology. Clini Chim Acta; Int J Clin Chem 2005;362:12–25.
*[6] Abreu T, Braganca M. The bipolarity of light and dark: a review on Bipolar Disorder and circadian cycles. J Affect Disord 2015;185:219–29.
[7] Judd LL, Akiskal HS, Schettler PJ, Endicott J, Maser J, Solomon DA, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatr 2002;59:530–7.
[8] Post RM, Denicoff KD, Leverich GS, Altshuler LL, Frye MA, Suppes TM, et al. Morbidity in 258 bipolar outpatients followed for 1 year with daily prospective ratings on the NIMH life chart method. J Clin Psychiatr 2003;64:680–90.
[9] Duffy A, Jones S, Goodday S, Bentall R. Candidate risks indicators for bipolar disorder: early intervention opportunities in high-risk youth. Int J Neuropsychopharmacol 2016;19(1):pyv017.
[10] Mayeux R. Biomarkers: potential uses and limitations. NeuroRx 2004;1:182–8.
[11] Higgins JPT GS. Cochrane handbook for systematic reviews of interventions 5 ed.: The Cochrane Collaboration.
[12] Dagan Y, Borodkin K. Behavioral and psychiatric consequences of sleep-wake schedule disorders. Dialogues Clin Neurosci 2005;7:357–65.
[13] Harvey AG. Sleep and circadian rhythms in bipolar disorder: seeking synchrony, harmony, and regulation. Am J Psychiatr 2008;165:820–9.
[14] Wirz-Justice A. How to measure circadian rhythms in humans. Medicographia.29:84–90.
[15] Lack LC, Wright HR, Bootzin RR. Delayed sleep-phase disorder sleep medicine clinics. 2009. p. 229–39.
[16] Shibui K, Uchiyama M, Okawa M. Melatonin rhythms in delayed sleep phase syndrome. J Biol Rhythm 1999;14:72–6.
*[17] Shirayama M, Shirayama Y, Iida H, Kato M, Kajimura N, Watanabe T, et al. The psychological aspects of patients with delayed sleep phase syndrome (DSPS). Sleep Med 2003;4:427–33.
[18] Regestein QR, Monk TH. Delayed sleep phase syndrome: a review of its clinical aspects. Am J Psychiatr 1995;152:602–8.
[19] Abe T, Inoue Y, Komada Y, Nakamura M, Asaoka S, Kanno M, et al. Relation between morningness–eveningness score and depressive symptoms among patients with delayed sleep phase syndrome. Sleep Med 2011;12:680–4.
[20] Kalsbeek A, Perreau-Lenz S, Buijs RM. A network of (autonomic) clock outputs. Chronobiol Int 2006;23:521–35.
[21] Buhr ED, Yoo SH, Takahashi JS. Temperature as a universal resetting cue for mammalian circadian oscillators. Science 2010;330(6002):379–85.
[22] Micic G, de Bruyn A, Lovato N, Wright H, Gradisar M, Ferguson S, et al. The endogenous circadian temperature period length (tau) in delayed sleep phase disorder compared to good sleepers. J Sleep Res 2013;22:617–24.
*[23] Micic G, Lovato N, Gradisar M, Burgess HJ, Ferguson SA, Kennaway DJ, et al. Nocturnal melatonin profiles in patients with delayed sleep-wake phase disorder and control sleepers. J Biol Rhythm 2015;30:437–48.
[24] Campbell SS, Murphy PJ. Delayed sleep phase disorder in temporal isolation. Sleep 2007;30(9):1225–8.
*[25] Duffy JF, Wright KP. Entrainment of the human circadian system by light. J Biol Rythms 2005;4:326–38.
[26] Van Cauter E, Sturis J, Byrne MM, Blackman JD, Scherberg NH, Leproult R, et al. Preliminary studies on the immediate phase-shifting effects of light and exercise on the human circadian clock. J Biol Rhythm 1993;(8 Suppl):S99–108.
[27] Minors DS, Waterhouse JM, Wirz-Justice A. A human phase-response curve to light. Neurosci Lett 1991;133:36–40.
[28] Dijk DJ, Cajochen C, Borbely AA. Effect of a single 3-hour exposure to bright light on core body temperature and sleep in humans. Neurosci Lett 1991;121:59–62.
[29] Benedetti F, Dallaspezia S, Colombo C, Pirovano A, Marino E, Smeraldi E. A length polymorphism in the circadian clock gene Per3 influences age at onset of bipolar disorder. Neurosci Lett 2008;445:184–7.
*[30] Takahashi JS, Hong HK, Ko CH, McDearmon EL. The genetics of mammalian circadian order and disorder: implications for physiology and disease. Nat Rev Genet 2008;9:764–75.
[31] Ebisawa T, Uchiyama M, Kajimura N, Mishima K, Kamei Y, Katoh M, et al. Association of structural polymorphisms in the human period3 gene with delayed sleep phase syndrome. EMBO Rep 2001;2:342–6.
*[32] Archer SN, Robilliard DL, Skene DJ, Smits M, Williams A, Arendt J, et al. A length polymorphism in the circadian clock gene Per3 is linked to delayed sleep phase syndrome and extreme diurnal preference. Sleep 2003;26:413–5.
[33] Jones KH, Ellis J, von Schantz M, Skene DJ, Dijk DJ, Archer SN. Age-related change in the association between a polymorphism in the PER3 gene and preferred timing of sleep and waking activities. J Sleep Res 2007;16:12–6.
[34] Patke A, Murphy PJ, Onat OE, Krieger AC, Ozcelik T, Campbell SS, et al. Mutation of the human circadian clock gene CRY1 in familial delayed sleep phase disorder. Cell 2017;169. 203–215 e13.
[35] Hohjoh H, Takasu M, Shishikura K, Takahashi Y, Honda Y, Tokunaga K. Significant association of the arylalkylamine N-acetyltransferase (AA-NAT) gene with delayed sleep phase syndrome. Neurogenetics 2003;4:151–3.
[36] Ancoli-Israel S, Schnierow B, Kelsoe J, Fink R. A pedigree of one family with delayed sleep phase syndrome. J Biol Med Rhythm Res 2001;18:831–40.
[37] Dagan YEM. Circadian rhythm sleep disorders: toward a more precise definition and diagnosis. Chronobiol Int 1999;16:213–22.
[38] Hur YM, Bouchard TJ, Lykken DT. Genetic and environmental influence on morningness–eveningness. Pers Indiv Differ 1998;25:917–25.
[39] Koskenvuo M, Hublin C, Partinen M, Heikkila K, Kaprio J. Heritability of diurnal type: a nationwide study of 8753 adult twin pairs. J Sleep Res 2007;16:156–62.
[40] Vink JM, Groot AS, Kerkhof GA, Boomsma DI. Genetic analysis of morningness and eveningness. Chronobiol Int 2001;18:809–22.
[41] Nicola L, Barclay ET, Buysse DJ, Archer SN, Gregory AM. Diurnal preference and sleep quality: same genes? A study of young adult twins. Chronobiol Int 2010;27:278–96.
[42] Fukuda K. Twins under shift work: a case study of sleep log data. Percept Mot Skills 1997;84:931–7.
[43] Gonzalez R. The relationship between bipolar disorder and biological rhythms. J Clin Psychiatr 2014;75:e323–31.
[44] Gold AK, Sylvia LG. The role of sleep in bipolar disorder. Nat Sci Sleep 2016;8:207–14.
[45] Takaesu Y, Inoue Y, Murakoshi A, Komada Y, Otsuka A, Futenma K, et al. Prevalence of circadian rhythm sleep-wake disorders and associated factors in euthymic patients with bipolar disorder. PLoS One 2016;11. e0159578.
[46] Pflug B, Engelmann W. Chronobiology of lithium–studies on healthy, middle-aged women. Pharmacopsychiatry 1987;20:181–8.
[47] Etain B, Milhiet V, Bellivier F, Leboyer M. Genetics of circadian rhythms and mood spectrum disorders. Eur Neuropsychopharmacol 2011;21(Suppl 4):S676–82.
[48] McClung CA. How might circadian rhythms control mood? Let me count the ways. Biol Psychiatr 2013;74:242–9.
[49] Hallam KT, Olver JS, Chambers V, Begg DP, McGrath C, Norman TR. The heritability of melatonin secretion and sensitivity to bright nocturnal light in twins. Psychoneuroendocrinology 2006;31:867–75.
*[50] Wood J, Birmaher B, Axelson D, Ehmann M, Kalas C, Monk K, et al. Replicable differences in preferred circadian phase between bipolar disorder patients and control individuals. Psychiatr Res 2009;166:201–9.
[51] Geoffroy PA, Etain B, Sportiche S, Bellivier F. Circadian biomarkers in patients with bipolar disorder: promising putative predictors of lithium response. Int J Bipolar Disord 2014;2:28.
[52] Wyatt JK, Stepanski EJ, Kirkby J. Circadian phase in delayed sleep phase syndrome: predictors and temporal stability across multiple assessments. Sleep 2006;29:1075–80.
[53] Novakova M, Prasko J, Latalova K, Sladek M, Sumova A. The circadian system of patients with bipolar disorder differs in episodes of mania and depression. Bipolar Disord 2015;17:303–14.
[54] Kalelioglu T, Akkus M, Karamustafalioglu N, Genc A, Genc ES, Cansiz A, et al. Neutrophil-lymphocyte and platelet-lymphocyte ratios as inflammation markers for bipolar disorder. Psychiatr Res 2015;228:925–7.

* The most important references are denoted by an asterisk.

[55] Pandi-Perumal SR, Smits M, Spence W, Srinivasan V, Cardinali DP, Lowe AD, et al. Dim light melatonin onset (DLMO): a tool for the analysis of circadian phase in human sleep and chronobiological disorders. Prog Neuro-Psychopharmacol Biol Psychiatr 2007;31:1–11.

[56] Kim DR, Czarkowski KA, Epperson CN. The relationship between bipolar disorder, seasonality, and premenstrual symptoms. Curr Psychiatr Rep 2011;13:500–3.

[57] Sack RL, Lewy AJ, White DM, Singer CM, Fireman MJ, Vandiver R. Morning vs evening light treatment for winter depression. Evidence that the therapeutic effects of light are mediated by circadian phase shifts. Arch Gen Psychiatr 1990;47:343–51.

[58] Lewy AJ, Sack RL, Singer CM, White DM. The phase shift hypothesis for bright light's therapeutic mechanism of action: theoretical considerations and experimental evidence. Psychopharmacol Bull 1987;23:349–53.

[59] Dahl K, Avery DH, Lewy AJ, Savage MV, Brengelmann GL, Larsen LH, et al. Dim light melatonin onset and circadian temperature during a constant routine in hypersomnic winter depression. Acta Psychiatr Scand 1993;88:60–6.

[60] Nurnberger JI, Adkins S, Lahiri DK, Mayeda A, Hu K, Lewy A, et al. Melatonin suppression by light in euthymic bipolar and unipolar patients. Arch Gen Psychiatr 2000;57:572–9.

[61] Robillard R, Naismith SL, Rogers NL, Scott EM, Ip TK, Hermens DF, et al. Sleep-wake cycle and melatonin rhythms in adolescents and young adults with mood disorders: comparison of unipolar and bipolar phenotypes. Eur Psychiatr 2013;28:412–6.

[62] Nurnberger JI, Koller DL, Jung J, Edenberg HJ, Foroud T, Guella I, et al. Identification of pathways for bipolar disorder: a meta-analysis. JAMA Psychiatr 2014;71:657–64.

[63] Bumb JM, Enning F, Mueller JK, van der List T, Rohleder C, Findeisen P, et al. Differential melatonin alterations in cerebrospinal fluid and serum of patients with major depressive disorder and bipolar disorder. Compr Psychiatr 2016;68:34–9.

[64] Lewy AJ, Nurnberger Jr JI, Wehr TA, Pack D, Becker LE, Powell RL, et al. Supersensitivity to light: possible trait marker for manic-depressive illness. Am J Psychiatr 1985;142:725–7.

[65] Hallam KT, Olver JS, Norman TR. Effect of sodium valproate on nocturnal melatonin sensitivity to light in healthy volunteers. Neuropsychopharmacology 2005;30:1400–4.

[66] Whalley LJ, Perini T, Shering A, Bennie J. Melatonin response to bright light in recovered, drug-free, bipolar patients. Psychiatr Res 1991;38:13–9.

[67] J.E.Nagtegaal GA, Nagtegaal JE, Kerkhof GA, Smits MG, Swart AC, Van Der Meer YG. J Sleep Res 1998;7:135–43.

*[68] Rahman SA, Kayumov L, Shapiro CM. Antidepressant action of melatonin in the treatment of delayed sleep phase syndrome. Sleep Med 2010;11:131–6.

[69] Calabrese JR, Guelfi JD, Perdrizet-Chevallier C, Agomelatine Bipolar Study G. Agomelatine adjunctive therapy for acute bipolar depression: preliminary open data. Bipolar Disord 2007;9:628–35.

[70] Fornaro M, McCarthy MJ, De Berardis D, De Pasquale C, Tabaton M, Martino M, et al. Adjunctive agomelatine therapy in the treatment of acute bipolar II depression: a preliminary open label study. Neuropsychiatric Dis Treat 2013;9:243–51.

[71] Zupancic M, Guilleminault C. Agomelatine: a preliminary review of a new antidepressant. CNS Drugs 2006;20:981–92.

*[72] Armstrong SM, McNulty OM, Guardiola-Lemaitre B, Redman JR. Successful use of S20098 and melatonin in an animal model of delayed sleep-phase syndrome (DSPS). Pharmacol Biochem Behav 1993;46:45–9.

[73] Grassi-Zucconi G, Harris JA, Mohammed AH, Ambrosini MV, Kristensson K, Bentivoglio M. Sleep fragmentation, and changes in locomotor activity and body temperature in trypanosome-infected rats. Brain Res Bull 1995;37:123–9.

[74] Grassi-Zucconi G, Semprevivo M, Mocaer E, Kristensson K, Bentivoglio M. Melatonin and its new agonist S-20098 restore synchronized sleep fragmented by experimental trypanosome infection in the rat. Brain Res Bull 1996;39:63–8.

[75] Ying SW, Rusak B, Delagrange P, Mocaer E, Renard P, Guardiola-Lemaitre B. Melatonin analogues as agonists and antagonists in the circadian system and other brain areas. Eur J Pharmacol 1996;296:33–42.

[76] Ying SW, Rusak B, Mocaer E. Chronic exposure to melatonin receptor agonists does not alter their effects on suprachiasmatic nucleus neurons. Eur J Pharmacol 1998;342:29–37.

[77] Le Strat Y, Gorwood P. Agomelatine, an innovative pharmacological response to unmet needs. J Psychopharmacol 2008;22:4–8.

[78] Redman JR, Francis AJ. Entrainment of rat circadian rhythms by the melatonin agonist S-20098 requires intact suprachiasmatic nuclei but not the pineal. J Biol Rhythm 1998;13:39–51.

[79] Pandi-Perumal SR, Zisapel N, Srinivasan V, Cardinali DP. Melatonin and sleep in aging population. Exp Gerontol 2005;40:911–25.

[80] Michele Fornaro DP, Salvatore Colicchio Giulio Perugi. A systematic, updated review on the antidepressant agomelatine focusing on its melatonergic modulation. Curr Neuropharmacol 2010;vol. 8:287–304.

[81] Stephan FK, Zucker I. Circadian rhythms in drinking behavior and locomotor activity of rats are eliminated by hypothalamic lesions. Proc Natl Acad Sci U S A 1972;69:1583–6.

[82] Quera Salva MA, Vanier B, Laredo J, Hartley S, Chapotot F, Moulin C, et al. Major depressive disorder, sleep EEG and agomelatine: an open-label study. Int J Neuropsychopharmacol 2007;10:691–6.

[83] Hallam KT, Olver JS, Horgan JE, McGrath C, Norman TR. Low doses of lithium carbonate reduce melatonin light sensitivity in healthy volunteers. Int J Neuropsychopharmacol 2005;8:255–9.

[84] Manning JS. Valproate in bipolar disorder: case examples from a family practice. Prim Care Companion J Clin Psychiatr 1999;1:71–3.

[85] Henriksen TE, Skrede S, Fasmer OB, Schoeyen H, Leskauskaite I, Bjorke-Bertheussen J, et al. Blue-blocking glasses as additive treatment for mania: a randomized placebo-controlled trial. Bipolar Disord 2016;18:221–32.

[86] Findling RL, Robb A, McNamara NK, Pavuluri MN, Kafantaris V, Scheffer R, et al. Lithium in the acute treatment of bipolar I disorder: a double-blind, placebo-controlled study. Pediatrics 2015;136:885.

[87] Knapen SE, Riemersma-van der Lek RF, Haarman BC, Schoevers RA. Coping with a life event in bipolar disorder: ambulatory measurement, signalling and early treatment. BMJ Case Rep 2016;2016.

[88] Milhiet V, Etain B, Boudebesse C, Bellivier F. Circadian biomarkers, circadian genes and bipolar disorders. J Physiol Paris 2011;105:183–9.

*[89] Nievergelt CM, Kripke DF, Barrett TB, Burg E, Remick RA, Sadovnick AD, et al. Suggestive evidence for association of the circadian genes PERIOD3 and ARNTL with bipolar disorder. Am J Med Genet B Neuropsychiatr Genet 2006;141B:234–41.

[90] Karthikeyan R, Marimuthu G, Ramasubramanian C, Arunachal G, BaHammam AS, Spence DW, et al. Association of Per3 length polymorphism with bipolar I disorder and schizophrenia. Neuropsychiatric Dis Treat 2014;10:2325–30.

[91] Matsuo M, Shiino Y, Yamada N, Ozeki Y, Okawa M. A novel SNP in hPer2 associates with diurnal preference in a healthy population. Sleep Biol Rhythm 2007;5:141–5.

[92] Pereira DS, Tufik S, Louzada FM, Benedito-Silva AA, Lopez AR, Lemos NA, et al. Association of the length polymorphism in the human Per3 gene with the delayed sleep-phase syndrome: does latitude have an influence upon it? Sleep 2005;28:29–32.

[93] Benedetti F, Serretti A, Colombo C, Barbini B, Lorenzi C, Campori E, et al. Influence of CLOCK gene polymorphism on circadian mood fluctuation and illness recurrence in bipolar depression. Am J Med Genet B Neuropsychiatr Genet 2003;123B:23–6.

[94] Etain B, Dumaine A, Bellivier F, Pagan C, Francelle L, Goubran-Botros H, et al. Genetic and functional abnormalities of the melatonin biosynthesis pathway in patients with bipolar disorder. Hum Mol Genet 2012;21:4030–7.

[95] Kripke DF1 NC, Tranah GJ, Murray SS, McCarthy MJ, Rex KM, Parimi N, et al. Polymorphisms in melatonin synthesis pathways: possible influences on depression. J Circadian Rhythm 2011;9:8.

[96] Geoffroy PA, Lajnef M, Bellivier F, Jamain S, Gard S, Kahn JP, et al. Genetic association study of circadian genes with seasonal pattern in bipolar disorders. Sci Rep 2015;5:10232.

[97] Prickaerts J, Moechars D, Cryns K, Lenaerts I, van Craenendonck H, Goris I, et al. Transgenic mice overexpressing glycogen synthase kinase 3beta: a putative model of hyperactivity and mania. J Neurosci 2006;26:9022–9.

[98] Can A, Schulze TG, Gould TD. Molecular actions and clinical pharmacogenetics of lithium therapy. Pharmacol Biochem Behav 2014;123:3–16.

[99] Goodwin GM. Evidence-based guidelines for treating bipolar disorder: revised second edition—recommendations from the British Association for Psychopharmacology. J Psychopharmacol 2009;23:346–88.

[100] Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Moller HJ, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2010 on the treatment of acute bipolar depression. World J Biol Psychiatr 2010;11:81–109.

[101] Jope RS, Roh MS. Glycogen synthase kinase-3 (GSK3) in psychiatric diseases and therapeutic interventions. Curr Drug Targets 2006;7:1421–34.

[102] Roybal K, Theobold D, Graham A, DiNieri JA, Russo SJ, Krishnan V, et al. Mania-like behavior induced by disruption of CLOCK. Proc Natl Acad Sci U S A 2007;104:6406–11.

[103] Klemfuss H, Kripke DF. Antimanic drugs stabilize hamster circadian rhythms. Psychiatr Res 1995;57:215–22.

[104] Ewald H, Wang AG, Vang M, Mors O, Nyegaard M, Kruse TA. A haplotype-based study of lithium responding patients with bipolar affective disorder on the Faroe Islands. Psychiatr Genet 1999;9:23–34.

[105] Turecki G, Grof P, Cavazzoni P, Duffy A, Grof E, Martin R, et al. Lithium responsive bipolar disorder, unilineality, and chromosome 18: a linkage study. Am J Med Genet 1999;88:411–5.

[106] Evans LM, Akiskal HS, Greenwood TA, Nievergelt CM, Keck Jr PE, McElroy SL, et al. Suggestive linkage of a chromosomal locus on 18p11 to cyclothymic temperament in bipolar disorder families. Am J Med Genet B Neuropsychiatr Genet 2008;147:326–32.

[107] Geoffroy PA, Bellivier F, Leboyer M, Etain B. Can the response to mood stabilizers be predicted in bipolar disorder? Front Biosci (Elite Ed) 2014;6:120–38.

[108] Morissette J, Villeneuve A, Bordeleau L, Rochette D, Laberge C, Gagne B, et al. Genome-wide search for linkage of bipolar affective disorders in a very large pedigree derived from a homogeneous population in quebec points to a locus of major effect on chromosome 12q23-q24. Am J Med Genet 1999;88:567–87.
[109] Shink E, Morissette J, Sherrington R, Barden N. A genome-wide scan points to a susceptibility locus for bipolar disorder on chromosome 12. Mol Psychiatr 2005;10:545–52.
[110] Turecki G, Grof P, Grof E, D'Souza V, Lebuis L, Marineau C, et al. Mapping susceptibility genes for bipolar disorder: a pharmacogenetic approach based on excellent response to lithium. Mol Psychiatr 2001;6:570–8.
[111] Lopez de Lara C, Jaitovich-Groisman I, Cruceanu C, Mamdani F, Lebel V, Yerko V, et al. Implication of synapse-related genes in bipolar disorder by linkage and gene expression analyses. Int J Neuropsychopharmacol 2010;13:1397–410.
[112] Fukuhara C. Lithium, circadian rhythm, and bipolar disorder National Institute of Health. Atlanta, GA, United States: Morehouse School of Medicine; 2008.