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CLINICAL REVIEW

Chronotype and circadian rhythm in bipolar disorder: A systematic review

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SUMMARY

Despite a complex relationship between mood, sleep and rhythm, the impact of circadian disruptions on bipolar disorder (BD) has not been clarified. The purpose of this systematic review was to define current evidence regarding chronotype and circadian rhythm patterns in BD patients. 42 studies were included, involving 3432 BD patients. Disruption of the biological rhythm was identified, even in drug-naïve BD patients and independently of mood status. Daily profiles of melatonin levels and cortisol indicated a delayed phase. Depression was more frequently associated with circadian alterations than euthymia. Few studies evaluated mania, demonstrating irregular rhythms. Evening type was more common in BD adults. Studies about the influence of chronotype on depressive symptoms showed conflicting results. Only one investigation observed the influences of chronotype in mania, revealing no significant association. Effects of psychoeducation and lithium on rhythm in BD patients were poorly studied, demonstrating no improvement of rhythm parameters. Studies about genetics are incipient. In conclusion, disruption in circadian rhythm and eveningness are common in BD. Prospective research evaluating the impact of circadian disruption on mood symptoms, metabolism, seasonality, the influence of age and the effects of mood stabilizers are needed.

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Background

Mood disorders are multifactorial and heterogeneous conditions influenced by genetic and environmental factors. They are often associated with alterations of sleep and circadian rhythm through a complex and bidirectional relationship [1]. In bipolar disorder (BD), an association between sleep disorders, circadian rhythmicity, chronotype preference, residual mood symptoms and mood episode recurrence is suggested [2].

Circadian rhythmicity and chronotype preference are closely related. Chronotype or morningness–eveningness is the individual preference of the day's period for carrying out activities [3]. It reflects the 24 h or ultradian propensity for the individual either to be alert or to sleep. Three different chronotypes are identified: morning types, evening types and neither (indifferent) [4].

Circadian rhythmicity describes variability, stability and period functional performance. Actigraphic measures can provide elements of circadian rhythmicity expressed as relative amplitude, interdaily stability and intradaily variability [5].

Behavior alterations of the sleep–wake schedule in relation to the external environment e.g., shift work and jet lag can result in circadian rhythm and sleep–wake disorders potentially altering the alignment of the internal circadian clock with the external environment [6]. Commonly, this rhythm disruption tends to precipitate or exacerbate mood episodes [7]. Furthermore, in animal models, sleep deprivation induces manic episodes [8,9]. It is questioned whether sleep and circadian alterations are triggers for mood symptoms [10].

Conversely, circadian disruptions and sleep complaints also can be consequence of mood disorders [11,12]. Manic episodes are frequently characterized by reduced sleep need, while insomnia and hypersomnia occur frequently in depressive phases [13]. Interestingly, sleep loss confers a poor prognosis, increasing the risk of suicide in patients with a suicide attempt history [14]. Even in euthymia, BD patients show more sleep alterations than controls

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Abbreviations

AUC	area under the curve
ASMT	acetylserotonin O-methyltransferase
BD	bipolar disorder
BOLD	blood oxygen-dependent level
BRIAN	biological rhythm interview of assessment in neuropsychiatry
CAT	catalase
CSM	composite scale of morningness
DLMO	dim light melatonin onset
DLPFC	dorsolateral prefrontal cortex
fMRI	functional magnetic resonance imaging

GSS	global seasonality score
GST	glutathione S-transferase
L5	Least5
M10	Most10
MCTQ	Munich chronotype questionnaire
MDA	malondialdehyde
MDD	major depressive disorder
MEQ	morningness–eveningness questionnaire
MRI	magnetic resonance imaging
SAD	seasonal affective disorders
SRM	social rhythm metric
SOD	superoxide dismutase

[15]. Given all this evidence, some authors theorize that BD clinical manifestations and pathogenesis can be understood as circadian rhythm alterations [16–18].

Genetic evidence shows a strong relationship between circadian genes and susceptibility to BD [19–21]. Specific gene variants link to different kinds of mood disorders. Two polymorphisms of *CLOCK* (rs1801260 and rs11932595) relate with BD-II¹; and two of *TM* (rs2291739, rs11171856), with unipolar depression [22]. Furthermore, circadian clock components can influence the response to mood stabilizers. Some circadian clock components, e.g., *Per2*, *Cry1* and *Rev-erba*, probably increase individual sensibility to the therapeutic effects of lithium [23,24].

Chronotherapeutic interventions have been successfully used in BD. Sleep deprivation combined with intensive light therapy is a good adjunct to standard treatments for depressive episodes [25]. The blue-blocking regime in mania, a virtual darkness therapy, was followed by a rapid and sustained decline in mood symptoms accompanied by a reduction in total sleep, a reduction in motor activity during sleep intervals, and an increased regularity of sleep intervals [26]. Interpersonal and social rhythm therapy potentially improves mood symptoms and prevents relapse of mood episodes [27]. A recent metanalysis involving 489 BD patients showed that light therapy reduces disease severity [28]. All these findings indicate the importance of studying the relationship between sleep, circadian rhythm and mood.

Previous evidence shows that different physiological aspects are associated with chronotypes. It is linked to both positive and negative affects, and to specific clinical conditions e.g., metabolic and sleep disorders [29–33]. Eveningness is associated with many mental disorders [34]. It is a probable independent risk factor related to severity, suicidal ideation, nonremission and poor response to treatment in depressive episodes [35–38]. Despite all this evidence, clinical repercussions of circadian rhythm alterations and chronotype preferences in BD patients need more clarification.

The objective of this study is to perform a systematic review to define current evidence about chronotype and circadian rhythm patterns in patients with bipolar disorder.

Methods

Search strategies

This review focuses on circadian rhythm and chronotype. Measures included behavior questionnaires, actigraphy, genetic

and hormonal evaluation. Two researchers performed an electronic search of PubMed, Cochrane Library and ClinicalTrials.gov. Keywords used were ‘chronotype’ or ‘circadian rhythm’ or ‘biological rhythm’ or ‘sleep’ AND ‘bipolar disorder’ or ‘mania’ or ‘bipolar depression’. Manual searches were also conducted, using reference lists from identified articles.

We included all articles published in the last 20 y (1995–2015) evaluating chronotype and circadian variations in BD patients. Reviews, case reports, conference abstracts, expert opinions, animal experiments and incomplete clinical trials were excluded. Articles duplicated or unavailable in the English language were removed. Research with patients with mental disorders that did not analyze bipolar disorder and other mental diseases separately was not considered. Articles that reported only sleep patterns or sleep disorders but not chronotype or circadian variations were excluded. Genetic studies were limited to those that identified relations between genes and their repercussions on biological rhythm. Interventional studies that evaluated the impact on circadian functioning were included. Articles measuring levels of hormones such as melatonin or cortisol and their daily hormonal profile were selected.

Sleep and rhythm measures

Behavior questionnaires and/or actigraphy assessed sleep and rhythm providing information about individual differences and their relationship with other biological functions. The morningness eveningness questionnaire (MEQ) is an instrument with good reliability and stability, used to describe chronotype or phase preference [39]. The circadian type questionnaire investigates the amplitude and stability of circadian rhythm [40,41]. The composite scale of morningness (CSM) consists of 13 items from two different scales: MEQ and diurnal type scale. It assesses individual differences in the time of day that a person prefers to carry out various activities, and classifies people as morning-type or evening-type [42]. The CSM demonstrated good test-retest reliability and adequate external validity [43]. The social rhythm metric (SRM) is a self-report instrument designed to quantify social rhythm regularity. It helps to structure the day cognitively and to plan possible changes routines. The Munich chronotype questionnaire (MCTQ), a recent instrument used to determine the circadian type, is a good indicator of melatonin onset; the MCTQ is calculated by the midpoint of sleep between onset and offset on days off from work [42]. The biological rhythm interview of assessment in neuropsychiatry (BRIAN) consists of 18 items evaluating five domains: sleep, activity, sociality, eating habits and rhythm and it refers to the last 14 d [44].

Circadian rhythm analysis can be yielded by actigraphy. Several components of circadian rhythm i.e., as relative amplitude,

¹ Bipolar disorder can be classified into type I and II. BD-I is characterized by at least one manic episode, while BD-II is marked by at least one episode of hypomania and at least one episode of major depression

interdaily stability and intradaily variability are provided. It is a good instrument for estimating sleep length and fragmentation in bipolar disorder, revealing a good correlation with polysomnography [45]. Measures such as the Least5 (L5) and Most10 (M10) indicate the regularity of sleep, activity or inactivity. The L5 provides the average activity level for the sequence of the least five active hours indicating how restful (inactive) and regular the sleep periods are. The M10 average provides the average activity level for the sequence of the highest (most) 10 active hours. The onset of L5 (restful hours) and M10 (active hours) gives an indication of the phase preference or chronotype. Among BD patients in euthymia, comparisons between objective and subjective sleep and circadian markers suggest that CSM has a good association with M10 onset and L5 onset measured in actigraphy [5,40].

Hormonal levels such as melatonin or cortisol, determined throughout the day, can express endogenous circadian rhythm. However, isolated measures have lower reliability as a tool to indicate circadian rhythm [46]. In this review, these cases were not included.

Data analysis

All articles were displayed on a table in chronological sequence with the following data: names of authors, publication year, study design, participants, mood status, sleep and rhythm measures and main results. The results were organized, considering the following topics: 1) disruption of biological rhythm – 19 studies (45.2%); 2) chronotype – 15 studies (35.7%); 3) circadian rhythm and biomarkers – six studies (14.3%); 4) genetics – six studies (14.3%).

Results

Study selection

The initial electronic database search from 1995 to 2015 resulted in 1654 hits. Additionally, four records were found in the reference list of identified studies. Initially, 1658 articles were included. After careful examination, 1514 were excluded: 509 were published before 1995; 479 focused on other conditions; 236 were reviews, conference abstracts, and expert's opinions; 143 were duplicate; 51 animal experiments; 42 case reports; 21 incomplete studies, and

31 did not analyze bipolar disorder and other mental diseases separately; and two were unavailable in English language. Thus, 144 articles were selected about sleep and rhythm in bipolar disorder.

Thereafter, 102 articles were removed because referred to other topics: 65 concerned only sleep parameters; 12 only people at high risk for bipolar disorder (not bipolar patients); two compared objective and subjective sleep measures; and 23 focused on a population with multiple psychiatric disorders. 42 studies were finally selected (Fig. 1).

Study description

Overall, 3432 BD patients were finally included in this review. Table 1 shows data in the following order: author and year, study design, participants (number), mood status, other characteristics (gender, age, etc.), main outcomes (sleep, rhythm, etc.) and summary results. Number of patients per study varied from 8 to 260. Studies were mostly cross-sectional and case control.

Two intervention studies were found. One randomized clinical trial (45 patients) evidenced no significant impact of psycho-education on biological rhythms in BD [47]. Another study (29 patients) registered melatonin levels before and after exposure to light. Euthymic BD patients showed lower melatonin levels on the light night, at baseline and following light exposure and a later peak time for melatonin on the dark night [48].

Two prospective cohorts were identified. Seleem et al., 2015 (257 patients) demonstrated that evening preference is a chronic characteristic in BD patients. In this study, evening preference was not associated with polarity type, or mood state in BD, suggesting that this characteristic may be a trait marker [49]. Shen et al., 2008 (206 patients) suggested that circadian irregularity is a prognostic factor related to shorter euthymia periods. Survival analyses indicated that both diagnosis and social rhythm regularity significantly predicted the time to participants' first prospective onset of major depressive, hypomanic and manic episodes [50].

The majority of studies – 23 studies including 2798 patients (81.5%) – were based only on subjective measures. Most used scales were composite scale of morningness (CSM) – nine studies involving 1556 patients (45.3%); biological rhythm interview of assessment in neuropsychiatry (BRIAN) – six studies, 593 patients

Fig. 1. Flowchart for study selection.

Table 1
Summary of study design.

Authors, year of publication	Study design	Participants	Mood status	Other characteristics	Sleep and rhythm measures	Main results
Ashman et al., 1999 [53]	Case–control study	9 BD and 9 controls	Any	Rapid cycling. Age 29–61 y.	SRM	Patients had lower activity levels and more phase delay. Depression phase was associated with more phase delay than euthymia and hypomania.
Nurnberger et al., 2000 [48]	Intervention study	29 BD, 24 MDD and 50 controls	Euthymia	Age 22–63 y.	Melatonin levels	BD patients were exposed to a 500-lux light and showed lower melatonin levels on the light night and later peak time for melatonin on the dark night.
Hakkarainen et al., 2003 [76]	Retrospective cohort	39 BD, 8 non-BD and 20 controls	Any	Twins. Age 29–57 y.	SPAQ and MEQ	No significant differences in morningness–eveningness between BD and controls. Preference for evening was associated with a higher global seasonality score. BD slept longer, compared with controls.
Jones et al., 2005 [57]	Case–control study	19 BD and 19 controls	Euthymia	F/M: 2.8. Mean age 44.37 y.	SRM and actigraphy for 7 days	BD had less stable and more variable circadian activity patterns than controls and more intradaily variability. No differences found on objective sleep measures.
Mansour et al., 2005 [75]	Case–control study	75 BD, 81 Sz/ SzA, and 349 controls	Any	No-specified	CSM	BD showed different rhythm from controls: lower CSM scores. Different from other groups, CSM scores were distributed bimodally among BD: Rapid cycling BD were more likely to have lower CSM scores.
Benedetti et al., 2007 [66]	Cross-sectional	39 BD	Depression without psychosis	M/F: 1.05.	Actigraphy for 48 h	<i>CLOCK</i> variant showed a significantly higher evening activity and a reduced amount of sleep during the night. Lithium-treated patients had higher activity levels in the evening and a trend toward a later morning awakening.
Ahn et al., 2008 [68]	Case–control study	92 BD, 113 Sz, and 95 controls	Euthymia	F/M: 1.1. Mean age 34.3 y.	CSM	BD had lower CSM scores and greater preference for evening activity and late sleep timing than controls. Sz patients did not show different patterns in circadian preference.
Salvatore et al., 2008 [61]	Case–control study	36 manic/ mixed BD, and 32 controls	Manic, mixed status and euthymia	F/M = 4.15. Mean age: 44.4 y.	Actigraphy for 72 h	Both manic/mixed and recovered BD had acrophase advance and lower daily activity. Euthymic BD had lower mean of 24-h motor activity and higher total sleep.
Shen et al., 2008 [50]	Cohort study (~33 mo)	206 BD and 208 controls	Not specified	F/M: 1.43. Age 18–24 y.	SRM	BD reported fewer regular daily activities. Less social rhythm regularity predicted a shorter time to onset of affective episode.
Kripke et al., 2009 [85]	Case–control study	130 BD and 561 relatives	Not specified	No-specified	Basic language morningness (BALM) scale	Polymorphisms of <i>PER3</i> and <i>CSNK1E</i> were associated with greater eveningness in BD patients.
Soreca et al., 2009 [78]	Cross-sectional	29 BD	Euthymia	F/M = 1.36. Age 18–60 y	CSM and PSQI	Evening preference was associated with higher percentage of body fat.
Wood et al., 2009 [70]	Case–control study	190 BD and 128 controls	Any	F/M = 4.13. Mean age 39.76 y.	CSM	BD patients are more likely to be evening types. CSM scores for BD-I and BD-II were different from the controls. High depressive mood scores are more likely to be associated with evening type.
Giglio et al., 2010 [71]	Case–control study	81 BD and 79 controls	Euthymia	F/M = 2.57. Mean age 43.5 y.	PSQI and biological rhythms interview	BD had more evening preference. Subthreshold depressive and manic symptoms were unrelated to chronotype in patients. Circadian preference was associated only with sleep latency and there was no association with other PSQI subscales.
Lee et al., 2010 [83]	Case–control study	260 BD and 350 controls	Not specified	F/M = 1.34. Mean age 35.5 y.	CSM	<i>CLOCK</i> 3111T/C showed a genotypic association with bipolar disorder. C allele carriers (C/C and C/T genotypes) were more associated with eveningness.
Minassian et al., 2010 [63]	Case–control study	28 BD, 17 Sz, and 21 controls	Mania	M/F = 1.15. Mean age 34.1 y.	LifeShirt, a monitoring device in the form of a wearable upperbody garment	Manic BD had higher levels of motor activity than Sz. Motor activity showed a modest relationship with symptom ratings of mania and psychosis.

Brambilla et al., 2012 [77]	Cross-sectional study	67 BD and 46 remitted MDD	Euthymia	F/M = 2.42. Mean age 51.32 y.	SPAQ, MEQ, and medical outcomes study sleep scale	MDD had greater sleep disturbance than BD. Morningness type had less disturbed and more adequate sleep quality. A family history for mood disorders was associated with higher fluctuations throughout seasons.
Chung et al., 2012 [74]	Cross-sectional study	106 BD-I, 43 BD-II, and 108 MDD	Not specified	F/M = 2.34. Mean age: 38 y (type I) and 32 y (II).	CSM	No difference in CSM total score among the three groups. BD-I had a higher score of evening tiredness than BD-II. BD-I had a higher mean score than MDD in morning alertness.
Faurholt-Jepsen et al., 2012 [67]	Case–control study	18 BD, 20 MDD, and 31 controls	Euthymia or depression	F/M = 1.56. Age 18–60 y.	Combined heart rate and movement sensor	BD and MDD had higher sleeping heart rates than controls. Fitness, acceleration and activity energy expenditure were lower in unipolar patients, whereas there was no significant difference between BD and controls.
van der Werf-Eldering et al., 2012 [81]	Cross-sectional study	65 BD	Euthymia or depression	F/M = 2.1. Age 18–65 y.	Diurnal cortisol levels and cortisol suppression test.	An association between depressive symptoms and cognitive impairment was found. Correlations between HPA axis activity and cognitive functioning or depressive symptoms were not identified.
Boudebessé et al., 2013 [41]	Cross-sectional study	140 BD and 156 controls	Euthymia	F/M = 1.05. Mean age: 41.57 y.	CTI and CSM	BD patients were more languid and showed an evening preference, but they did not differ from the controls with regard to flexibility/rigidity.
Robillard et al., 2013 [79]	Case–control study	18 BD and 14 MDD	Depression	F/M = 3. Age 15–30 y.	Actigraphy – 7 days and melatonin levels	Evening melatonin onset was reduced and delayed in a great proportion of young people with mood disorders, and these abnormalities were more prominent in those with bipolar as compared to unipolar depression.
Rosa et al., 2013 [65]	Case–control study	107 BD and 100 controls	Euthymia	M/F = 1.28. Mean age 43 y.	BRIAN	BD experienced greater biological rhythm alterations and more impaired sleep/social and activity domains. Correlation was found between biological rhythms with residual depressive symptoms and functioning.
Saunders et al., 2013 [73]	Retrospective cohort study	119 BD and 136 controls	Euthymia	F/M = 2. Mean age 41 y.	PSQI, ESS and MCTQ	Chronotype did not differ between two groups. BD had poorer sleep quality in PSQI and its subscales: sleep latency, subjective quality, sleep disturbance, sleep medication, and daytime dysfunction. BD also had more sleepiness.
Baek et al., 2014 [69]	Case–control study	200 BD and 270 controls	Euthymia	F/M = 1.9. Age 18–45 y.	CSM, STQ and SPAQ	BD-I and BD-II had lower CSM scores, higher global seasonality scores and more SAD as compared to controls. BD-II had lower CSM scores than BD-I. Patients with BD and SAD had more evening preference.
Cudney et al., 2014 [51]	Case–control study	52 BD and 30 controls	Euthymia and depression	All females. Mean age 40.75 y.	BRIAN	BRIAN scores showed a greater circadian rhythm disruption. Circadian rhythms disruption and number of psychiatric medications were independent predictors of lipid damage and malondialdehyde levels in BD.
Etain et al., 2014 [19]	Case–control study	239 BD and 873 controls	Euthymia	M/F = 1.3.	CSM and CTI	Polymorphisms rs774045 was associated with eveningness; and rs782931 was correlated with rigid circadian type.
Faria et al., 2014 [47]	Randomized clinical trial	45 BD	Any	Mean age 24 y.	BRIAN	One group received psychoeducation and medication (combined intervention); and the other, only medication (standard intervention). Both groups had remission of depressive symptoms, but none showed reduction of manic symptoms. No influence of psychoeducation on rhythm. Only the standard intervention group improved the BRIAN domains: sleep, activity, social rhythm and total score.
Geoffroy et al., 2014 [62]	Case–control study	25 BD and 28 controls	Euthymia	F/M = 1.2. Mean age 53.50 y.	PSQI and actigraphy	An association between the GG genotype, longer sleep duration ($p = 0.03$), greater activity ($p = 0.015$) and a higher interday stability ($p = 0.003$) was shown.

(continued on next page)

Table 1 (continued)

Authors, year of publication	Study design	Participants	Mood status	Other characteristics	Sleep and rhythm measures	Main results
Gonzalez et al., 2014 [56]	Cross-sectional study	42 BD	Any	F/M = 1.8. Age mean 53.50 y.	Actigraphy – 7 days	Greater severity of manic symptoms correlated with a lower degree of rhythmicity and less robust rhythms. No relationship was noted between the degree of depression and 24-h autocorrelation scores or circadian quotient
Kim et al., 2014 [72]	Case–control study	30 BD teens and 45 controls	Any	Age 7–17 y.	MESC	BD teens reported greater eveningness. No difference between two groups in latency age (<13 y old)
Krane-Gartiser et al., 2014 [64]	Case–control study	18 BD with mania, 12 BD with depression and 28 controls	Mania and Depression	Hospitalized patients. F/M = 1.5.	Actigraphy – 24 h	BD with depression had a lower mean activity level, but higher variability. The motor activity was lower in mania and depression in the morning ($p < 0.001$), but not in evening. In depression, BD had lower activity and higher variability than mania and controls.
Kripke et al., 2014 [84]	Case–control study	8 BD and 37 controls	Not specified	Not specified	MEQ and actigraphy – 14 days	Delayed sleep and “eveningness” were inversely associated with loci in circadian genes (rs2482705) and RORC (rs3828057). A group of haplotypes overlapping <i>BHLHE40</i> was associated with non-24-h sleep-wake cycles, and less robustly, with delayed sleep and bipolar disorder.
McKenna et al., 2014 [58]	Case–control study	14 BD and 14 controls	Euthymia	Age 30–79 y.	Actigraphy – 24 h	BD had less efficient sleep, less activity, less robust rhythm, and a smaller amplitude-to-width ratio. Variability in sleep/circadian rhythm was associated with degree of abnormality of brain response in the dorsolateral prefrontal cortex and supramarginal gyri brain response on a working memory task.
Rock et al., 2014 [60]	Case–control study	19 BD and 21 controls	Euthymia	F/M = 1.1. Mean age 20.1 y.	MEQ and actigraphy – 14 days	BD had increased movement during sleep, as assessed by the fragmentation index. BD had lower circadian amplitude and greater activity levels during their least active sleep phase (02:00–07:00 h).
Duarte Faria et al., 2015 [52]	Case–control study	49 drug-naïve BD, 74 MDD, and 94 controls	Any	F/M: 3.8. Mean age 21.88	BRIAN	Disruption in biological rhythm was higher in BD than MDD and controls. Biological rhythm was associated with bipolar disorder independently of current mood state, differently of MDD.
Nováková et al., 2015 [80]	Case–control study	60 BD in mania, 22 in depression, and 19 controls	Mania and Depression	Mean age 44.5 y in depression, and 40.4 y in mania.	Daily profiles of melatonin levels	Melatonin higher during daytime in mania phase; the Per1 and Nr1d1 profiles were advanced in mania compared with depression phase. The amplitude of the Nr1d1 expression profile was higher in mania than in depression.
Pinho et al., 2015 [54]	Case–control study	260 BD and 191 controls	Any	F/M: 3.8. Mean age 21.9 y.	BRIAN	BD had more biological rhythms disruption, an independent predictor of poor functioning. Depressed patients had greater biological rhythm disturbance than euthymic patients and controls.
Seleem et al., 2015 [49]	Cohort study (27 mo)	257 BD, 105 non-BD and 55 controls	Any	F/M: 2.1. Mean age 43 y.	CSM and sleep diary – 27 mo	BD had an evening preference. BD also had a higher sleep onset latency, higher wakening after sleep onset and less bedtime stability and awakening time stability.
Cudney et al., 2016 [55]	Cross-sectional	80 BD	Euthymia and depression	F/M: 4. Mean age 42.6 y.	BRIAN and PSQI	Disruption in biological rhythm is associated with poor quality of life in BD, independent of sleep disturbance, sleep medication use, and severity of depression.
Faedda et al., 2016 [59]	Case–control study	48 BD, 44 ADHD and 42 controls	Not specified	F/M: 1.1. Children (Mean age 10.1 y).	Actigraphy – 3–5 days	BD had a reduced circadian amplitude compared to the three other groups. This study confirms prior reports of hyperactivity in subjects with mania or hypomania.
Girshkin et al., 2016 [82]	Case–control study	56 BD, 56 Sz and 59 controls	Not specified	F/M: 1.7. Mean age 37.21 y.	Cortisol levels	Waking cortisol levels were greater in BD relative to Sz. Lower waking cortisol levels were associated with longer illness duration in BD. On the other hand, lower antipsychotic dose was related to greater symptom severity in Sz.

Grierson et al., 2016 [10]	Cross-sectional	30 BD and 33 MDD	Any	F/M: 1.7. Age 13 –25 y.	Actigraphy – 14 days	Reduced circadian rhythmicity and lower levels of activity were observed in individuals with longer time of mood disorder. Different from depression, there was a delay of maximum activity in mania. The rhythmicity was less robust in patients with more severe mood symptoms in BD but not MDD.
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ADHD, attention-deficit and hyperactivity disorder; BD, bipolar disorder; BRIAN, biological rhythm interview of assessment in neuropsychiatry; CSM, composite scale of morningness; CTI, circadian type inventory; ESS, Epworth sleepiness scale; F, female; HPA, hypothalamic–pituitary–adrenal; M, male; MCTQ, Munich chronotype questionnaire; MDD, major depressive disorder; MEQ, morningness–eveningness questionnaire; MESC, morningness–eveningness scale for children; PSQI, Pittsburgh sleep quality index; SAD, seasonal affective disorders; SPAQ, sleep practices and attitudes questionnaire; SRM, social rhythm metric; STQ, sleep timing questionnaire; Sz, schizophrenia.

(17.3%); social rhythm metric (SRM) – three studies, 234 patients (6.8%); and morningness–eveningness questionnaire (MEQ) – four studies, 133 patients (3.9%). 12 studies involving 356 patients (10.4%) used objective parameters: 11 used actigraphy; and one, LifeShirt, a monitoring device in the form of a wearable upperbody garment. Three studies (129 patients, 3.8%) measured melatonin levels; and two (121 patients, 3.5%) evaluated daily profiles of cortisol. Only one (14 patients) examined brain function using functional magnetic resonance imaging (fMRI) (Table 1).

Mood status of patients varied widely among studies: 14 evaluated patients in euthymia (1180 patients, 34.3%); 11 evaluated patients in any mood stage (1016 patients, 29.6%); two, only depression (57 patients, 1.7%); one, only mania (28 patients, 0.8%); seven evaluated two or more mood status (341 patients, 9.9%); and seven did not specify (814 patients, 23.7%). Two articles assessed rapid cycling BD (84 patients; 2.4%).

Disruption of biological rhythm

19 studies (45.2%) focused on regulation of biological rhythm in BD patients and its relationships with clinical variables. All five studies (576 patients) that used subjective measures of rhythm indicated a disruption of the biological rhythm in BD patients in comparison to controls [50–55]. This was also evidenced even in drug-naïve BD patients [39]. It is suggested that disruption of biological rhythm in BD occurs independently of current mood state ($p < 0.001$). Differently, the biological rhythm disruption is dependent on current mood symptoms in subjects with major depressive disorder (MDD) [52].

Four studies using actigraphy (105 patients) confirmed a less stable and more variable circadian activity patterns in BD, even in euthymia [10,56–59]. Smaller amplitude and alterations in mean activity were demonstrated in four actigraphic studies, including pediatric samples (117 patients) [58–61].

Individuals with bipolar disorder showed longer sleep duration, greater activity in active periods of sleep and greater interday stability. Geoffroy et al., 2014 showed that the association between BD and interday stability remain significant after correction for multiple testing [61].

The link between quality of life and rhythm was poorly investigated in BD patients. Cudney et al., 2016 showed that rhythm dysregulation is associated with poor quality of life in BD, independent of sleep disturbance, sleep medication, and severity of mood symptoms. Treatment strategies targeting regulation of biological rhythms may improve quality of life in this population [55].

Few articles evaluated the bidirectional relationship between mood status and social rhythm activity. Only one prospective cohort (involving 206 patients) investigated the impact of biological rhythm on mood status. Importantly, social rhythm regularity significantly predicted the onset of major depressive, hypomanic and manic episodes [50].

Four studies (136 patients) focused on mania; all of them were case–control. Minassian et al., 2010 (28 patients) demonstrated that manic BD exhibited higher levels of motor activity when exploring novel environments [63]. Krane-Gartiser et al., 2014 (30 patients) reported lower motor activity in mania and depression compared to controls in the morning ($p < 0.001$), but not in the evening [64]. Mania and mixed status were associated with acrophase advance ($p < 0.001$) and lower daily activity ($p < 0.05$) than controls [47]. It was suggested that greater severity of manic symptoms correlated with less robust rhythms of locomotor activity [57].

Circadian disturbances were more frequent in depression phase in comparison to euthymia and controls (four studies; 260 patients)

[53,54,64,65]. Even in residual depressive symptoms, this relationship was observed ($p < 0.001$) (66). In opposition, only one study (42 patients) found no relationship between the degree of depression and circadian quotient ($p = 0.96$) (57). Depression was associated with lower mean activity level, higher variability, delay of circadian rhythm in evening and morning activities and poor functioning [53,54,64,65]. Severity of mood symptoms correlated to less robust rhythms in BD, but not MDD [10].

Only one study evaluated the repercussions of psychoeducation on circadian rhythm on BD. 45 patients were divided into two groups: one group received a short-term psychoeducation model and medication (combined intervention), and the other received only medication (standard intervention). The model was summarized in a protocol of six individual sessions of one hour each about BD, mood status and treatment. Both groups showed remission of depressive symptoms ($p = 0.04$), but none showed a statistically significant reduction of manic symptoms. No influence of psychoeducation on biological rhythm was observed; however, only the standard intervention group showed improvement in the following BRIAN domains: sleep ($p = 0.01$), activity ($p < 0.001$), social rhythm ($p = 0.002$) and total score ($p = 0.001$) [48].

Only one study analyzed the impact of mood stabilizers on rhythm in BD. In lithium-treated patients ($n = 39$), activity levels in the evening were higher and there was a trend toward a later morning awakening during depressive episodes [66]. Other drugs were not investigated, and further studies are necessary.

A single study (18 patients) used a combined heart rate and movement registration as an indicator of rhythm alterations. It concluded that fitness, acceleration and activity energy expenditure were lower in unipolar patients, but not in the BD group (in depression or euthymia) [67].

Circadian alterations in 14 euthymic BD patients were related to structural abnormalities in the brain, mainly concerning the dorsolateral prefrontal cortex (DLPFC) and supramarginal gyri. In the right DLPFC, positive associations were found between the mean abnormal blood oxygen-dependent level (BOLD) and amplitude of circadian rhythm while an opposite effect was found in the left side [58].

Chronotype

15 studies (35.7%) evaluated chronotype in BD patients. Bipolar disorder was often associated with eveningness. Six studies involving 850 patients showed that evening type was more common in BD as compared to controls [41,68–72]. Eveningness was maintained for a long time and therefore, it was considered a trait marker [49]. In opposition to these findings, one study (119 patients) did not evidence difference between euthymic BD and controls [73]. Chung et al., 2012 compared the chronotypes of BD and MDD patients and no difference in circadian preference was found [74].

Considering the BD types, rhythm comparisons between BD-I and BD-II were scarce and showed unclear results. Baek et al., 2014 (200 patients) revealed that BD-II had higher eveningness scores than BD-I during euthymia [69]; in contrast, Chung et al., 2012 (106 patients) did not evidence differences; however, mood status was not specified [74].

Studies about rapid cycling, a particular type of BD, were few (two studies involving 84 patients). Rapid cycling BD often had less rhythmic daily routines ($p = 0.01$) and completed fewer activities ($p = 0.01$) than controls [53]. Compared to non-rapid cycling BD, they were more likely to have evening preference ($p < 0.02$) [75].

Only one study described the chronotype in 30 BD children. No differences between children with BD and controls were found.

However, BD adolescents (ages 13 y and older) endorsed greater eveningness compared to controls, similar to adults with BD [72].

Few studies ($n = 306$) showed an interface between chronotype, depressive symptoms and seasonality. In general, BD-I and BD-II had a higher global seasonality score – GSS ($p < 0.028$) and more seasonal affective disorders – SAD ($p < 0.001$) [69]. There was also a preference for evening ($p < 0.01$) [67,74]. Higher fluctuations throughout seasons were also associated with a family history for mood disorders ($p = 0.035$) [77].

Although very important, the relationship between chronotype and metabolism was rarely studied. Soreca et al., 2009 ($n = 29$) reported that eveningness was associated with higher percentage of body fat ($p = 0.004$) in euthymia, measured by a dual x-ray absorptiometry. The CSM score was associated with an increase of 19% of the variance in percentage of body fat, independently of age, sex, 12-wk depression, mania score, and sleep quality [78].

Few studies reported the relationship between chronotype, functionality and sleep in euthymia. Evening type was related to a poor sleep quality ($p = 0.01$) in one study (67 patients) [77] and to poor functionality in BD ($p < 0.001$) in another (107 patients) [65].

Studies about the influence of chronotype on depressive symptoms showed conflicting results. Wood et al., 2009 (190 patients) reported that high depression scores are more likely to be associated with evening type [70]. On the other hand, Gonzalez et al., 2014 (42 patients) found no relationship between the degree of depression and circadian quotient [57]. Furthermore, Rosa et al., 2013 (107 patients) reported a correlation between biological rhythms with residual depressive symptoms ($p < 0.001$) [65], while Giglio et al., 2010 (81 patients) indicated no association between subthreshold depressive symptoms and chronotype in BD [71]. To this date, only one investigation (81 patients) observed the influences of chronotype in mania, revealing that subthreshold manic symptoms were unrelated to chronotype [71].

Circadian rhythm and biomarkers

Six studies (14.3%) evaluated biomarker changes throughout a day. Three of them (129 patients) measured the daily profiles of melatonin [50,79,80]; and two (121 patients) evaluated cortisol levels [81,82]. Another one (52 patients) analyzed lipid peroxidation, measuring malondialdehyde (MDA) levels and the activity of total and extracellular superoxide dismutase (SOD), catalase (CAT) and glutathione S-transferase (GST) [51].

Evidence indicates that daily levels of melatonin may assume a different pattern during mania as compared to controls and to patients with depression. Novakova et al., 2015 (60 patients) demonstrated that the melatonin levels in mania at 15:00 and 19:00 h were significantly higher than in controls and depression, corresponding to nearly 50% of the maximal nocturnal levels. Moreover, at 07:00 h, they were significantly lower. Otherwise, no differences were found between melatonin profiles of controls and depressive patients [80]. Melatonin secretion abnormalities were confirmed in a subgroup of euthymic BD patients: lower melatonin levels and a later peak time for melatonin was confirmed [48]. Another study (18 patients) compared melatonin levels in depressive BD and MDD groups, concluding that BD patients showed later dim light melatonin onset – DLMO (melatonin concentration above 3.000 pg/mL) and smaller melatonin area under the curve – AUC (corresponding mean melatonin concentrations over the day) than the MDD patients. In this study, DLMO occurred after habitual sleep onset in one third of patients with mood disorders. Thereby, these findings indicate that BD patients show delayed and lower evening melatonin secretion [79].

The cortisol daily profile of BD patients probably presents a specific pattern. Girshkin et al., 2016 (56 patients) showed that BD

had higher levels of cortisol at waking and increased cortisol levels in response to a stressful exam (magnetic resonance imaging – MRI) than schizophrenia (but not controls). Interestingly, cortisol patterns were associated with different variables in BD and schizophrenia: lower waking cortisol indices related to longer illness duration in BD, and to greater symptom severity in schizophrenia [82]. Associations between cortisol levels and cognitive functioning or depressive symptoms were not evidenced [81].

Cudney et al., 2014 (52 patients) suggested that circadian disturbance was independently associated with increased lipid peroxidation in BD ($p < 0.05$), but not in controls. A reduced extracellular SOD ($p < 0.05$) in BD was observed, but no differences in total SOD, CAT or GST activity was found [51]. No study correlated inflammatory cytokines and rhythm disorders in BD.

Genetics

Six studies (14.3%) evaluated the impact of genetic alterations on circadian rhythm: two (299 patients) analyzed the *CLOCK* gene [64,81]; one (25 patients), *acetylserotonin O-methyltransferase* (*ASMT*) gene [60]; the fourth (8 patients) investigated polymorphisms in 15 genes: *ARNTL*, *BHLHE40*, *BHLHE41*, *CLOCK*, *CRY1*, *CRY2*, *CSNK1D*, *CSNK1E*, *DBP*, *NFIL3*, *NPAS2*, *NR1D1*, *PER1*, *PER2*, and *PER3* [82]. Two studies evaluated polymorphisms in other circadian genes [19,85].

Lee et al., 2010 (260 patients) studied a single nucleotide polymorphism (SNP) in the 3'-flanking region of *CLOCK* (3111T/C; rs1801260), whose 3111T/C variant showed significant allelic and genotypic associations with bipolar disorder ($p = 0.012$ and $p = 0.033$). Furthermore, C allele carriers (C/C and C/T genotypes) were more associated with eveningness ($p = 0.041$) [83]. Similarly, Benedetti et al., 2007 (39 patients) found that C variant was associated with higher evening activity ($p = 0.007$), a delayed sleep onset (mean 79 min later), and a reduced amount of sleep during the night (mean 75 min less) [66].

Geoffroy et al., 2014 (25 patients) focused on polymorphism (rs4446909) of the promoter of the *ASMT* gene, encoding one of the two enzymes involved in melatonin biosynthesis. An association between the GG at-risk genotype was found with each of the following variables: longer sleep duration ($p = 0.03$), greater activity during active periods of the night ($p = 0.015$) and higher interday stability ($p = 0.003$) [62].

Kripke et al., 2014 (8 patients) showed that delayed sleep and "eveningness" were inversely associated with loci in circadian genes *NFIL3* (rs2482705) and *RORC* (rs3828057). Some *BHLHE40* alleles were associated with non-24-h sleep-wake cycles, and less robustly, with delayed sleep and bipolar disorder (e.g., rs34883305, rs34870629, rs74439275, and rs3750275) [84].

Kripke et al., 2009 (130 patients) revealed that bipolar disorder was associated with genes *NR1D1* (rs2314339), suggesting that perturbations of the circadian gene network at several levels may influence mood disorders [85]. Polymorphisms of *PER3* and *CSNK1E* were associated with greater eveningness in BD patients.

Etain et al., 2014 (239 patients) demonstrated that rs774045 in *TIMELESS* was associated with eveningness whereas rs782931 in *RORA* was associated with rigid circadian type indicating these variants in the *TIMELESS* and *RORA* genes may confer susceptibility to BD and impact on circadian phenotypes in carriers [19].

Discussion

The vast majority of studies showed a disruption of circadian rhythm and an evening preference in BD patients, independently of mood status. Interestingly, MDD contrasts with this evidence, demonstrating that rhythm disruption is dependent on current

mood symptoms [52]. Some studies showed that circadian alterations in BD were more frequent in individuals with depression than in euthymic patients [53,54,64,65]. Circadian disruptions were established even in drug naïve patients [52]. Actigraphic studies confirmed the disruption of the circadian rhythm [10,56–59]. Based on all this evidence, it is licit to conclude that circadian rhythm alterations are present in BD; however, the role of mood status is unclear.

Few studies involved patients in manic state. Mania and mixed status were associated with acrophase advance and lower daily activity [61]. In addition, greater severity of manic symptoms correlated with less robust rhythms [56]. The paucity of evidence related to mania possibly relates to the obvious clinical limitations of studying these patients. This aspect needs more clarification.

Circadian disturbances may have a role in the pathogenesis of mood disorders. Robillard et al., 2013 showed that young patients with mood disorders, especially those with BD, are likely to have a delayed sleep phase [86]. Actigraphic studies in BD patients show sleep abnormalities during depressive, manic, and interepisode periods [87]. In light of these evidences, when analyzing sleep disturbances, attention to age, circadian changes and levels of residual depressive symptoms must be taken into consideration [88].

Similarly, patients with other psychiatric disorders, such as major depression, anxiety disorders and schizophrenia often show circadian dysregulation of hormonal and behavioral processes contributing to major functional impairment [89,90]. Rhythm disruption has been associated with disease severity in some psychiatric disorders, e.g., increased suicidal ideation in patients with MDD [58].

Evidence on circadian alterations in BD is mostly based on cross-sectional evaluations; therefore, a cause–effect relationship cannot be established. Interestingly, one prospective study showed that less social rhythm regularity predicted a shorter time between affective episodes [50]. These preliminary results are promising and it is fair to hypothesize that interference in the circadian rhythm could reduce affective symptoms.

One study tested the effects of psychoeducation in BD patients and suggested no significant influence on circadian changes [48]. Psychoeducation is not a conventional and recommended measure to modify circadian patterns. A change of rhythm can be achieved using measures such as light exposure, physical exercise and sleep hygiene [20,91]. Randomized trials focusing on circadian changes may clarify whether a long-term interference will affect the expression of mood symptoms.

One important and isolated study demonstrated effects of lithium therapy on circadian patterns in BD patients, characterized by higher evening activity and later morning awakening [66]. In vitro studies of fibroblasts from BD patients show weaker amplification of circadian rhythm by lithium and this possibly relates to calcium signaling. Possibly, a low amplitude circadian rhythm associated with lithium therapy could influence therapeutic results [23,92]. Genetic studies further confirm a relationship between circadian rhythm and lithium showing that the expression of circadian clock components, including *Per2*, *Cry1* and *Rev-erb α* , is affected by lithium treatment [24]. A systematic review reveals that chronic lithium treatment stabilizes activity rhythms: it delays circadian rhythms and peak of body temperature, and reduces amplitude and duration of activity rhythms [18]. Given all this evidence, clinical studies evaluating the impact of lithium and other mood stabilizers on circadian rhythm and the influence on therapeutic results are warranted.

A single study shows that circadian alterations in BD are linked to structural abnormalities in the brain mainly concerning the dorsolateral prefrontal cortex (DLPFC) and supramarginal gyri. Prefrontal dysregulation is associated with trait impulsivity and

impairment in working memory [93,94]. Reduced white matter integrity is also observed in bipolar patients, suggesting cognitive repercussions [95,96]. Studies investigating alterations of functional neuroimaging in BD related to rhythm disruption were not found. These preliminary findings deserve confirmation.

Interestingly, one single study showed that children with BD did not have eveningness preference; in contrast, eveningness was already present in adolescents [72]. Recently, objective measures of sleep, circadian rhythmicity, and hyperactivity were abnormal in children with BD [59]. Reduced relative circadian amplitude was a distinctive feature. Generally, adolescents tend to sleep less, go to bed and get up later, and experience greater daytime sleepiness and weekend compensation for sleep shortage on weekdays, compared to younger children [97]. In fact, studies investigating sleep–wake patterns in preadolescents and in children are scarce [98,99]. Future samples should include both youth and adults with BD.

Comparisons between chronotype preference and BD types were scarce. One study showed that BD-II was more associated with eveningness. Abé et al., 2015 indicated that both BD subtypes showed cortical abnormalities, such as lower volume, thickness and surface area in frontal brain regions. However, BD-I had abnormally low cortical volume and thickness in temporal and medial prefrontal regions [100]. More studies on neuroanatomy and pathophysiology could possibly explain the differences in clinical manifestation and patterns of circadian rhythm between BD-I and II.

In BD, few studies showed an interface between chronotype, depressive symptoms and seasonality. Preliminary evidence showed that BD-I and BD-II had a higher GSS and more seasonal affective disorders [69]. Higher fluctuations throughout seasons were also associated with a family history for mood disorders in bipolar patients [76]. The latter evidence helps to consolidate the common biological ground between mood, circadian rhythm and seasonality in BD. Recently, two rare variants in the circadian clock gene *PERIOD3* (*PER3*-P415A/H417R) in humans with familial advanced sleep phase and depression and seasonality were identified indicating a possible role for *PER3* in mood regulation [101]. Seasonal affective disorders are frequently reported during winter in regions with reduced levels of light; however, the effects of seasonal variation on circadian rhythm, chronotype expression, sleep and mood symptoms are unclear [102].

Studies about influence of chronotype on depressive symptoms showed conflicting results. To this date, only one investigation observed the impact of circadian preference in mania, revealing that subthreshold manic symptoms were unrelated to chronotype [71]. In population based studies, eveningness has been associated with depressive symptoms [103,104]. In MDD, evening preference was related to poor therapeutic response [37,38]. Jankowski et al., 2016 suggested that morning affect may be responsible for the link between circadian preference and depressive symptoms. People with eveningness without low morning affect had less depressed/somatic symptoms [105]. To the best of our knowledge, this issue has not been investigated in BD patients.

Despite the clinical relevance due to its frequency, morbidity and mortality, metabolic abnormalities, eating patterns and circadian variations were rarely evaluated in BD patients. Previously, eveningness was associated with higher percentage of body fat and depressive symptoms [78]. Changes in the clock system alter the neuroendocrine pathways within the hypothalamus. These structures are involved in feeding and energetics [106]. Chronically, rhythm desynchronization can enhance inflammatory mediators and may increase the risk of cardiovascular and metabolic diseases [107]. Previously, a link between a high BMI

and several sleep disturbances in BD, including lower sleep efficiency has been established [108]. Given the high prevalence of these diseases, it is important to identify the impact of sleep and circadian disorders in the development and course of metabolic disease.

Considering biomarkers, preliminary evidence showed a dysregulation of daily levels of melatonin and cortisol. In relation to oxidative stress, circadian rhythm disturbance was associated with increased lipid peroxidation in BD [51]. Many authors consider BD an inflammatory condition [109–111]. To date, no study focused on the relationship between inflammatory cytokines and biological rhythms. Of note, circadian dysregulation entails changes in immune system and increase vulnerability to infections. Immune parameters also show daily variations, demonstrating a circadian pattern [112].

Currently, studies involving genetics are incipient. Many circadian genes have been associated with BD [113–115]. However, studies assessing how these genes influences circadian rhythm in BD are less frequent. It is suggested that chronotherapies, including sleep deprivation and sleep phase advance, modify clock gene machinery and it can represent a pathophysiological explanation to improvement of mood symptoms [116].

Several limitations need to be acknowledged. Different study designs, various kinds of circadian rhythm outcomes, and heterogeneous mood status prevented us from performing a meta-analysis. Most studies were cross-sectional, hampering a cause–effect relationship. The majority of them were based only on subjective parameters, and studies with actigraphy or biomarkers were less frequent. However, this review included 3432 patients with BD evaluating aspects related to chronotype, circadian disruption, disease severity, biomarkers, genetic influences and therapeutic aspects. The evidence clarifies some issues and gives avenues to new investigations.

In conclusion, circadian rhythm disruption and eveningness are common in BD. However, the impact on mood status is still unclear. More prospective research is needed. Future studies should focus on therapy, outcomes, metabolic alterations, rapid cycling, biomarkers variability, children's evaluation, and brain structural abnormalities. Longitudinal data that assess when/how circadian preference/rhythms change, and how these changes relate to age of diagnosis and symptom severity could expand the knowledge about the subject.

Practice points

- 1) Disruption of circadian rhythm was identified, even in drug-naïve BD patients. Actigraphy confirmed this finding, independently of mood status. Studies showing alterations in daily profiles of melatonin levels and cortisol reinforced circadian dysregulations in BD.
- 2) Evening type was more common in BD adults. It was suggested that children did not show eveningness; however, this circadian preference was already found in adolescents. The influence of chronotype on mood symptoms remains unclear.
- 3) Genetic studies involving circadian rhythm are incipient. Analysis of the circadian genes suggested that eveningness is more associated with C allele carriers in *CLOCK* genes and inversely related to loci in circadian genes *NFIL3* (rs2482705) and *RORC* (rs3828057).

Research agenda

Areas for future research may include:

- 1) Repercussions of circadian disruption on mood symptoms.
- 2) Influence of morning affect on chronotype and mood symptoms.
- 3) Relationships between metabolic abnormalities, eating patterns and circadian variations.
- 4) Profile of the circadian rhythm in children, adolescents and adults with BD.
- 5) Relationship between rapid cycling, chronotype and biological rhythm.
- 6) Effects of mood stabilizers on circadian patterns.
- 7) Associations between neuroanatomy, inflammatory mediators and biological rhythm.

Conflicts of interest

The authors do not have any conflicts of interest to disclose.

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