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Minireviews

The impact of lithium on circadian rhythms and implications for bipolar disorder pharmacotherapy

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ABSTRACT

Bipolar disorder (BD) is characterized by disrupted circadian rhythms affecting sleep, arousal, and mood. Lithium is among the most effective mood stabilizer treatments for BD, and in addition to improving mood symptoms, stabilizes sleep and activity rhythms in treatment responsive patients. Across a variety of experimental models, lithium has effects on circadian rhythms. However, uncertainty exists as to whether these actions directly pertain to lithium's therapeutic effects. Here, we consider evidence from mechanistic studies in animals and cells and clinical trials in BD patients that identify associations between circadian rhythms and the therapeutic effects of lithium. Most evidence indicates that lithium has effects on cellular circadian rhythms and increases morningness behaviors in BD patients, changes that may contribute to the therapeutic effects of lithium. However, much of this evidence is limited by cross-sectional analyses and/or imprecise proxy markers of clinical outcomes and circadian rhythms in BD patients, while mechanistic studies rely on inference from animals or small numbers of patients . Further study may clarify the essential mechanisms underlying lithium responsive BD, better characterize the longitudinal changes in circadian rhythms in BD patients, and inform the development of therapeutic interventions targeting circadian rhythms.

1. Introduction

Bipolar disorder (BD) is a common and severe neuropsychiatric disorder that affects 1–2% of the world's population, causing adverse effects on psychological, social, and occupational outcomes [1]. Among BD patients, 10–20% die by suicide, a risk estimated to be 20–30 times higher than the general population [2]. BD is defined by discrete mood episodes of depression and mania/hypomania, interspersed with prolonged euthymic intervals where symptoms are mild or absent. Other defining characteristics of BD include disruption of sleep, activity, arousal, attention, cognition, and appetite, all of which involve physiological systems that oscillate over daily 24 h cycles (i.e. circadian rhythms). In addition to these episodic features associated with mood symptoms, BD patients also show persistent differences in circadian rhythms that occur even during euthymic intervals. Even in the absence of mood symptoms, BD patients commonly show disrupted daily patterns in sleep characterized by low rhythm amplitude (i.e. signal strength), delayed onset/offset of activity [3,4], and evening chronotype (i.e. preference for late activity) [5,6]. Moreover, genetic risk factors for BD susceptibility overlap with risk for sleep disorders and determinants of chronotype, suggesting common biological underpinnings of BD and circadian rhythms [7–9]. Thus, circadian rhythm disruption may be a fundamental aspect of BD affecting mood episodes, genetic vulnerability, and stable characteristics of the disorder [10].

In humans, the master circadian timekeeper is located in the hypothalamic suprachiasmatic nucleus (SCN). Within SCN neurons, molecular transcriptional/translational feedback loops maintain cellular rhythms (Fig. 1A). At the core of this loop, the proteins CLOCK and BMAL1 bind to form a heterodimeric transcription factor complex. This CLOCK/BMAL1 complex then binds to DNA at E-box promoter regulatory elements, driving the expression of "clock genes" including *PER1/2/3* and *CRY1/2*, which act as transcriptional repressors to inhibit their

Abbreviations: BD, bipolar disorder; SCN, suprachiasmatic nucleus; SNP, single nucleotide polymorphism; GSK3, glycogen synthase kinase 3; MAPK, mitogen-activated protein kinase; PER2::LUC, PERIOD2::LUCIFERASE; PGBD, Pharmacogenomics of Bipolar Disorder; BDI, bipolar disorder type I; BDII, bipolar disorder type II; ERK, extracellular receptor kinase; IMP, inositol monophosphatase; IP_3, inositol trisphosphate; Li-R, lithium responders; Li-NR, lithium non-responders; iPSC, induced-pluripotent stem cell.

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own expression. This cycle generates a ~24 h transcriptional/translational feedback loop causing oscillations in clock gene expression and cellular rhythms [11]. Additional loops comprised of *REV-ERB* and *ROR* genes and post-translational regulation of clock proteins further modulate these cellular rhythms. Dynamic features of rhythms are commonly described in terms of period, phase, and amplitude (Fig. 1B). The molecular clock is expressed in cells throughout the body including the brain and peripheral organs [12]. Although the SCN acts as the master clock coordinating cells and tissues throughout the body with each other and the environment, other tissue clocks maintain their own endogenous rhythms even in isolated, experimental preparations [13,14]. Variation (e.g. single nucleotide polymorphisms, SNPs) in the circadian oscillator genes or accessory pathways can affect aspects of their function including the timing and intensity of gene expression and post-translational modification [15,16]. In humans, these may lead to individual phenotypic differences in circadian rhythms, commonly observed as different chronotypes and/or sleep behaviors. Chronotype frequently correlates with internal circadian timing (i.e. phase) and is commonly used as a proxy marker for circadian rhythm studies in humans [17,18]. Sleep phenotypes affecting duration, consolidation, or onset/offset may reflect both circadian disruption (low amplitude or phase shifts) and/or non-circadian features related to sleep homeostasis [19].

Lithium has been in use for >7 decades and remains an essential mood stabilizer with efficacy across the clinical spectrum of BD. Lithium has a unique pharmacological profile and has been shown to affect a variety of neuronal signaling mechanisms including glycogen synthase kinase 3 (GSK3) [20], inositol metabolism [21], and mitogen-activated protein kinases (MAPK) [22] causing effects on brain gray matter and white matter volume [23,24], autophagy [25], neurogenesis [26], synaptogenesis [27,28], neuroprotection [29], and circadian rhythms. Due to the diversity of drug effects, there remains considerable uncertainty as to which mechanism(s) are most relevant for the therapeutic effects of lithium in BD. Lithium treatment is not without problems: only 30% of BD patients fully respond to long-term therapy, side effects are common, and the toxicity profile is relatively poor, necessitating frequent laboratory monitoring [30]. Limited understanding of lithium's mechanism of action in BD has impeded optimal treatment selection for patients and hindered the development of more effective and safer mood stabilizers. Given the disruptions of circadian rhythms observed in BD and evidence that lithium alters circadian rhythms, this review addresses the question of whether engagement with molecular circadian clocks is essential for the therapeutic mechanism of lithium. We consider evidence from a variety of sources including animal studies, cell-based experiments, and human clinical trials and consider the potential utility of circadian rhythms as a biomarker for predicting lithium response.

2. Lithium effects on circadian rhythms in rodents, non-human primates, and healthy humans.

Lithium alters circadian rhythms in behavior and physiology across a variety of mammalian species [31]. Specifically, lithium lengthens circadian period (i.e. time between activity onset on consecutive cycles) in rodent wheel-running behavior under constant darkness [32–35]. In addition, lithium causes phase delays and/or period lengthening in circadian rhythms of melatonin, body temperature, and serum metabolites [31,36,37]. More recent studies have used bioluminescent reporters such as PERIOD2::LUCIFERASE (PER2::LUC) to study the effects of lithium on circadian rhythms in peripheral organs of behaving mice [38]. These approaches offer a means of studying rhythms in clock gene expression without subjecting animals to stressful manipulations that could alter physiology and provide a means for conducting longitudinal, within-subject studies. As with wheel-running studies, lithium reversibly lengthens the period of PER2::LUC rhythms in the kidneys of mice *in vivo* at concentrations similar to therapeutic levels in humans (1 mM) [38]. Interestingly, *in vivo* kidney PER2::LUC rhythms were more sensitive to lithium's period lengthening effects than *ex vivo* kidney slices that required drug concentrations that would be supratherapeutic in humans (10 mM) [38]. This demonstrates the importance of *in vivo* recording to capture the circadian response to lithium in intact animals and indicates that drug sensitivity may be context-dependent and possibly more potent *in vivo*. Methods for long-term bioluminescence rhythm recording in mouse brains *in vivo* have been developed [39], but to date have not been used to study the effects of lithium.

Few studies have been conducted in primates and humans testing the circadian effects of lithium treatment. In a laboratory study of diurnal squirrel monkeys maintained under constant light conditions and treated with lithium for 4–6 weeks, lithium caused a mean period lengthening of 0.6 h. Lithium serum levels were found to be similar to the therapeutic levels used in humans (0.76–2.02 mM) but with considerable variation. Interestingly, the degree of period change correlated only modestly with serum drug levels [40], suggesting the presence of inherent, individual differences in sensitivity to lithium's chronobiological effect. Studies of lithium in healthy humans have also been conducted, but have typically been small and not conducted under laboratory conditions that adequately control for masking due to light/dark cycles or other environmental factors, which hinder the accuracy of circadian rhythm measurements. Among 22 healthy human volunteers taking either placebo or lithium, self-reported sleep time was delayed by 14 min during lithium treatment [41]. In a different cohort of eight healthy volunteers living in isolated conditions in the arctic, four subjects showed period lengthening of temperature, sleep, and activity rhythms while the other four did not [42]. This variability further suggests the presence of individual differences in the chronobiological effects of lithium. In non-human primates and healthy humans, these individual chronobiological responses to lithium may have a genetic basis. If so, genetically encoded differences in the molecular targets of lithium may affect not only lithium's effects on rhythms but overlap with drug targets that determine therapeutic response to lithium in BD patients.

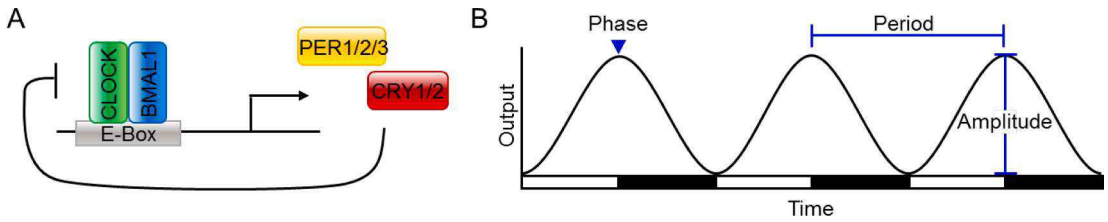

Fig. 1. Molecular and dynamic features of the circadian clock. A) Core molecular clock feedback loop. The protein heterodimer CLOCK/BMAL1 binds to the E-box and promotes the transcription of *PER1/2/3* and *CRY1/2*. The protein products of these genes then inhibit their own transcription generating ~24 h rhythm in gene expression. B) Fundamental properties of circadian rhythms include phase, period, and amplitude. *Phase* refers to the timing of a reference point in the cycle relative to a fixed event (i.e. peak of the rhythm). *Period* refers to the time interval between two reference points in the rhythm (i.e. number of hours between two consecutive peaks). *Amplitude* refers to the differences in the output level between the peak and trough values of the rhythm. These parameters can be derived in cells (e.g. *Per2-luc* expression), physiology (e.g. melatonin levels), and behavior (e.g. sleep/wake behaviors).

3. Lithium effects on circadian rhythm proxy measures in BD patients.

There are no laboratory studies testing the effect of lithium on circadian rhythms in BD patients. However, a variety of proxy markers for circadian rhythms have been studied including chronotype measures and actigraphy. A few studies in BD patients have found a relationship between lithium use and chronotype [43–45]. In two small cross-sectional studies, BD patients on lithium exhibited more morningness compared to those taking other medications [44,45]. A third cross sectional study of BD patients (149 subjects on lithium, 376 subjects not on lithium) found no differences in chronotype between groups [46]. A *meta*-analysis of these results concluded that lithium caused a nominal trend ($p = 0.08$) towards increased morningness [47]. However, none of the studies measured drug effects across time or correlated changes in chronotype with therapeutic lithium response. In a small set of clinically responsive BD patients ($n = 11$) treated with lithium over one year, there was no change in morningess, even as average scores for depression and manic symptoms tended to decrease [48].

The Pharmacogenomics of Bipolar Disorder (PGBD) study conducted a prospective clinical trial of lithium monotherapy in 386 adult BD type I (BDI) patients [43,49,50]. Participants were assessed at baseline and at regular intervals to determine their mood state and occurrence of manic/depressive symptoms and relapse. Similar to the cross-sectional studies, those who entered the study currently stabilized on lithium had higher levels of morningness and lower scores on a composite measure of circadian disruption compared to unstable BD patients with no prior exposure to lithium [43]. Patients who were previously treated with lithium but did not fully stabilize showed intermediate levels of morningness and circadian disruption [43]. Lithium was then prescribed for the first time to a subset of 88 PGBD patients who were prospectively assessed for 12 weeks. Of the 88 PGBD patients, half were later determined to be lithium responders. Baseline morningness did not differ between lithium responders and non-responders. Lithium responders improved across all domains of depression, including affective symptoms of anhedonia, hopelessness, and suicidal ideation, as well as circadian symptoms related to sleep, activity, and energy. Lithium non-responders who became unstable during the observation period demonstrated improvement in affective symptoms of depression but failed to show improvement in circadian symptoms. Changes in manic symptoms were generally mild and similar across groups [43]. These data suggest that improvement in circadian symptoms of depression selectively distinguished lithium responders/non-responders and was essential to mood stabilization. Therefore, the chronobiological effects of lithium seem necessary for achieving a therapeutic lithium response.

Studies using actigraphy offer another means of estimating circadian rhythms in BD patients. In a study of 90 outpatients with BD (78% BDI) and a history of lithium treatment (classified retrospectively as lithium responders/non-responders), actigraphy was measured for 21 days. More robust rhythms correlated with lithium response, especially in BDI [51]. Four rhythm parameters distinguished the lithium responders/non-responders: intra-daily variability, activity level, amplitude, and relative amplitude of activity [52]. In another prospective, randomized trial of lithium versus quetiapine in BD type II (BDII) patients, both drugs improved the coherence of activity rhythms after 8 weeks of treatment, but only quetiapine caused a phase delay [53]. These results again suggest an effect of lithium on rhythms. Interestingly, the latter study indicates that other mood stabilizing drugs may also impact rhythms, but perhaps in distinct ways. This study introduces the notion that different mood stabilizer drugs may be able to alter rhythms in particular ways and that depending on the change required, chronobiological information may be informative in making personalized treatment decisions for BD patients.

The emerging evidence from these clinical studies of circadian proxy markers indicates that lithium responders have increased morningness and that lithium increases rhythm amplitude specifically in lithium responders. However, there are relatively few of these studies and most have small sample sizes and/or are confounded by the use of additional medications and/or retrospective clinical assessment. Only in a few cases can changes in rhythm proxy-measures be identified prospectively and distinguished from patient characteristics that preceded treatment. Importantly, actigraphy, chronotype, and symptom scale assessments are only indirect measures of endogenous circadian rhythms. Actigraphy is prone to artefacts from masking and has a reduced specificity in detecting wake, which can be particularly problematic for patient populations or those with irregular schedules [54,55]. Further studies, including additional controlled laboratory experiments, are required to clarify these points.

4. Lithium effects on cellular clocks.

To resolve the molecular mechanisms underlying lithium's circadian effects and overcome some of the limitations of studying circadian rhythms in humans, *ex vivo* and cellular methods have been developed.

4.1. Rhythm studies in explants and transgenic animals

In whole brain tissue from mice, lithium upregulated expression of *Per1*, *Per2*, and *Cry1* [56]. Gene expression studies in mouse fibroblasts also indicated that lithium (20 mM) increased *Per2* and *Cry1* expression, decreased *Per3*, *Bmal1*, and *Rev-Erbα* expression, and lengthened the period of *Per2* expression [57]. Further, lithium altered clock gene expression and timing in the mouse striatum, which is an important brain region for motivated behavior regulation. Specifically, lithium increased *Cry1* and *Per2* expression and decreased *Rev-Erbα* expression in the middle of the light phase. Lithium also shifted the phase of CRY1 protein expression in the striatum [58].

In mouse SCN explants, neuronal action potential frequency is rhythmic, and lithium caused a concentration-dependent period lengthening of this rhythm [59]. Interestingly, there was no effect of lithium at a therapeutically relevant concentration (1 mM) but only concentrations that exceeded the therapeutic range (3–6 mM) [59].

In tissues harvested from PER2::LUC mice, lithium lengthened the period and increased rhythm amplitude. Interestingly, while 2 mM of lithium was required for a response in *ex vivo* SCN rhythms, responses in lung tissue and fibroblasts required higher lithium concentrations (5–10 mM) [34]. This suggests differences in lithium sensitivity across different tissue types. Differences in lithium sensitivity were also observed when the effects of lithium were measured across multiple brain regions. Four different brain regions (SCN, median eminence, substantia nigra, and olfactory bulb) displayed concentration-dependent effects of lithium on period and amplitude. However, the magnitude of these effects differed by brain region [60].

Clock genes also seem to be involved in lithium's effects on anxiety and depression-like behaviors. For instance, lithium treatment improved performance on the forced swim test in wild-type mice, but *Cry1* null mutants did not show any improvement after lithium. *Cry1* null mutants also displayed more manic-like exploratory locomotor activity in an O-maze compared to wild-type mice at baseline, and lithium reduced this behavior exclusively in the *Cry1* null mutants [58]. These results suggest that the loss of *Cry1* and perhaps other clock genes may prevent lithium's beneficial effects on anxiety/depression-like behaviors in mice, which indicates that a functional molecular clock could be a necessary mechanistic component of lithium's beneficial effects in these models.

4.2. Cellular and molecular mechanisms of lithium

Lithium is a GSK3 inhibitor and alters the stability and/or nuclear translocation of clock proteins including CLOCK, CRY2, PER2, and REV-ERBα (Fig. 2A) [61–66]. In fibroblasts, lithium also stimulates calcium, extracellular receptor kinase (ERK) signaling, and the transcription factors Elk1 and Egr1 to increase *Per2-luc* amplitude [67,68]. Like

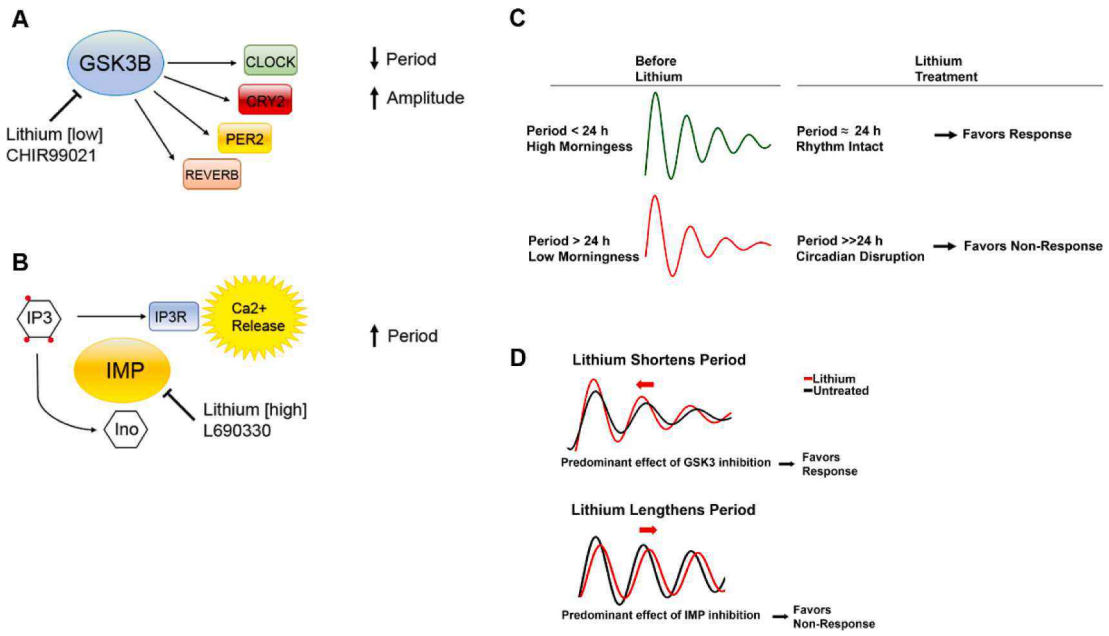

Fig. 2. Proposed model of lithium molecular mechanisms of circadian regulation. The sensitivity of circadian rhythms to lithium is context dependent. Sensitivity is cell type and brain region dependent as well as typically greater *in vivo* compared to *ex vivo* or in cell cultures. A) At low concentrations, lithium inhibits glycogen synthase kinase 3 beta (GSK3B), which shortens period and increases amplitude through changes in post-translational modification of clock proteins. Selective chemical inhibitors of GSK3, such as CHIR99021, mimic these circadian effects. B) At higher concentrations, lithium lengthens period, possibly by inhibiting inositol monophosphatase (IMP). IMP inhibition causes changes in the turnover of IP_3 and can extend the duration of its signaling activity, which modulates intracellular calcium release. Selective chemical inhibitors of IMP, such as L690330, mimic the period lengthening effects of lithium. Additionally, lithium inhibits other enzymes in the inositol pathway not included in the figure (e.g. inositol polyphosphatases) whose roles in circadian rhythms remain unknown. C) Model 1: Cellular rhythm features and chronotype of BD patients before treatment determine the subsequent impact of lithium on rhythms and mood. In this model, patients with short circadian period and a morning chronotype can tolerate the period lengthening in response to lithium. Patients with a longer period and low levels of morningness would be adversely affected by the period lengthening effects of lithium and prone to disrupted circadian rhythms. These effects may be observed as low amplitude behavioral rhythms in sleep and activity and/or overall failure to improve mood. D) Model 2: Biological variability among BD patients determines the impact of lithium on circadian rhythms *in vivo*. When lithium shortens period (left pointing arrow), patients will develop higher levels of morningness, higher amplitude behavioral rhythms, and mood improvement (i.e. favors lithium response). In contrast, when lithium lengthens period (right pointing arrow), patients have a greater likelihood of circadian disruption and fail to stabilize mood (i.e. favors lithium non-response). Genetic variability affecting the GSK3 and IMP pathways may influence which effect of lithium predominates. Abbreviations: GSK3B: Glycogen synthase kinase 3 beta, IP3, inositol trisphosphate; IP3R, inositol trisphosphate receptor; Ino, myo-inositol.

lithium, GSK3 inhibitors or genetic inhibition of GSK3β increases rhythm amplitude. However, these GSK3 interventions shorten period, which is the opposite effect as lithium in behavioral and cellular assays [61]. The period lengthening effects of lithium were mimicked by selective inhibitors of inositol monophosphatase (IMP) and in mouse cell lines reversed by blocking inositol trisphosphate (IP_3) receptors with antagonists or siRNA knockdown of *Itpr3* [48]. Therefore, the effects of lithium on circadian rhythms involve distinct and partly dissociable molecular mechanisms that affect amplitude and period (Fig. 2A-B). In cells, effects on amplitude are typically observed at low concentrations of lithium (1–5 mM), while effects on period require higher concentrations (10–20 mM). Differences in GSK3β expression and/or inositol-related signaling pathways across cell types may explain some of the cell-type specific differences in lithium sensitivity. Interestingly, convergence of the IP_3 and GSK3β pathways may occur through inositol pyrophosphates. Knockdown of *Ipmk* encoding inositol polyphosphate multikinase in mouse cell lines reduces the effect of lithium on *Per2-luc* amplitude and period [69]. However, it remains unclear how the integration of these pathways affects behavior.

4.3. Rhythm studies in human BD cell lines

In single cells, autonomous fibroblast clocks are mechanistically similar to neuronal clocks [12], allowing human rhythms to be studied *in vitro* [70]. Early studies of fibroblasts from BD patients revealed molecular clock gene and phosphorylated-GSK3β expression abnormalities [71]. In later studies using *Per2-luc* reporter assays, BD patient fibroblasts were found to have a longer period compared to healthy controls. In healthy control donor fibroblasts, lithium increased amplitude and lengthened period (at 1 mM and 10 mM, respectively). However, in BD fibroblasts, both of these circadian rhythm effects of lithium were attenuated [72]. A general resistance to pharmacological period lengthening in BD patient fibroblasts was independently reported using other drugs with distinct molecular mechanisms [73]. Subsequent analysis determined that the lack of amplitude response to lithium in BD fibroblasts was associated with a genetic polymorphism in *CACNA1C*, a BD-risk associated allele in a calcium channel gene. Moreover, the lithium-stimulated release of intracellular calcium and ERK1/2 activation was attenuated in BD samples [67,68]. However, due to clinical heterogeneity and lack of prospective evaluation in the patient donors, none of these studies were able to correlate cellular rhythms with clinical response to lithium.

To address this gap, a sample of lithium responders (Li-R) and lithium non-responders (Li-NR) from the PGBD prospective lithium monotherapy trial donated skin biopsies for use in cellular *Per2-luc* rhythm studies. In general, Li-R fibroblasts had shorter periods than Li-NR fibroblasts [48]. However, there was period variability among the Li-R fibroblasts, and in the subset of Li-R fibroblasts with longer periods, *in vitro* lithium treatment (1 mM) selectively shortened period. In contrast, lithium treatment had no significant effect on circadian period in Li-NR fibroblasts. This suggests that some Li-R fibroblasts have distinct rhythm characteristics even before treatment with lithium, while others have

differential sensitivity to the chronobiological effects of lithium.

Both GSK3β and the IMP/IP_3 pathways have been implicated in lithium's cellular rhythm effects in BD patient fibroblasts. *ITPR3* genotype predicted whether *in vitro* lithium treatment would lengthen fibroblast period [67]. GSK3β genotype corresponded with lithium-dependent period and amplitude changes in patient fibroblasts [72]. These data suggest that individual genetic variation in GSK3β and the IMP/IP_3 pathway components may contribute to the differential circadian effects of lithium in cells and perhaps influence the therapeutic response in people with BD.

Fibroblasts from a subset of PGBD clinical trial participants were reprogrammed into induced pluripotent stem cells (iPSCs), developed into neuronal progenitor cells, and differentiated into glutamatergic neurons [74]. The phase dispersion of *Per2-luc* rhythms in BD neurons was greater than control neurons, regardless of treatment outcomes. In Li-NR neurons, amplitude was also reduced and there were fewer rhythmic neurons compared to control and Li-R neurons. This suggests that circadian rhythms in BD neurons are less coordinated and overall, less rhythmic. Further, *in vitro* lithium treatment (10 mM) lengthened circadian period in control and Li-R neurons only [74]. These data suggests that underlying cellular rhythm characteristics and drug-induced effects on rhythms in neurons both correlate with lithium response in BD patients.

Taken together, the cellular studies of BD patient fibroblasts and iPSC-derived neurons indicated that there are stable trait-like circadian rhythm characteristics in the absence of lithium that are associated with Li-R, but that in some samples, lithium-induced effects on circadian rhythms may also be important. Since inhibition of GSK3 and IMP have opposite effects on period and lithium inhibits both enzymes, individual differences in BD patients may determine which effects dominate at low lithium concentrations that correspond to the therapeutic serum levels in humans (0.5–1.0 mM). Notably, while the human actigraphy studies in patients and iPSC-neuron studies *in vitro* both implicate low amplitude as a marker of Li-NR, increased amplitude in cellular rhythms either at baseline or after drug treatment does not appear to predict lithium response. In fact, both Li-R and Li-NR show a lack of rhythm amplification after lithium treatment *in vitro*, suggesting this may be a general biomarker for BD.

5. Conclusion

Circadian rhythms are a pervasive feature of biology regulating nearly every cell in the body. It has been estimated that in any given cell, 10% of the genome is rhythmically expressed, and nearly half the genome is rhythmically expressed in at least one cell type [75,76]. With this in mind, it is not surprising that some aspects of the lithium response intersect with circadian rhythms, but it remains unclear whether lithium effects on circadian rhythms are necessary for the therapeutic lithium response and whether manipulation of circadian rhythms by other means could similarly accomplish favorable treatment outcomes in BD.

Data indicate that lithium has effects on circadian rhythms in animals and humans, both in cells and *in vivo* with differences in drug sensitivity across cell types. While limited to laboratory evaluations of peripheral organs in mice and uncontrolled human studies using proxy measures, the effects of lithium on rhythms *in vivo* appear more potent than in cellular assays or tissue explant studies. In BD patients, Li-R appear to have a more favorable profile of circadian rhythms with more robust rhythms, better sleep characteristics, and a morning chronotype, whereas Li-NR show low amplitude rhythms and circadian disruption. However, most of these studies are cross-sectional and cannot distinguish pre-existing patient characteristics from the effects of drug treatment. In addition, all clinical studies to date rely upon proxy measures of rhythms such as self-report scales and/or actigraphy. Cellular studies have shown differences in circadian rhythms of BD patients including longer period and reduced amplitude, and again suggest important differences between Li-R/Li-NR. A therapeutic lithium response can be predicted based on circadian traits prior to lithium treatment as well as in response to lithium *in vitro*. Overall, the clinical evidence offers some support that lithium corrects sleep deficits, increases morningness, and amplifies rhythms, but this evidence is preliminary and offers comparatively weak support for the hypothesis that chronobiological features are essential for the therapeutic actions of lithium.

5.1. Chronobiological models of lithium response

Given the available data regarding lithium response and circadian rhythms, two possible summary models are proposed (Fig. 2C-D). First, differential levels of morningness at baseline may determine which patients can tolerate the period lengthening effects of lithium (Fig. 2C). In this model, Li-R enter treatment with high morningness, which allows them to tolerate the period lengthening "chronobiological side effects" of lithium, while Li-NR have low morningness and experience worsened circadian disruption due to period lengthening that causes poorly entrained, low amplitude rhythms. These circadian disruptions in Li-NR are predicted to cause ill effects on mood and sleep leading to an overall lack of improvement in symptoms and/or an inability to tolerate lithium. In this scenario, a biomarker indicating a shorter circadian cellular period and/or high baseline levels of morningness behaviors would suggest a good prognostis. Furthermore, because Li-NR are predicted to display increased circadian disruption in response to lithium, measurements of circadian rhythms shortly after lithium treatment could be used to distinguish this subset quickly and alternative medications could be administered. The second model proposes that by shortening cellular period, lithium increases morningness in a subset of BD patients who are sensitive to this pharmacological effect by virtue of genetic variability in key regulatory pathways (Fig. 2D). In this model, biomarkers that predict an individual's sensitivity to period shortening may be predictive of Li-R. This model may require a patient to have a longer period at baseline so that any shortening maintains an optimal rhythm of ~24 h. The majority of evidence presented here supports the first model but supporting evidence for the second model is also available. Importantly, these models are not mutually exclusive and may be reinforcing in some instances.

5.2. Role of circadian rhythm modulation in mood stabilizers

Additional mood stabilizer medications may employ chronobiological mechanisms to induce a therapeutic response including quetiapine [53], lurasidone [77], valproic acid [78,79], and ketamine [80–82]. It will be an important area of future research to determine the extent to which these chronobiological mechanisms impact the course of BD and how the various effects on rhythms can be deployed strategically to optimize clinical outcomes and/or personalize treatment for a particular symptom profile or set of biomarkers.

Identifying the essential molecular targets of lithium may help improve the development of future therapeutics. It remains to be determined if engagement with the circadian system is 1) sufficient in itself to be therapeutic, 2) an antecedent to a distinct neuronal process (e.g. neuroprotection); or 3) a component of a complex process requiring several cellular changes to co-occur simultaneously. If alterations to the molecular clock alone are therapeutic, prospective clinical trials could be conducted to evaluate other means of adjusting rhythms in BD patients experiencing either depression or mania. To resolve the other two possibilities, prospective clinical studies with careful use of biomarkers for both circadian and non-circadian processes must be performed in BD patients. Further, animal and human cellular studies with targeted interventions may increase understanding of the molecular mechanisms of lithium and other mood stabilizing drugs. The financial incentives to invest in lithium studies may be limited if proposed in isolation. Therefore, such studies must be incorporated into larger efforts to identify the molecular mechanisms of circadian rhythm modulation and

mood stabilization.

Author contributions

KER and MJM jointly conceived the project and wrote the paper.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: MJM has received consulting fees from Alkermes Pharmaceuticals for work unrelated to the current project.

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References

[1] K.R. Merikangas, R. Jin, J.P. He, R.C. Kessler, S. Lee, N.A. Sampson, M.C. Viana, L. H. Andrade, C. Hu, E.G. Karam, M. Ladea, M.E. Medina-Mora, Y. Ono, J. Posada-Villa, R. Sagar, J.E. Wells, Z. Zarkov, Prevalence and correlates of bipolar spectrum disorder in the World Mental Health Survey Initiative, Arch. Gen. Psychiatry. 68 (2011) 241–251, https://doi.org/10.1001/archgenpsychiatry.2011.12.

[2] R.J. Baldessarini, G.H. Vázquez, L. Tondo, Bipolar depression: a major unsolved challenge, Int. J. Bipolar Disord. 8 (2020) 1–13, https://doi.org/10.1186/s40345-019-0160-1.

[3] K.R. Merikangas, J. Swendsen, I.B. Hickie, L. Cui, H. Shou, A.K. Merikangas, J. Zhang, F. Lamers, C. Crainiceanu, N.D. Volkow, V. Zipunnikov, Real-time mobile monitoring of the dynamic associations among motor activity, energy, mood, and sleep in adults with bipolar disorder, JAMA Psychiatry 76 (2019) 190–198, https://doi.org/10.1001/jamapsychiatry.2018.3546.

[4] L. Pagani, P.A.S. Clair, T.M. Teshiba, S.K. Service, S.C. Fears, C. Araya, X. Araya, J. Bejarano, M. Ramirez, G. Castrillón, J. Gomez-Makhinson, M.C. Lopez, G. Montoya, C.P. Montoya, I. Aldana, L. Navarro, D.G. Freimer, B. Safaie, L. W. Keung, K. Greenspan, K. Chou, J.I. Escobar, J. Ospina-Duque, B. Kremeyer, A. Ruiz-Linares, R.M. Cantor, C. Lopez-Jaramillo, G. Macaya, J. Molina, V.I. Reus, C. Sabatti, C.E. Bearden, J.S. Takahashi, N.B. Freimer, Genetic contributions to circadian activity rhythm and sleep pattern phenotypes in pedigrees segregating for severe bipolar disorder, Proc. Natl. Acad. Sci. U. S. A. 113 (2016) E754–E761, https://doi.org/10.1073/pnas.1513525113.

[5] J. Wood, B. Birmaher, D. Axelson, M. Ehmann, C. Kalas, K. Monk, S. Turkin, D. J. Kupfer, D. Brent, T.H. Monk, V.L. Nimgainkar, Replicable differences in preferred circadian phase between bipolar disorder patients and control individuals, Psychiatry Res. 166 (2009) 201–209, https://doi.org/10.1016/j.psychres.2008.03.003.

[6] F. Romo-Nava, T.J. Blom, A.B. Cuellar-Barboza, S.J. Winham, C.L. Colby, N. A. Nunez, J.M. Biernacka, M.A. Frye, S.L. McElroy, Evening chronotype as a discrete clinical subphenotype in bipolar disorder, J. Affect. Disord. 266 (2020) 556–562, https://doi.org/10.1016/j.jad.2020.01.151.

[7] A. Di Florio, K.J.S. Lewis, A. Richards, R. Karlsson, G. Leonenko, S.E. Jones, H. J. Jones, K. Gordon-Smith, L. Forty, V. Escott-Price, M.J. Owen, M.N. Weedon, L. Jones, N. Craddock, I. Jones, M. Landén, M.C. O'Donovan, Comparison of genetic liability for sleep traits among individuals with bipolar disorder I or II and control participants, JAMA Psychiatry. 77 (2020) 303–310, https://doi.org/10.1001/jamapsychiatry.2019.4079.

[8] N. Mullins, A.J. Forstner, K.S. O'Connell, B. Coombes, J.R.I. Coleman, Z. Qiao, T. D. Als, T.B. Bigdeli, S. Børte, J. Bryois, A.W. Charney, O.K. Drange, M.J. Gandal, S. P. Hagenaars, M. Ikeda, N. Kamitaki, M. Kim, K. Krebs, G. Panagiotaropoulou, B. M. Schilder, L.G. Sloofman, S. Steinberg, V. Trubetskoy, B.S. Winsvold, H.H. Won, L. Abramova, K. Adorjan, E. Agerbo, M. Al Eissa, D. Albani, N. Alliey-Rodriguez, A. Anjorin, V. Antilla, A. Antoniou, S. Awasthi, J.H. Baek, M. Bækvad-Hansen, N. Bass, M. Bauer, E.C. Beins, S.E. Bergen, A. Birner, C. Bøcker Pedersen, E. Bøen, M.P. Boks, R. Bosch, M. Brum, B.M. Brumpton, N. Brunkhorst-Kanaan, M. Budde, J. Bybjerg-Grauholm, W. Byerley, M. Cairns, M. Casas, P. Cervantes, T.K. Clarke, C. Cruceanu, A. Cuellar-Barboza, J. Cunningham, D. Curtis, P.M. Czerski, A. M. Dale, N. Dalkner, F.S. David, F. Degenhardt, S. Djurovic, A.L. Dobbyn, A. Douzenis, T. Elvsåshagen, V. Escott-Price, I.N. Ferrier, A. Fiorentino, T. M. Foroud, L. Forty, J. Frank, O. Frei, N.B. Freimer, L. Frisén, K. Gade, J. Garnham, J. Gelernter, M. Giørtz Pedersen, I.R. Gizer, S.D. Gordon, K. Gordon-Smith, T. A. Greenwood, J. Grove, J. Guzman-Parra, K. Ha, M. Haraldsson, M. Hautzinger, U. Heilbronner, D. Hellgren, S. Herms, P. Hoffmann, P.A. Holmans, L. Huckins, S. Jamain, J.S. Johnson, J.L. Kalman, Y. Kamatani, J.L. Kennedy, S. Kittel-Schneider, J.A. Knowles, M. Kogevinas, M. Koromina, T.M. Kranz, H.R. Kranzler, M. Kubo, R. Kupka, S.A. Kushner, C. Lavebratt, J. Lawrence, M. Leber, H.J. Lee, P. H. Lee, S.E. Levy, C. Lewis, C. Liao, S. Lucae, M. Lundberg, D.J. MacIntyre, S. H. Magnusson, W. Maier, A. Maihofer, D. Malaspina, E. Maratou, L. Martinsson, M. Mattheisen, S.A. McCarroll, N.W. McGregor, P. McGuffin, J.D. McKay, H. Medeiros, S.E. Medland, V. Millischer, G.W. Montgomery, J.L. Moran, D. W. Morris, T.W. Mühleisen, N. O'Brien, C. O'Donovan, L.M. Olde Loohuis, L. Oruc, S. Papiol, A.F. Pardiñas, A. Perry, A. Pfennig, E. Porichi, J.B. Potash, D. Quested, T. Raj, M.H. Rapaport, J.R. DePaulo, E.J. Regeer, J.P. Rice, F. Rivas, M. Rivera, J. Roth, P. Roussos, D.M. Ruderfer, C. Sánchez-Mora, E.C. Schulte, F. Senner, S. Sharp, P.D. Shilling, E. Sigurdsson, L. Sirignano, C. Slaney, O.B. Smeland, D. J. Smith, J.L. Sobell, C. Søholm Hansen, M. Soler Artigas, A.T. Spijker, D.J. Stein, J. S. Strauss, B. Świątkowska, C. Terao, T.E. Thorgeirsson, C. Toma, P. Tooney, E. E. Tsermpini, M.P. Vawter, H. Vedder, J.T.R. Walters, S.H. Witt, S. Xi, W. Xu, J.M. K. Yang, A.H. Young, H. Young, P.P. Zandi, H. Zhou, L. Zillich, R. Adolfsson, I. Agartz, M. Alda, L. Alfredsson, G. Babadjanova, L. Backlund, B.T. Baune, F. Bellivier, S. Bengesser, W.H. Berrettini, D.H.R. Blackwood, M. Boehnke, A. D. Børglum, G. Breen, V.J. Carr, S. Catts, A. Corvin, N. Craddock, U. Dannlowski, D. Dikeos, T. Esko, B. Etain, P. Ferentinos, M. Frye, J.M. Fullerton, M. Gawlik, E. S. Gershon, F.S. Goes, M.J. Green, M. Grigoroiu-Serbanescu, J. Hauser, F. Henskens, J. Hillert, K.S. Hong, D.M. Hougaard, C.M. Hultman, K. Hveem, N. Iwata, A.V. Jablensky, I. Jones, L.A. Jones, R.S. Kahn, J.R. Kelsoe, G. Kirov, M. Landén, M. Leboyer, C.M. Lewis, Q.S. Li, J. Lissowska, C. Lochner, C. Loughland, N.G. Martin, C.A. Mathews, F. Mayoral, S.L. McElroy, A. M. McIntosh, F.J. McMahon, I. Melle, P. Michie, L. Milani, P.B. Mitchell, G. Morken, O. Mors, P.B. Mortensen, B. Mowry, B. Müller-Myhsok, R.M. Myers, B. M. Neale, C.M. Nievergelt, M. Nordentoft, M.M. Nöthen, M.C. O'Donovan, K. J. Oedegaard, T. Olsson, M.J. Owen, S.A. Paciga, C. Pantelis, C. Pato, M.T. Pato, G. P. Patrinos, R.H. Perlis, D. Posthuma, J.A. Ramos-Quiroga, A. Reif, E. Z. Reininghaus, M. Ribasés, M. Rietschel, S. Ripke, G.A. Rouleau, T. Saito, U. Schall, M. Schalling, P.R. Schofield, T.G. Schulze, L.J. Scott, R.J. Scott, A. Serretti, C. Shannon Weickert, J.W. Smoller, H. Stefansson, K. Stefansson, E. Stordal, F. Streit, P.F. Sullivan, G. Turecki, A.E. Vaaler, E. Vieta, J.B. Vincent, I. D. Waldman, T.W. Weickert, T. Werge, N.R. Wray, J.A. Zwart, J.M. Biernacka, J. I. Nurnberger, S. Cichon, H.J. Edenberg, E.A. Stahl, A. McQuillin, A. Di Florio, R. A. Ophoff, O.A. Andreassen, Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology, Nat. Genet. 53 (2021) 817–829, https://doi.org/10.1038/s41588-021-00857-4.

[9] A. Ferguson, L.M. Lyall, J. Ward, R.J. Strawbridge, B. Cullen, N. Graham, C. L. Niedzwiedz, K.J.A. Johnston, D. MacKay, S.M. Biello, J.P. Pell, J. Cavanagh, A. M. McIntosh, A. Doherty, M.E.S. Bailey, D.M. Lyall, C.A. Wyse, D.J. Smith, Genome-wide association study of circadian rhythmicity in 71,500 UK Biobank participants and polygenic association with mood instability, EBioMedicine 35 (2018) 279–287, https://doi.org/10.1016/j.ebiom.2018.08.004.

[10] M.J. McCarthy, J.F. Gottlieb, R. Gonzalez, C.A. McClung, L.B. Alloy, S. Cain, D. Dulcis, B. Etain, B.N. Frey, C. Garbazza, K. Ketchesin, D. Landgraf, H.J. Lee, C. Marie-Claire, R. Nusslock, A. Porcu, R. Porter, P. Ritter, J. Scott, D. Smith, H. A. Swartz, G. Murray, Neurobiological and behavioral mechanisms of circadian rhythm disruption in bipolar disorder: A critical multi-disciplinary literature review and agenda for future research from the ISBD task force on chronobiology, Bipolar Disord. (2021) 1–32, https://doi.org/10.1111/bdi.13165.

[11] C.L. Partch, C.B. Green, J.S. Takahashi, Molecular architecture of the mammalian circadian clock, Trends Cell Biol. 24 (2014) 90–99, https://doi.org/10.1016/j.tcb.2013.07.002.

[12] A.C. Liu, D.K. Welsh, C.H. Ko, H.G. Tran, E.E. Zhang, A.A. Priest, E.D. Buhr, O. Singer, K. Meeker, I.M. Verma, F.J. Doyle, J.S. Takahashi, S.A. Kay, Intercellular coupling confers robustness against mutations in the SCN circadian clock network, Cell. 129 (2007) 605–616, https://doi.org/10.1016/j.cell.2007.02.047.

[13] S.A. Brown, G. Zumbrunn, F. Fleury-Olela, N. Preitner, U. Schibler, Rhythms of mammalian body temperature can sustain peripheral circadian clocks, Curr. Biol. 12 (2002) 1574–1583, https://doi.org/10.1016/S0960-9822(02)01145-4.

[14] U. Schibler, I. Gotic, C. Saini, P. Gos, T. Curie, Y. Emmenegger, F. Sinturel, P. Gosselin, A. Gerber, F. Fleury-Olela, G. Rando, M. Demarque, P. Franken, Clock-Talk: Interactions between central and peripheral circadian oscillators in mammals, Cold Spring Harb. Symp. Quant. Biol. 80 (2016) 223–232, https://doi.org/10.1101/sqb.2015.80.027490.

[15] K.L. Toh, C.R. Jones, Y. He, E.J. Eide, W.A. Hinz, D.M. Virshup, L.J. Ptáček, Y. H. Fu, An hPer2 phosphorylation site mutation in familial advanced sleep phase syndrome, Science. 291 (2001) 1040–1043, https://doi.org/10.1126/science.1057499.

[16] Y. He, C.R. Jones, N. Fujiki, Y. Xu, B. Guo, J.L. Holder, M.J. Rossner, S. Nishino, Y. H. Fu, The transcriptional repressor DEC2 regulates sleep length in mammals, Science 325 (2009) 866–870, https://doi.org/10.1126/science.1174443.

[17] A.M. Chang, J.F. Duffy, O.M. Buxton, J.M. Lane, D. Aeschbach, C. Anderson, A. C. Bjonnes, S.W. Cain, D.A. Cohen, T.M. Frayling, J.J. Gooley, S.E. Jones, E. B. Klerman, S.W. Lockley, M. Munch, S.M.W. Rajaratnam, M. Rueger, M.K. Rutter, N. Santhi, K. Scheuermaier, E. Van Reen, M.N. Weedon, C.A. Czeisler, F.A.J. L. Scheer, R. Saxena, Chronotype genetic variant in PER2 is associated with intrinsic circadian period in humans, Sci. Rep. 9 (2019) 1–10, https://doi.org/10.1038/s41598-019-41712-1.

[18] A.M. Reiter, C. Sargent, G.D. Roach, Concordance of chronotype categorisations based on dim light melatonin onset, the morningness-eveningness questionnaire, and the Munich chronotype questionnaire, Clocks & Sleep 3 (2021) 342–350, https://doi.org/10.3390/clockssleep3020021.

[19] A.A. Borbély, S. Daan, A. Wirz-Justice, T. Deboer, The two-process model of sleep regulation: a reappraisal, J. Sleep Res. 25 (2016) 131–143, https://doi.org/10.1111/jsr.12371.

[20] P.S. Klein, D.A. Melton, A molecular mechanism for the effect of lithium on development, Bipolar Disord. Sci. Ment. Heal. 93 (2019) 235–240, https://doi.org/10.4324/9781315054308-24.

[21] M.J. Berridge, C.P. Downes, M.R. Hanley, Neural and developmental actions of lithium: A unifying hypothesis, Bipolar Disord. Sci. Ment. Heal. 59 (2019) 225–233, https://doi.org/10.4324/9781315054308-23.
[22] R. Pardo, A.G. Andreolotti, B. Ramos, F. Picatoste, E. Claro, Opposed effects of lithium on the MEK-ERK pathway in neural cells: Inhibition in astrocytes and stimulation in neurons by GSK3 independent mechanisms, J. Neurochem. 87 (2003) 417–426, https://doi.org/10.1046/j.1471-4159.2003.02015.x.
[23] D.P. Hibar, L.T. Westlye, N.T. Doan, N. Jahanshad, J.W. Cheung, C.R.K. Ching, A. Versace, A.C. Bilderbeck, A. Uhlmann, B. Mwangi, B. Krämer, B. Overs, C. B. Hartberg, C. Abe, D. Dima, D. Grotegerd, E. Sprooten, E. Ben, E. Jimenez, F. M. Howells, G. Delvecchio, H. Temmingh, J. Starke, J.R.C. Almeida, J.M. Goikolea, J. Houenou, L.M. Beard, L. Rauer, L. Abramovic, M. Bonnin, M.F. Ponteduro, M. Keil, M.M. Rive, N. Yao, N. Yalin, P. Najt, P.G. Rosa, R. Redlich, S. Trost, S. Hagenaars, S.C. Fears, S. Alonso-Lana, T.G.M. Van Erp, T. Nickson, T.M. Chaim-Avancini, T.B. Meier, T. Elvsashagen, U.K. Haukvik, W.H. Lee, A.H. Schene, A. J. Lloyd, A.H. Young, A. Nugent, A.M. Dale, A. Pfennig, A.M. McIntosh, B. Lafer, B. T. Baune, C.J. Ekman, C.A. Zarate, C.E. Bearden, C. Henry, C. Simhandl, C. McDonald, C. Bourne, D.J. Stein, D.H. Wolf, D.M. Cannon, D.C. Glahn, D. J. Veltman, E. Pomarol-Clotet, E. Vieta, E.J. Canales-Rodriguez, F.G. Nery, F.L. S. Duran, G.F. Busatto, G. Roberts, G.D. Pearlson, G.M. Goodwin, H. Kugel, H. C. Whalley, H.G. Ruhe, J.C. Soares, J.M. Fullerton, J.K. Rybakowski, J. Savitz, K. T. Chaim, M. Fatjó-Vilas, M.G. Soeiro-De-Souza, M.P. Boks, M.V. Zanetti, M.C. G. Otaduy, M.S. Schaufelberger, M. Alda, M. Ingvar, M.L. Phillips, M.J. Kempton, M. Bauer, M. Landén, N.S. Lawrence, N.E.M. Van Haren, N.R. Horn, N.B. Freimer, O. Gruber, P.R. Schofield, P.B. Mitchell, R.S. Kahn, R. Lenroot, R. Machado-Vieira, R.A. Ophoff, S. Sarró, S. Frangou, T.D. Satterthwaite, T. Hajek, U. Dannlowski, U. F. Malt, V. Arolt, W.F. Gattaz, W.C. Drevets, X. Caseras, I. Agartz, P.M. Thompson, O.A. Andreassen, Cortical abnormalities in bipolar disorder: An MRI analysis of 6503 individuals from the ENIGMA Bipolar Disorder Working Group, Mol. Psychiatry. 23 (2018) 932–942, https://doi.org/10.1038/mp.2017.73.
[24] M. Berk, O. Dandash, R. Daglas, S.M. Cotton, K. Allott, A. Fornito, C. Suo, P. Klauser, B. Liberg, L. Henry, C. Macneil, M. Hasty, P. McGorry, C.S. Pantelis, M. Yöcel, Neuroprotection after a first episode of mania: A randomized controlled maintenance trial comparing the effects of lithium and quetiapine on grey and white matter volume, Transl. Psychiatry. 7 (2017), https://doi.org/10.1038/tp.2016.281.
[25] S. Sarkar, R.A. Floto, Z. Berger, S. Imarisio, A. Cordenier, M. Pasco, L.J. Cook, D. C. Rubinsztein, Lithium induces autophagy by inhibiting inositol monophosphatase, J. Cell Biol. 170 (2005) 1101–1111, https://doi.org/10.1083/jcb.200504035.
[26] G. Chen, G. Rajkowska, F. Du, N. Seraji-Bozorgzad, H.K. Manji, Enhancement of hippocampal neurogenesis by lithium, J. Neurochem. 75 (2000) 1729–1734, https://doi.org/10.1046/j.1471-4159.2000.0751729.x.
[27] G. Shaltiel, E.C. Dalton, R.H. Belmaker, A.J. Harwood, G. Agam, Specificity of mood stabilizer action on neuronal growth cones, Bipolar Disord. 9 (2007) 281–289, https://doi.org/10.1111/j.1399-5618.2007.00400.x.
[28] J.K. Hee, S.A. Thayer, Lithium increases synapse formation between hippocampal neurons by depleting phosphoinositides, Mol. Pharmacol. 75 (2009) 1021–1030, https://doi.org/10.1124/mol.108.052357.
[29] H.K. Manji, G.J. Moore, G. Chen, Lithium up-regulates the cytoprotective protein Bcl-2 in the CNS in vivo: A role for neurotrophic and neuroprotective effects in manic depressive illness, J. Clin. Psychiatry. 58 (1997) 82–96.
[30] R.W. Licht, P. Vestergaard, N. Rasmussen, K. Jepsen, A. Brodersen, P.E.B. Hansen, A lithium clinic for bipolar patients: 2-year outcome of the first 148 patients, Acta Psychiatr. Scand. 104 (2001) 387–390.
[31] H. Klemfuss, Rhythms and the pharmacology of lithium, Pharmacol. Ther. 56 (1992) 53–78, https://doi.org/10.1016/0163-7258(92)90037-Z.
[32] H. Klemfuss, D.F. Kripke, Potassium advances circadian activity rhythms: interactions with lithium, Brain Res. 492 (1989) 300–304, https://doi.org/10.1016/0006-8993(89)90913-X.
[33] D.F. Kripke, V. Grant Wyborney, Lithium slows rat circadian activity rhythms, Life Sci. 26 (1980) 1319–1321, https://doi.org/10.1016/0024-3205(80)90091-0.
[34] J. Li, W.Q. Lu, S. Beesley, A.S.I. Loudon, Q.J. Meng, Lithium impacts on the amplitude and period of the molecular circadian clockwork, PLoS One. 7 (2012) 1–8, https://doi.org/10.1371/journal.pone.0033292.
[35] B. Possidente, R.H. Exner, Gene-dependent effect of lithium on circadian rhythms in mice (mus musculus), Chronobiol. Int. 3 (1986) 17–21, https://doi.org/10.3109/07420528609083155.
[36] H. Nagayama, Chronic administration of imipramine and lithium changes the phase-angle relationship between the activity and core body temperature circadian rhythms in rats, Chronobiol. Int. 13 (1996) 251–259, https://doi.org/10.3109/07420529609020905.
[37] P. Subramanian, V.P. Menon, F.V. Arokiam, V. Rajakrishnan, E. Balamurugan, Lithium modulates biochemical circadian rhythms in Wistar rats, Chronobiol. Int. 15 (1998) 29–38, https://doi.org/10.3109/07420529808998667.
[38] Y. Sawai, T. Okamoto, Y. Muranaka, R. Nakamura, R. Matsumura, K. Node, M. Akashi, In vivo evaluation of the effect of lithium on peripheral circadian clocks by real-time monitoring of clock gene expression in near-freely moving mice, Sci. Rep. 9 (2019) 1–12, https://doi.org/10.1038/s41598-019-47053-3.
[39] L. Mei, Y. Fan, X. Lv, D.K. Welsh, C. Zhan, E.E. Zhang, Long-term in vivo recording of circadian rhythms in brains of freely moving mice, Proc. Natl. Acad. Sci. U. S. A. 115 (2018) 4276–4281, https://doi.org/10.1073/pnas.1717735115.
[40] D.K. Welsh, M.C. Moore-Ede, Lithium lengthens circadian period in a diurnal primate, Saimiri sciureus, Biol. Psychiatry. 28 (1990) 117–126, https://doi.org/10.1016/0006-3223(90)90629-G.
[41] D.F. Kripke, L.L. Judd, B. Hubbard, D.S. Janowsky, L.Y. Huey, The effect of lithium carbonate on the circadian rhythm of sleep in normal human subjects, Biol. Psychiatry. 14 (1979) 545–548.
[42] A. Johnsson, W. Engelmann, B. Pflug, W. Klemke, Period lengthening of human circadian rhythms by lithium carbonate, a prophylactic for depressive disorders, Int. J. Chronobiol. 8 (1983) 129–147.
[43] M. Federoff, M.J. McCarthy, A. Anand, W.H. Berrettini, H. Bertram, A. Bhattacharjee, C.V. Calkin, C. Conroy, W.H. Coryell, N. D'Arcangelo, A. DeModena, C. Fisher, S. Feeder, N. Frazier, M.A. Frye, K. Gao, J. Garnham, E. S. Gershon, N. Alliey-Rodriguez, K. Glazer, F. Goes, T. Karberg, G. Harrington, P. Jakobsen, M. Kamali, M. Kelly, S.G. Leckband, F. Lohoff, A.X. Maihofer, M. G. McInnis, F. Mondimore, G. Morken, J.I. Nurnberger, K.J. Oedegaard, M. Ritchey, K. Ryan, M. Schinagle, H. Schoeyen, C. Schwebel, M. Shaw, P. D. Shilling, C. Slaney, A. Stautland, B. Tarwater, J.R. Calabrese, M. Alda, C. M. Nievergelt, P.P. Zandi, J.R. Kelsoe, Correction of depression-associated circadian rhythm abnormalities is associated with lithium response in bipolar disorder, Bipolar Disord. (2021) 1–9, https://doi.org/10.1111/bdi.13162.
[44] K. Kanagarajan, K. Gou, C. Antinora, A. Buyukkurt, O. Crescenzi, S. Beaulieu, K. F. Storch, O. Mantere, Morningness-Eveningness questionnaire in bipolar disorder, Psychiatry Res. 262 (2018) 102–107, https://doi.org/10.1016/j.psychres.2018.02.004.
[45] E. Dopierala, A. Chrobak, F. Kapczinski, M. Michalak, A. Tereszko, E. Ferensztajn-Rochowiak, D. Dudek, J. Jaracz, M. Siwek, J.K. Rybakowski, A Study of Biological Rhythm Disturbances in Polish Remitted Bipolar Patients using the BRIAN, CSM, and SWPAQ Scales, Neuropsychobiology. 74 (2017) 125–130, https://doi.org/10.1159/000458527.
[46] P.A. Geoffroy, J. Scott, C. Boudebesse, M. Lajnef, C. Henry, M. Leboyer, F. Bellivier, B. Etain, Sleep in patients with remitted bipolar disorders: A meta-analysis of actigraphy studies, Acta Psychiatr. Scand. 131 (2015) 89–99, https://doi.org/10.1111/acps.12367.
[47] N. Xu, K. Shinohara, K.E.A. Saunders, J.R. Geddes, A. Cipriani, Effect of lithium on circadian rhythm in bipolar disorder: A systematic review and meta-analysis, Bipolar Disord. 23 (2021) 445–453, https://doi.org/10.1111/bdi.13070.
[48] M.J. McCarthy, H. Wei, C.M. Nievergelt, A. Stautland, A.X. Maihofer, D.K. Welsh, P. Shilling, M. Alda, N. Alliey-Rodriguez, A. Anand, O.A. Andreasson, Y. Balaraman, W.H. Berrettini, H. Bertram, K.J. Brennand, J.R. Calabrese, C. V. Calkin, A. Claasen, C. Conroy, W.H. Coryell, D.W. Craig, N. D'Arcangelo, A. Demodena, S. Djurovic, S. Feeder, C. Fisher, N. Frazier, M.A. Frye, F.H. Gage, K. Gao, J. Garnham, E.S. Gershon, K. Glazer, F. Goes, T. Goto, G. Harrington, P. Jakobsen, M. Kamali, E. Karberg, M. Kelly, S.G. Leckband, F. Lohoff, M. G. McInnis, F. Mondimore, G. Morken, J.I. Nurnberger, S. Obral, K.J. Oedegaard, A. Ortiz, M. Ritchey, K. Ryan, M. Schinagle, H. Schoeyen, C. Schwebel, M. Shaw, T. Shekhtman, C. Slaney, E. Stapp, S. Szelinger, B. Tarwater, P.P. Zandi, J. R. Kelsoe, Chronotype and cellular circadian rhythms predict the clinical response to lithium maintenance treatment in patients with bipolar disorder, Neuropsychopharmacology. 44 (2019) 620–628, https://doi.org/10.1038/s41386-018-0273-8.
[49] Y. Lin, A.X. Maihofer, E. Stapp, M. Ritchey, N. Alliey-Rodriguez, A. Anand, Y. Balaraman, W.H. Berrettini, H. Bertram, A. Bhattacharjee, C.V. Calkin, C. Conroy, W. Coryell, N. D'Arcangelo, A. DeModena, J.M. Biernacka, C. Fisher, N. Frazier, M. Frye, K. Gao, J. Garnham, E. Gershon, K. Glazer, F.S. Goes, T. Goto, E. Karberg, G. Harrington, P. Jakobsen, M. Kamali, M. Kelly, S.G. Leckband, F. W. Lohoff, A. Stautland, M.J. McCarthy, M.G. McInnis, F. Mondimore, G. Morken, J.I. Nurnberger, K.J. Oedegaard, V.E.G. Syrstad, K. Ryan, M. Schinagle, H. Schoeyen, O.A. Andreassen, M. Shaw, P.D. Shilling, C. Slaney, B. Tarwater, J. R. Calabrese, M. Alda, C.M. Nievergelt, P.P. Zandi, J.R. Kelsoe, Clinical predictors of non-response to lithium treatment in the Pharmacogenomics of Bipolar Disorder (PGBD) study, Bipolar Disord. 23 (2021) 821–831, https://doi.org/10.1111/bdi.13078.
[50] K.J. Oedegaard, M. Alda, A. Anand, O.A. Andreassen, Y. Balaraman, W. H. Berrettini, A. Bhattacharjee, K.J. Brennand, K.E. Burdick, J.R. Calabrese, C. V. Calkin, A. Claasen, W.H. Coryell, D. Craig, A. DeModena, M. Frye, F.H. Gage, K. Gao, J. Garnham, E. Gershon, P. Jakobsen, S.G. Leckband, M.J. McCarthy, M. G. McInnis, A.X. Maihofer, J. Mertens, G. Morken, C.M. Nievergelt, J. Nurnberger, S. Pham, H. Schoeyen, T. Shekhtman, P.D. Shilling, S. Szelinger, B. Tarwater, J. Yao, P.P. Zandi, J.R. Kelsoe, The Pharmacogenomics of Bipolar Disorder study (PGBD): Identification of genes for lithium response in a prospective sample, BMC Psychiatry. 16 (2016) 1–15, https://doi.org/10.1186/s12888-016-0732-x.
[51] B. Etain, M. Meyrel, V. Hennion, F. Bellivier, J. Scott, Can actigraphy be used to define lithium response dimensions in bipolar disorders? J. Affect. Disord. 283 (2021) 402–409, https://doi.org/10.1016/j.jad.2021.01.060.
[52] J. Scott, V. Hennion, M. Meyrel, F. Bellivier, B. Etain, An ecological study of objective rest-activity markers of lithium response in bipolar-I-disorder, Psychol. Med. (2020), https://doi.org/10.1017/S0033291720004171.
[53] J.Y. Hwang, J.W. Choi, S.G. Kang, S.H. Hwang, S.J. Kim, Y.J. Lee, Comparison of the effects of quetiapine XR and lithium monotherapy on actigraphy-measured circadian parameters in patients with bipolar II depression, J. Clin. Psychopharmacol. 37 (2017) 351–354, https://doi.org/10.1097/JCP.0000000000000699.
[54] S. Ancoli-Israel, R. Cole, C. Alessi, M. Chambers, W. Moorcroft, C.P. Pollak, The role of actigraphy in the study of sleep and circadian rhythms, Sleep. 26 (2003) 342–392, https://doi.org/10.1093/sleep/26.3.342.
[55] A. Sadeh, The role and validity of actigraphy in sleep medicine: An update, Sleep Med. Rev. 15 (2011) 259–267, https://doi.org/10.1016/j.smrv.2010.10.001.
[56] A. McQuillin, M. Rizig, H.M.D. Gurling, A microarray gene expression study of the molecular pharmacology of lithium carbonate on mouse brain mRNA to

understand the neurobiology of mood stabilization and treatment of bipolar affective disorder, Pharmacogenet, Genomics. 17 (2007) 605–617, https://doi.org/10.1097/FPC.0b013e328011b5b2.
[57] T.M. Osland, J. Fernø, B. Håvik, I. Heuch, P. Ruoff, O.D. Lærum, V.M. Steen, Lithium differentially affects clock gene expression in serum-shocked NIH-3T3 cells, J. Psychopharmacol. 25 (2011) 924–933, https://doi.org/10.1177/0269881110379508.
[58] A. Schnell, F. Sandrelli, V. Ranc, J.A. Ripperger, E. Brai, L. Alberi, G. Rainer, U. Albrecht, Mice lacking circadian clock components display different mood-related behaviors and do not respond uniformly to chronic lithium treatment, Chronobiol. Int. 32 (2015) 1075–1089, https://doi.org/10.3109/07420528.2015.1062024.
[59] M. Abe, E.D. Herzog, G.D. Block, Lithium lengthens the circadian period of individual suprachiasmatic nucleus neurons, Neuroreport. 11 (2000) 3261–3264, https://doi.org/10.1097/00001756-200009280-00042.
[60] T. Yoshikawa, S. Honma, Lithium lengthens circadian period of cultured brain slices in area specific manner, Behav. Brain Res. 314 (2016) 30–37, https://doi.org/10.1016/j.bbr.2016.07.045.
[61] T. Hirota, W.G. Lewis, A.C. Liu, W.L. Jae, P.G. Schultz, S.A. Kay, A chemical biology approach reveals period shortening of the mammalian circadian clock by specific inhibition of GSK-3β, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 20746–20751, https://doi.org/10.1073/pnas.0811410106.
[62] Y. Harada, M. Sakai, N. Kurabayashi, T. Hirota, Y. Fukada, Ser-557-phosphorylated mCRY2 is degraded upon synergistic phosphorylation by glycogen synthase kinase-3β, J. Biol. Chem. 280 (2005) 31714–31721, https://doi.org/10.1074/jbc.M506225200.
[63] S. Sahar, L. Zocchi, C. Kinoshita, E. Borrelli, P. Sassone-Corsi, Regulation of BMAL1 protein stability and circadian function by GSK3β-mediated phosphorylation, PLoS One. 5 (2010), https://doi.org/10.1371/journal.pone.0008561.
[64] M.L. Spengler, K.K. Kuropatwinski, M. Schumer, M.P. Antoch, A serine cluster mediates BMAL1-dependent CLOCK phosphorylation and degradation, Cell Cycle. 8 (2009) 4138–4146, https://doi.org/10.4161/cc.8.24.10273.
[65] H.W. Ko, E.Y. Kim, J. Chiu, J.T. Vanselow, A. Kramer, I. Edery, A hierarchical phosphorylation cascade that regulates the timing of PERIOD nuclear entry reveals novel roles for proline-directed kinases and GSK-3β/SGG in circadian clocks, J. Neurosci. 30 (2010) 12664–12675, https://doi.org/10.1523/JNEUROSCI.1586-10.2010.
[66] L. Yin, J. Wang, P.S. Klein, M.A. Lazar, Nuclear receptor Rev-erbalpha is a critical lithium-sensitive component of the circadian clock, Sci. Reports. 311 (2006) 1002–1006.
[67] M.J. McCarthy, M.J. Le Roux, H. Wei, S. Beesley, J.R. Kelsoe, D.K. Welsh, Calcium channel genes associated with bipolar disorder modulate lithium's amplification of circadian rhythms, Neuropharmacology. 101 (2016) 439–448, https://doi.org/10.1016/j.neuropharm.2015.10.017.
[68] M.J. McCarthy, H. Wei, D. Landgraf, M.J. Le Roux, D.K. Welsh, Disinhibition of the extracellular-signal-regulated kinase restores the amplification of circadian rhythms by lithium in cells from bipolar disorder patients, Eur. Neuropsychopharmacol. 26 (2016) 1310–1319, https://doi.org/10.1016/j.euroneuro.2016.05.003.
[69] H. Wei, D. Landgraf, G. Wang, M.J. McCarthy, Inositol polyphosphates contribute to cellular circadian rhythms: Implications for understanding lithium's molecular mechanism, Cell. Signal. 44 (2018) 82–91, https://doi.org/10.1016/j.cellsig.2018.01.001.
[70] A. Balsalobre, F. Damiola, U. Schibler, A serum shock induces circadian gene expression in mammalian tissue culture cells, Cell. 93 (1998) 929–937, https://doi.org/10.1016/S0092-8674(00)81199-X.
[71] S. Yang, H.P.A. Van Dongen, K. Wang, W. Berrettini, M. Bućan, Assessment of circadian function in fibroblasts of patients with bipolar disorder, Mol. Psychiatry. 14 (2009) 143–155, https://doi.org/10.1038/mp.2008.10.
[72] M.J. McCarthy, H. Wei, Z. Marnoy, R.M. Darvish, D.L. McPhie, B.M. Cohen, D. K. Welsh, Genetic and clinical factors predict lithium's effects on PER2 gene expression rhythms in cells from bipolar disorder patients, Transl, Psychiatry. 3 (2013) e318–e328, https://doi.org/10.1038/tp.2013.90.
[73] H.R. Sanghani, A. Jagannath, T. Humberstone, F. Ebrahimjee, J.M. Thomas, G. C. Churchill, A. Cipriani, M.J. Attenburrow, O.V. Perestenko, S.A. Cowley, M. Z. Cader, S.N. Peirson, P.J. Harrison, R.G. Foster, G.M. Goodwin, S.R. Vasudevan, Patient fibroblast circadian rhythms predict lithium sensitivity in bipolar disorder, Mol. Psychiatry. 26 (2021) 5252–5265, https://doi.org/10.1038/s41380-020-0769-6.
[74] H.K. Mishra, N.M. Ying, A. Luis, H. Wei, M. Nguyen, T. Nakhla, S. Vandenburgh, M. Alda, W.H. Berrettini, K.J. Brennand, J.R. Calabrese, W.H. Coryell, M.A. Frye, F. H. Gage, E.S. Gershon, M.G. McInnis, C.M. Nievergelt, J.I. Nurnberger, P. D. Shilling, K.J. Oedegaard, P.P. Zandi, J.R. Kelsoe, D.K. Welsh, M.J. McCarthy, Circadian rhythms in bipolar disorder patient-derived neurons predict lithium response: preliminary studies, Mol. Psychiatry. 26 (2021) 3383–3394, https://doi.org/10.1038/s41380-021-01048-7.
[75] L.S. Mure, H.D. Le, G. Benegiamo, M.W. Chang, L. Rios, N. Jillani, M. Ngotho, T. Kariuki, H.M. Cooper, S. Panda, Diurnal transcriptome atlas of a primate aross major neural and peripheral tissues, Science (80-.). (2018) 1–16.
[76] R. Zhang, N.F. Lahens, H.I. Ballance, M.E. Hughes, J.B. Hogenesch, A circadian gene expression atlas in mammals: Implications for biology and medicine, Proc. Natl. Acad. Sci. U. S. A. 111 (2014) 16219–16224, https://doi.org/10.1073/pnas.1408886111.
[77] A.D. Krystal, G. Zammit, The sleep effects of lurasidone: a placebo-controlled cross-oer study using a 4-h phase-advance model of transient insomnia, Hum. Psychopharmacol. 31 (2016) 206–216, https://doi.org/10.1002/hup.2533.
[78] D. Landgraf, W.J. Joiner, M.J. McCarthy, S. Kiessling, R. Barandas, J.W. Young, N. Cermakian, D.K. Welsh, The mood stabilizer valproic acid opposes the effects of dopamine on circadian rhythms, Neuropharmacology. 107 (2016) 262–270, https://doi.org/10.1016/j.neuropharm.2016.03.047.
[79] A.S. Johansson, J. Brask, B. Owe-Larsson, J. Hetta, G.B.S. Lundkvist, Valproic acid phase shifts the rhythmic expression of PERIOD2::LUCIFERASE, J. Biol. Rhythms. 26 (2011) 541–551, https://doi.org/10.1177/0748730411419775.
[80] B.G. Bunney, J.Z. Li, D.M. Walsh, R. Stein, M.P. Vawter, P. Cartagena, J.D. Barchas, A.F. Schatzberg, R.M. Myers, S.J. Watson, H. Akil, W.E. Bunney, Circadian dysregulation of clock genes: Clues to rapid treatments in major depressive disorder, Mol. Psychiatry. 20 (2015) 48–55, https://doi.org/10.1038/mp.2014.138.
[81] S. Kohtala, O. Alitalo, M. Rosenholm, S. Rozov, T. Rantamäki, Time is of the essence: Coupling sleep-wake and circadian neurobiology to the antidepressant effects of ketamine, Pharmacol. Ther. 221 (2021), https://doi.org/10.1016/j.pharmthera.2020.107741.
[82] W.C. Duncan, E. Slonena, N.S. Hejazi, N. Brutsche, K.C. Yu, L. Park, E.D. Ballard, C. A. Zarate, Motor-Activity Markers of Circadian Timekeeping Are Related to Ketamine's Rapid Antidepressant Properties, Biol. Psychiatry. 82 (2017) 361–369, https://doi.org/10.1016/j.biopsych.2017.03.011.