

Effect of lithium on circadian rhythm in bipolar disorder: A systematic review and meta-analysis

Ni Xu¹  | Kiyomi Shinohara³ | Kate E. A. Saunders^{1,2} | John R. Geddes^{1,2} | Andrea Cipriani^{1,2} 

¹Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, UK

²Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford, UK

³Departments of Health Promotion and Human Behavior and of Clinical Epidemiology, Kyoto University Graduate School of Medicine, Kyoto, Japan

Correspondence

Ni Xu, Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, UK.
Email: niobiumni@gmail.com

Abstract

Objectives: Circadian rhythm disruption is commonly reported in patients with bipolar disorder. Lithium has been suggested to have effects on the circadian clock, the biological basis of the circadian rhythm. The objective of the current review was to review systematically the existing studies on the effect of lithium on circadian rhythm in patients with bipolar disorder.

Methods: We systematically searched the scientific literature up to September 2020 for experimental or observational studies which measured circadian rhythm in bipolar patients taking lithium (in comparison with placebo or other active treatments) and carried out a meta-analysis. Circadian rest-activity was our primary outcome, but we also collected data about sleep quality and chronotype (Morningness-Eveningness). The protocol was registered in PROSPERO (CRD42018109790).

Results: Four observational studies (n = 668) and one experimental study (n = 29) were included. Results from the meta-analysis suggest a potential association between lithium and shifts towards morningness (standardized mean difference [SMD]: 0.42, 95% confidence interval [CI]: -0.05 to 0.90). One cohort study with 21 days of follow-up found that patients treated with lithium had significantly larger amplitude (0.68, 0.01 to 1.36) when compared to anticonvulsants.

Conclusion: This review highlights the insufficient evidence to inform us about the effect of lithium on circadian rhythm. However, we found that chronotype can be a potential target for further exploration of biomarkers or biosignatures of lithium treatment in patients with bipolar disorder. Further studies with prospective and longitudinal study design, adopting actigraphy to monitor daily circadian rest-activity changes are needed.

KEYWORDS

bipolar disorder, circadian rhythm, lithium

1 | INTRODUCTION

Circadian rhythm is an internally driven process that regulates the sleep-wake cycle, body temperature regulation and hormone

secretion as well as other biological processes across a 24 h period.¹ In theory, any biological rhythms driven by the circadian clock can be used to measure circadian rhythm. However, rest-activity patterns measured by actigraphy, sleep parameters, chronotype measured by

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2021 The Authors. *Bipolar Disorders* published by John Wiley & Sons Ltd.

questionnaires, core body temperature, dim light melatonin onset and cortisol secretion profiles are the most commonly used measurements in practice.²

Circadian rhythm disruption has been well-documented in bipolar disorder.³ Studies using actigraphy, using a sensor worn on the non-dominant wrist of participants, have shown that patients with bipolar disorder have a more variable and less stable circadian rest-activity rhythm.^{4,5} Chronotype is the individual preference for the daily timing of activity, a behavioural manifestation of circadian rhythm.⁶ Morningness-Eveningness, also known as chronotype, was considered to be trait-like construct.⁷ However, a recent study showed its state-like aspects.⁸ Individuals who show more morningness have more alertness in the morning and a preference for morning activity. Eveningness, a general preference for evening activity and delayed sleep-wake phase were commonly noted in patients with bipolar disorder,^{3,9,10} which is consistent with findings in studies that patients with bipolar disorder showed delayed evening melatonin secretion.^{11,12}

Lithium is a first-line treatment for bipolar disorder, and it is widely used worldwide.^{13,14} However, its mechanism of action remains unknown. A systematic review examined the impact of lithium on circadian rhythm in cells, animal models and human, suggested that the chronobiological effects of lithium might be an inherent component of its therapeutic effect.¹⁵ The majority of included studies recruited BD patients are candidate gene association studies. We were interested in whether the circadian effects of lithium in laboratory settings translated to clinical context. In this systematic review we sought to update the previous review and focus on the effect of lithium on circadian rhythm only in people with bipolar disorder.

2 | METHODS

This review is reported in accordance with PRISMA guideline¹⁶ and the study protocol was registered on PROSPERO (CRD42018109790).

2.1 | Search strategy

We searched electronic databases including Cochrane Library, EMBASE, MEDLINE, PsycINFO, clinicaltrials.gov website and PubMed for published and unpublished trials from the inception of the databases until Sep 17st 2020 (see Appendix for details). No restrictions of language were imposed. The reference lists of included studies and systematic reviews in the field were screened for additional eligible studies.

2.2 | Inclusion and exclusion criteria

2.2.1 | Participants

We included patients with a primary diagnosis of bipolar disorder according to standardized diagnostic criteria from the International

Classification of Disease (ICD)-9, ICD-10 or the Diagnostic and Statistical Manual of Mental Disorders (DSM)-III, DSM-III-R, DSM-IV, DSM-IV-TR and DSM-5. There were no restrictions by age, gender, country, phase of illness, subtype (type I, type II, rapid cycling, not otherwise specified) and clinical setting.

2.2.2 | Interventions

Studies were included if lithium was administered orally within the therapeutic dose range 0.4–1.2 mmol/L, either as monotherapy or adjunct therapy.¹⁷

2.2.3 | Comparators

A placebo or comparator intervention (either pharmacological or non-pharmacological) was required for inclusion.

2.2.4 | Types of studies

We included both experimental studies (whether randomized or non-randomized) and observational studies where the primary outcome was a measure of circadian rhythm (see the section below for details).

2.2.5 | Primary outcomes

1. Circadian rest-activity was measured by actigraphy, considering the following ten measures: (i) Intradaily variability (IV), (ii) Interdaily stability (IS), (iii) the average activity during the most active 10-h period (M10), (iv) the average activity during the least active 5-h period (L5), (v) M10 onset time, (vi) L5 onset time, (vii) Relative amplitude. The following three parameters were generated by Cosinor rhythmometry analyses, an approach that fit a sinusoidal wave with a period of 24 h to the actigraphy¹⁸ data. (viii) Acrophase, time at which the maximal activity occurs (ix) Mesor, rhythm-adjusted mean of the sinusoidal wave (x) Amplitude, the difference between the peak and the mean value of a wave.¹⁹

2.2.6 | Secondary outcomes

2. Sleep quality measured by polysomnography, which includes the following measures: (i) Sleep onset latency, (ii) Wakefulness after sleep onset, (iii) Number of awakenings, (iv) The average of total sleep time, and (v) sleep efficiency.²⁰ If polysomnography was not used, we then considered the mean total score

of Pittsburgh Sleep Quality Index (PSQI), a lower PSQI total score indicates better sleep quality.²¹

3. Core body temperature.
4. Daily profiles of cortisol and melatonin levels.
5. Chronotype, measured by validated questionnaires, such as Morningness-Eveningness Questionnaire (MEQ), Munich Chronotype Questionnaire (MCTQ) and Composite Scale of Morningness (CSM).²²

2.3 | Data extraction and quality assessment

Two review authors (NX and KS) independently identified eligible studies from the retrieved publication, first by title and abstract, followed by screening the full text of potentially relevant studies. The same authors extracted the following information from the eligible studies using a data extraction spreadsheet: name of the first author, year of publication, type of study, follow-up period, diagnosis, current mood state, clinical setting, age, gender, treatment with dose information, number of participants of each group, outcomes measures and findings. Any discrepancies were resolved by discussing with the third review author (AC). If data were unavailable from published reports, authors were contacted.

Study quality was also assessed using the AXIS tool for cross-sectional studies,²³ the Cochrane Risk of Bias Tool for randomized controlled trials²⁴ and the Newcastle-Ottawa Quality Assessment Scale (NOS)²⁵ for cohort studies.

2.4 | Data synthesis and statistical analysis

If two or more studies reported about the same outcome, we conducted meta-analyses using Review Manager (RevMan) Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). For continuous outcomes, standardized mean differences (SMD) were calculated with 95% confidence interval (CI), which enabled comparison to be made among studies using different scales to measure the same outcome. Heterogeneity among studies was tested using I^2 statistic.²⁶ Expecting substantial heterogeneity among studies, we decided to pool the data using random-effects model.

3 | RESULTS

3.1 | Study selection

Our initial electronic searches, together with screening the reference lists of relevant records, yielded 1319 potentially relevant studies (Figure 1). After removing duplicates, we screened the title and abstracts of 1032 studies. Of these, 44 full texts were retrieved and assessed. After excluding 39 studies that did not fully meet the eligibility criteria, we included five independent studies, described in nine published articles. Kim et al and Hwang

et al^{27,28} are reports from the same study, each reporting different outcome measurements with Hwang selected on patients with BD II for its final analysis.

3.2 | Description of included studies

All included studies were published from 2014 to 2018. Four of the included studies were observational studies (three cross-sectional studies²⁹⁻³¹ and one cohort study³²) and the fifth was an 8-week, non-blind randomized controlled trial.²⁸ Full description of the characteristics of included studies is reported in Table 1.

All studies included mixed samples of bipolar I disorder (BD I, 10%–57%) and bipolar II disorder (BD II, 42–90%). In three studies all patients were euthymic³⁰⁻³²; the other two studies recruited patients who were experiencing a current mood episode.^{28,29} Four studies recruited from outpatient settings and a fifth from both outpatient and inpatient settings.²⁸ Five studies had between 29 and 525 participants, and only one study recruited more than 100 participants.³⁰ Hwang et al and Benizri et al compared lithium monotherapy with another mood stabilizer,^{28,32} whereas the other three studies compared two groups with multiple medications, one took lithium, the other did not.²⁹⁻³¹

3.3 | Quality assessment

The quality of the included studies ranged between moderate and low. The randomized control trial had a high risk of bias for blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and other sources of bias like sponsorship bias (see Table 2 in the Appendix). The cohort study reported unclear information about the follow-up (Appendix Table 3) and in all three cross-sectional studies there were limited measures undertaken to address and categorize non-responders which were susceptible to reporting bias (see Appendix Table 4).

3.4 | Circadian rest-activity

Only two studies evaluated the impact of lithium on circadian rest-activity using actigraphy. In the randomized controlled trial comparing lithium and quetiapine, acrophase, the authors reported that amplitude and mesor did not exhibit significant changes from baseline in the lithium group after 8 weeks treatment,²⁸ but they did not report the data, so their findings are not replicable and could not be incorporated in the meta-analysis. By contrast, the second study, a cohort study with 21 days of follow-up, found patients treated with lithium had significantly larger amplitude (SMD 0.68, 95% CI: 0.01 to 1.36), smaller intra-daily variability (SMD -0.45, 95% CI: -1.11 to 0.21) compared with patients treated with anticonvulsants. However, no differences on M10 onset time, L5 onset time were detected between two groups.³²

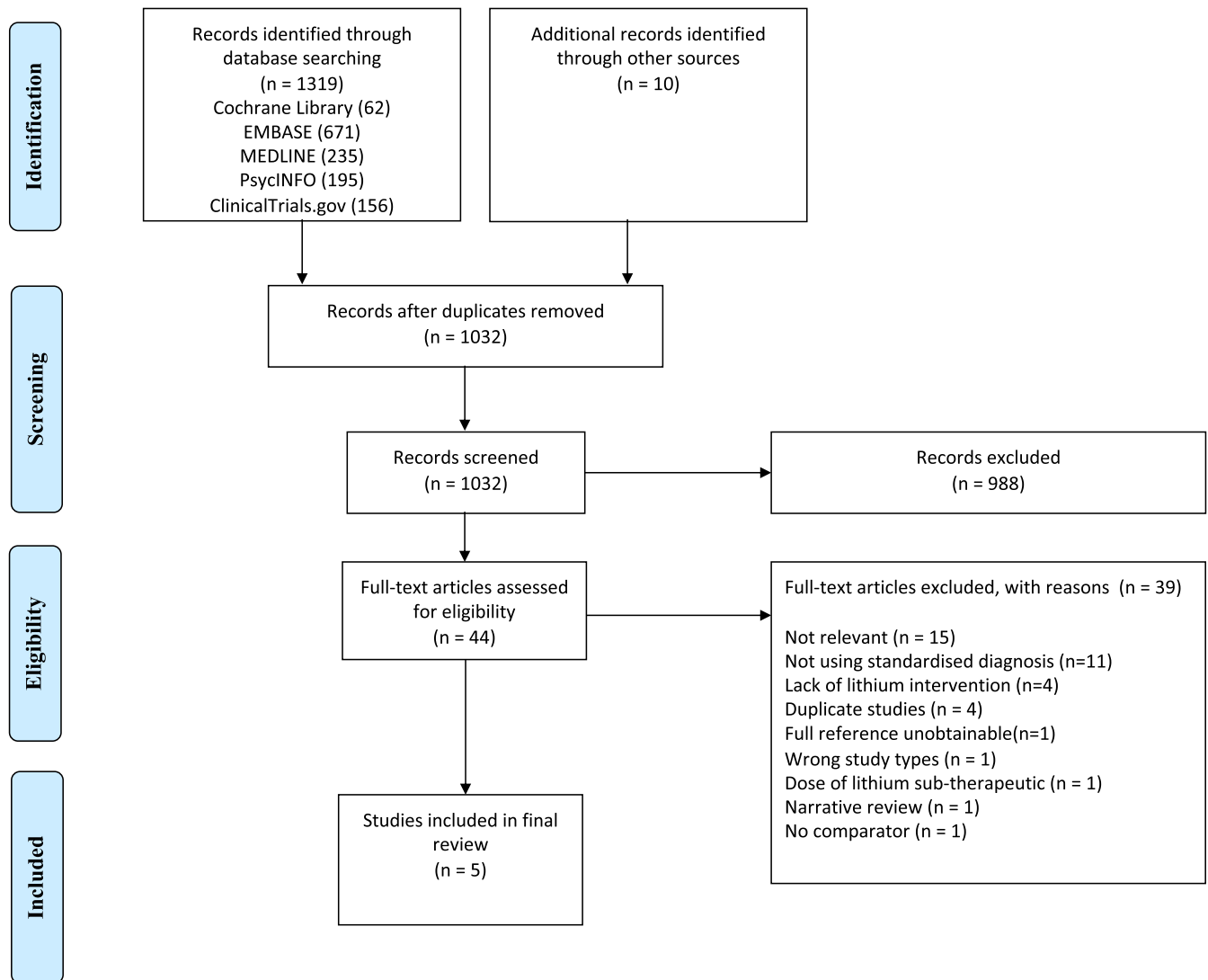


FIGURE 1 PRISMA flow diagram

3.5 | Sleep quality

Polysomnography (PSG) is widely considered as the gold standard of measuring sleep objectively.²⁰ All included studies adopted the Pittsburgh Sleep Quality Index (PSQI) rather than PSG.^{27,30} The randomized controlled trial did not detect any significant changes on PSQI scores at week 1, 2, 4, 6 and 8 compared with baseline. In addition, no significant changes were found on actigraphy measured sleep parameters including sleep latency, sleep efficiency, and wakefulness after sleep onset (WASO) in the lithium treatment group which was consistent with the subjective measurements.²⁷ Similarly, there were no significant differences in PSQI scores found between patients received lithium monotherapy and anticonvulsant monotherapy (SMD 0.06, 95% CI: -0.60 to 0.71).³² In contrast, a cross-sectional study with more than 100 patients in each arm found that lithium use was significantly associated with the lower PSQI scores in women who had BDI (-23% [-37% to -7%]), whereas such association was not noted in BD II or men who had BD I.³⁰

3.6 | Chronotype

Four observational studies reported data about chronotype and we meta-analysed the results.²⁹⁻³² Three of included studies adopted CSM scale,³⁰⁻³² the other one used the MEQ questionnaire.²⁹ Benizri et al., a cohort study with 21-day actigraphy recording, measured chronotype using CSM questionnaire at one point in time.³² Thus, we included it in the pooled analysis. Kanagarajan et al. recruited both patients with current mood episodes and euthymic patients, whereas the other included studies recruited only euthymic patients. No differences in CSM total scores were detected between these two groups of patients with different mood states.²⁹ The meta-analysis provided non-significant evidence ($p = 0.08$) that lithium is associated with higher level of morningness (SMD 0.42, 95% CI: -0.05 to 0.90) (Figure 2). Considerable heterogeneity was detected across the included studies ($I^2 = 74%$, $p = 0.009$).

TABLE 1 Characteristics of included studies

Study (Author, Year)	Methodology (Type of study)	Follow-up period	Diagnosis & Mood state & Setting	Mean Age (SD)	Gender (% Female)	Treatment (dose)	Number of participants for each arm	Outcome measures
Kanagarajan 2018	Cross-sectional study	NA	Outpatients with a DSM 5 diagnosis of Bipolar Disorder (I, II, NOS) and a current manic/hypomanic/depressive/mixed episode or euthymic	Tot: 46.6 (not reported)	Tot: 43%	Lithium Other medication except lithium	Li: 13 Other: 40	MEQ scores
Geoffroy 2016	Cross-sectional study	NA	Euthymic outpatients with DSM-IV diagnosis of Bipolar Disorder (I, II).	Li: 50.4 (12.3) Other: 47.1 (12.6)	Li: 52% Other: 61%	Lithium No lithium (with other mood-stabilizing medication)	Li: 149 Other: 376	CSM total scores PSQI total scores
Dopierala 2017	Cross-sectional study	NA	Patients with an ICD10 and DSM-IV diagnosis of Bipolar Disorder (I, II) and currently in remission (Unclear about the setting)	Tot: 52 (13)	Tot: 69%	Lithium (mostly combined with other mood stabilizers and antidepressant drugs) Other mood-stabilizing medication except Lithium	Li: 27 Other: 27	CSM scores
Hwang 2017	RCT	8 weeks	Inpatients and outpatients with a DSM-IV diagnosis of Bipolar Disorder II and a current depressive episode (Hamilton Depression Rating Scale 17-item score [HDRS-17] ≥ 20)	Li: 32.7 (8.7) Que: 37.2 (11.6)	Tot: 52% Que: 70% Li: 40%	Lithium monotherapy (serum lithium level was maintained at 0.8 to 1.2 mmol/L) Quetiapine XR monotherapy (target dose was 300 mg/d)	Li: 15 Que: 10	Actigraphy measures: acrophase, amplitude, mesor
Kim 2014	RCT	8 weeks	Inpatients and outpatients with a DSM-IV diagnosis of Bipolar Disorder (I, II) and a current depressive episode	Tot: 36.17 (10.4)	Tot: 55.2%	Lithium monotherapy (serum lithium level was maintained at 0.8 to 1.2 mmol/L) Quetiapine XR monotherapy (300 mg/day)	Li: 17 Que: 12	PSQI scores
Benizri 2015	Cohort study	21 days	Euthymic outpatients with a diagnosis of Bipolar Disorder (bipolar type not reported)	Not reported	Not reported	Lithium Anticonvulsants	Li: 17 Ant: 19	Actigraphy measures: Amplitude, IS, IV, L5 onset time, M10 onset time CSM scores PSQI scores

Anti, Anticonvulsants; CSM, Composite Scale of Morningness; DSM, The Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; IS, Interdaily stability; IV, Intradaily variability; L5 onset time, time of onset of lowest 5 h of activity; M10 onset time, time of onset of highest 10 h of activity; MEQ, The morningness-eveningness questionnaire; PSQI, Pittsburgh Sleep Quality Index; Que, quetiapine; RCT, randomized controlled trial; Tot, total sample.

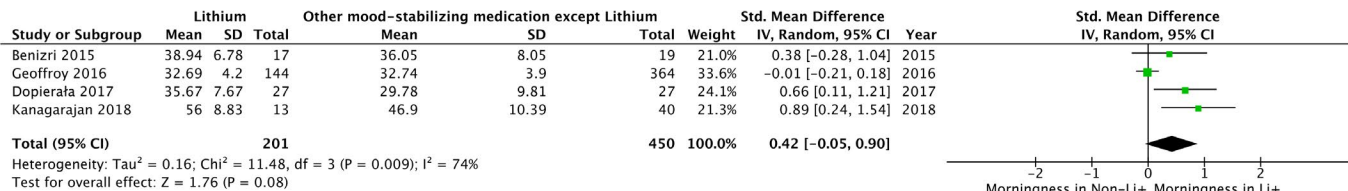


FIGURE 2 Morningness as a continuous measure on a validated chronotype rating scale in observational studies comparing lithium with other mood stabilizers except for lithium. CI, confidence interval; I², percentage of the variability in effect estimates due to heterogeneity; SD, standard deviation

4 | DISCUSSION

To our knowledge, this is the first systematic review of studies investigating the effect of lithium on circadian rhythm in patients with bipolar disorder. The findings should be interpreted with caution because only five studies were included, four of which were observational studies. The quality of evidence ranged from moderate to low. Bearing in mind these limitations, the main finding suggested a possible association between lithium and shifts towards morningness. We could not confirm the potential beneficial effect of lithium on sleep quality. Lithium treatment may increase amplitude of circadian rest-activity rhythm.

We noted substantial heterogeneity between studies. Nevertheless, there is no variation in direction of effects. In addition, most of the included studies were cross-sectional, precluding any valid conclusions about cause and effect. Given the limitations in the primary studies, the results of our meta-analysis may be susceptible to different interpretations. The first interpretation might be that patients on lithium differ on their pre-existing chronotype from patients on other mood stabilizers. None of the included studies differentiated lithium-responsive BD patients from lithium non-responders, which might also influence the detection of the effect of lithium on chronotype. A recent study used Basic Language Morningness scale (BALM) for chronotype analysis, found that lithium-responsive BD patients showed higher levels of morningness compared with lithium non-responders.³³ Fibroblasts cells from lithium-responsive bipolar patients showed a short period of the cellular circadian rhythm.^{33,34} A higher level of morningness was found to be associated with a shorter period.³⁵ With a similarly long period, phase advance was observed in lithium-responsive cells in comparison with lithium-nonresponsive cells.³³ These results also suggested that chronotype at baseline can be a potential candidate for the predictors of lithium responsiveness.

The second interpretation of this meta-analysis is that the phase advance or an increased level of morningness might be an early sign of the treatment effect of lithium. Morning chronotype was associated with fewer mood symptoms and past suicide attempt.³³ Another study showed that shifts towards morningness were associated with reductions in depression, increases in positive affect and improvements in sleep quality in military veterans receiving brief behavioural treatment for insomnia.⁸ It is unclear if lithium had an impact on chronotype independent of changes in mood symptoms.

Finally, the meta-analysis result indicates that increasing the level of morningness may be part of the mechanism of action of lithium.

Lithium showed a period-shortening effect in fibroblast cells from lithium-responsive BD patients.³³ The shorter period was associated with an increased level of morningness.³⁵ However, the translation of the preliminary findings in bipolar patient fibroblast cells to bipolar patients was incomplete.

All these interpretations of the meta-analysis prompt further investigation in research studies. To elucidate the role of chronotype or the phase changes of the circadian rhythm in the treatment of lithium, whether it serves as part of the mechanism of action or an early signal of a good response or an underlying circadian phenotype associated with lithium responsiveness. We need further investigation with rigorous study design. Therefore, randomized controlled trials with larger sample of BD patients treated with lithium, better control for mood symptoms and sleep quality are required to allow causal inferences to be made.

Sleep dysregulation is well-documented in bipolar disorder.³⁶ We found that the effects of lithium on sleep quality were mixed. In one included study, Geoffroy et al. found significantly lower PSQI scores in patients with BD I women, but not men, receiving lithium treatment.³⁰ We are not confident about the validity of these subgroup analysis which were not pre-planned. Any subgroup difference arises from post-hoc rather than a priori hypothesis undermines its credibility.³⁷ In Kim et al. study,²⁷ PSQI scores in lithium treatment group was significantly lower than quetiapine group at baseline. We do not know whether the failure of detection of any significant changes in sleep quality in lithium group is caused by their comparatively better sleep quality at baseline.

There are limited studies explored the effect of lithium on circadian rest-activity pattern by using actigraphy. Benziri et al. showed that BD patients received lithium treatment was associated with a larger amplitude of circadian rest activity rhythm compared with anticonvulsants treatment.³² The effect of lithium on amplitude has been reported in skin fibroblast cultures from healthy participants and BD patients. A rhythmically expressed, bioluminescent circadian rhythm reporter gene, *Per2::luc*, was used to indicate circadian rhythm changes.³⁸ Lithium had an impact on increasing the amplitude of circadian rhythm in fibroblast cultures from healthy participants but failed in BD patients, which may cause by differences in calcium channel and extracellular regulated kinase (ERK) signalling.³⁸⁻⁴⁰

Three of five included studies only adopted subjective measures like validated scales. Compared with other physiological markers of circadian rhythm, self-reported scales are more practical and cost-effective in large sample studies. However, its external validity has

been questioned. Some studies reported that BD participants underestimated their sleep durations using questionnaires and diaries.^{41,42} Thus, it is advisable to use both subjective and objective measurements to assess the circadian rhythm in BD patients.⁴³ Actigraphy, as one of the objective measurements, has increasingly been used in assessing circadian rhythm in mood disorder.^{36,44} Actigraphy provides continuous objective measurement of movement over time, which could provide more details of circadian rhythm changes, improve assessment by reducing recall bias.⁴⁵ Thus, actigraphy might be a useful tool to further explore the effect of lithium on circadian rhythm.

Mounting evidence supports that lithium has impact on circadian clock.^{15,46} There remains a large gap between positive results in the lab and the clinical effectiveness in the real-world clinical setting where the response of lithium treatment might be influenced by the adherence to medication, various adverse effects, different comorbidities, etc.^{47,48} Moreover, the translational potential of lab studies was hampered by the fact that few studies have integrated prospective longitudinal monitoring of illness activity, assessing clinically relevant phenotype with the biomarker research.⁴⁹ For example, an ongoing study, Response to Lithium Network (R-LiNK), is a prospective cohort study to identify biomarker or biosignatures of lithium treatment in patients with bipolar disorder I. R-LiNK will follow 300 participants prospectively for two years after the initiation of lithium treatment, using actigraphy to monitor daily circadian rest-activity variability. It will also monitor core BD symptoms and illness activity daily by using ecological momentary assessment (EMA) and assess medication adherence over time.⁵⁰

4.1 | Limitations

The main limitation in our systematic review is the lack of the available high-quality evidence to inform the question whether lithium has an impact on the circadian rhythm. Only five studies published between 2014 and 2018 were included in this study. Most of the included studies are cross-sectional, and there is only one randomized controlled trial, so causal inferences cannot be made. Studies have small sample size. Except for Geoffroy et al, included studies had between 29 and 54 participants. Of the three cross-sectional studies, usage of other medications was not properly controlled. Overall, the quality of evidence ranged from moderate to low. All three cross-sectional studies did not address non-responders, the cohort study did not have a clear information about the follow-up. Failure to address non-responders and participants were lost to follow-up which represent a distinctive group, precludes the generalization of the results in target population.^{51,52}

5 | CONCLUSIONS

There is a growing interest in the effect of lithium on circadian rhythm. Our meta-analysis suggests a possible association between lithium

and shifts towards morningness in BD patients. Chronotype could be a potential target of further exploration of biomarkers or biosignatures of lithium treatment. Our systematic review also highlights the paucity of high-quality evidence to elucidate the effect of lithium on circadian rhythm in patients with bipolar disorder. The field requires more high-quality studies where the primary outcome was a measure of circadian rhythm adopting prospective, longitudinal study design, using actigraphy to monitor daily changes of circadian rest activity.

ACKNOWLEDGEMENTS

We thank the following authors of studies for sharing the additional data: Dr Pierre Alexis Geoffroy, Dr Frank Bellivier, Dr Bruno Etain, Dr Ewa Kurczewska, Dr Outi Mantere

AUTHORS' CONTRIBUTIONS

NX conceived and designed the study. KEAS, JRG, AC provided supervision. NX and KS selected the articles and extracted the data. NX contacted authors to acquire unpublished data. NX and KS analysed, interpreted the data. NX wrote the first draft of the manuscript. KS, KEAS, JRG, AC critically reviewed the manuscript.

ETHICAL APPROVAL

Ethical approval was not needed for this project because it is a systematic review of aggregate data from existing primary studies.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Ni Xu  <https://orcid.org/0000-0002-4207-5655>

Andrea Cipriani  <https://orcid.org/0000-0001-5179-8321>

REFERENCES

- Grandin LD, Alloy LB, Abramson LY. The social zeitgeber theory, circadian rhythms, and mood disorders: review and evaluation. *Clin Psychol Rev*. 2006;26(6):679-694.
- Hofstra WA, de Weerd AW. How to assess circadian rhythm in humans: a review of literature. *Epilepsy Behav*. 2008;13(3):438-444.
- Melo MCA, Abreu RLC, Linhares Neto VB, de Bruin PFC, de Bruin VMS. Chronotype and circadian rhythm in bipolar disorder: a systematic review. *Sleep Med Rev*. 2017;34:46-58.
- Faedda GL, Ohashi K, Hernandez M, et al. Actigraph measures discriminate pediatric bipolar disorder from attention-deficit/hyperactivity disorder and typically developing controls. *J Child Psychol Psychiatry*. 2016;57(6):706-716.
- Jones SH, Hare DJ, Evershed K. Actigraphic assessment of circadian activity and sleep patterns in bipolar disorder. *Bipolar Disord*. 2005;7(2):176-186.
- Vitale JA, Roveda E, Montaruli A, et al. Chronotype influences activity circadian rhythm and sleep: differences in sleep quality between weekdays and weekend. *Chronobiol Int*. 2015;32(3):405-415.
- Klei L, Reitz P, Miller M, et al. Heritability of morningness-eveningness and self-report sleep measures in a family-based sample of 521 hutterites. *Chronobiol Int*. 2005;22(6):1041-1054.
- Hasler BP, Buysse DJ, Germain A. Shifts toward morningness during behavioral sleep interventions are associated with improvements

- in depression, positive affect, and sleep quality. *Behav Sleep Med*. 2016;14(6):624-635.
9. Takaesu Y, Inoue Y, Murakoshi A, et al. Prevalence of circadian rhythm sleep-wake disorders and associated factors in euthymic patients with bipolar disorder. *PLoS One*. 2016;11(7):e0159578.
 10. Steinar MK, Morken G, Lagerberg TV, et al. Delayed sleep phase: an important circadian subtype of sleep disturbance in bipolar disorders. *J Affect Disord*. 2016;191:156-163.
 11. Robillard R, Naismith SL, Rogers NL, et al. Sleep-wake cycle and melatonin rhythms in adolescents and young adults with mood disorders: comparison of unipolar and bipolar phenotypes. *Eur Psychiatry*. 2013;28(7):412-416.
 12. Nurnberger JI Jr, Adkins S, Lahiri DK, et al. Melatonin suppression by light in euthymic bipolar and unipolar patients. *Arch Gen Psychiatry*. 2000;57(6):572-579.
 13. Malhi GS, Gessler D, Outhred T. The use of lithium for the treatment of bipolar disorder: recommendations from clinical practice guidelines. *J Affect Disord*. 2017;217:266-280.
 14. Goodwin GM, Haddad PM, Ferrier IN, et al. Evidence-based guidelines for treating bipolar disorder: revised third edition recommendations from the British Association for Psychopharmacology. *J Psychopharmacol*. 2016;30(6):495-553.
 15. Moreira J, Geoffroy PA. Lithium and bipolar disorder: impacts from molecular to behavioural circadian rhythms. *Chronobiol Int*. 2016;33(4):351-373.
 16. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol*. 2009;62(10):e1-34.
 17. Taylor DM, Barnes TR, Young AH. *The Maudsley Prescribing Guidelines in Psychiatry*. John Wiley & Sons; 2018.
 18. Nelson W, Tong YL, Lee JK, Halberg F. Methods for cosinor-rhythmometry. *Chronobiologia*. 1979;6(4):305-323.
 19. Refinetti R, Lissen GC, Halberg F. Procedures for numerical analysis of circadian rhythms. *Biol Rhythm Res*. 2007;38(4):275-325.
 20. Kaplan KA, Talbot LS, Gruber J, Harvey AG. Evaluating sleep in bipolar disorder: comparison between actigraphy, polysomnography, and sleep diary. *Bipolar Disord*. 2012;14(8):870-879.
 21. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28(2):193-213.
 22. Di Milia L, Adan A, Natale V, Randler C. Reviewing the psychometric properties of contemporary circadian typology measures. *Chronobiol Int*. 2013;30(10):1261-1271.
 23. Downes MJ, Brennan ML, Williams HC, Dean RS. Development of a critical appraisal tool to assess the quality of cross-sectional studies (AXIS). *BMJ Open*. 2016;6(12):e011458.
 24. Higgins JP, Thomas J, Chandler J, et al. *Cochrane Handbook for Systematic Reviews of Interventions*. John Wiley and Sons; 2019.
 25. Wells G, Shea B, O'Connell D, et al. *Newcastle-Ottawa Quality Assessment Scale Cohort Studies*. University of Ottawa; 2014.
 26. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560.
 27. Kim SJ, Lee YJ, Lee YJ, Cho SJ. Effect of quetiapine XR on depressive symptoms and sleep quality compared with lithium in patients with bipolar depression. *J Affect Disord*. 2014;157:33-40.
 28. Hwang JY, Choi JW, Kang SG, Hwang SH, Kim SJ, Lee YJ. Comparison of the effects of quetiapine XR and lithium monotherapy on actigraphy-measured circadian parameters in patients with Bipolar II depression. *J Clin Psychopharmacol*. 2017;37(3):351-354.
 29. Kanagarajan K, Gou K, Antinora C, et al. Morningness-Eveningness questionnaire in bipolar disorder. *Psychiatry Res*. 2018;262:102-107.
 30. Geoffroy PA, Samalin L, Llorca PM, Curis E, Bellivier F. Influence of lithium on sleep and chronotypes in remitted patients with bipolar disorder. *J Affect Disord*. 2016;204:32-39.
 31. Dopierala E, Chrobak A, Tereszko A, Rybakowski J. Lithium influence on circadian rhythm assessed by the Composite Scale of Morningness in remitted bipolar patients. *Farmakoterapia w Psychiatrii i Neurologii*. 2017;33(1):9-20.
 32. Benizri C, Etain B, Geoffroy P, Boudebesse C, Bellivier F. Lithium and circadian rhythms in bipolar disorder. Paper presented at: EUROPEAN NEUROPSYCHOPHARMACOLOGY2015.
 33. McCarthy MJ, Wei H, Nievergelt CM, et al. Chronotype and cellular circadian rhythms predict the clinical response to lithium maintenance treatment in patients with bipolar disorder. *Neuropsychopharmacol*. 2019;44(3):620-628.
 34. Sanghani HR, Jagannath A, Humberstone T, et al. Patient fibroblast circadian rhythms predict lithium sensitivity in bipolar disorder. *Mol Psychiatry*. 2020;1-14.
 35. Duffy JF, Rimmer DW, Czeisler CA. Association of intrinsic circadian period with morningness-eveningness, usual wake time, and circadian phase. *Behav Neurosci*. 2001;115(4):895.
 36. Geoffroy PA, Scott J, Boudebesse C, et al. Sleep in patients with remitted bipolar disorders: a meta-analysis of actigraphy studies. *Acta Psychiatr Scand*. 2015;131(2):89-99.
 37. Sun X, Ioannidis JP, Agoritsas T, Alba AC, Guyatt G. How to use a subgroup analysis: users' guide to the medical literature. *JAMA*. 2014;311(4):405-411.
 38. McCarthy MJ, Wei H, Marnoy Z, et al. Genetic and clinical factors predict lithium's effects on PER2 gene expression rhythms in cells from bipolar disorder patients. *Transl Psychiat*. 2013;3:e318.
 39. McCarthy MJ, Le Roux MJ, Wei H, Beesley S, Kelsoe JR, Welsh DK. Calcium channel genes associated with bipolar disorder modulate lithium's amplification of circadian rhythms. *Neuropharmacology*. 2016;101:439-448.
 40. McCarthy MJ, Wei H, Landgraf D, Le Roux MJ, Welsh DK. Disinhibition of the extracellular-signal-regulated kinase restores the amplification of circadian rhythms by lithium in cells from bipolar disorder patients. *Eur Neuropsychopharmacol*. 2016;26(8):1310-1319.
 41. Ritter PS, Sauer C, Pfeiffer S, Bauer M, Pfennig A. Comparison of subjective and objective sleep estimations in patients with bipolar disorder and healthy control subjects. *Sleep Disord*. 2016;2016:4031535.
 42. Harvey AG, Schmidt DA, Scarna A, Semler CN, Goodwin GM. Sleep-related functioning in euthymic patients with bipolar disorder, patients with insomnia, and subjects without sleep problems. *Am J Psychiatry*. 2005;162(1):50-57.
 43. Boudebesse C, Geoffroy PA, Bellivier F, et al. Correlations between objective and subjective sleep and circadian markers in remitted patients with bipolar disorder. *Chronobiol Int*. 2014;31(5):698-704.
 44. Lyall LM, Wyse CA, Graham N, et al. Association of disrupted circadian rhythmicity with mood disorders, subjective wellbeing, and cognitive function: a cross-sectional study of 91 105 participants from the UK Biobank. *Lancet Psychiatry*. 2018;5(6):507-514.
 45. Ancoli-Israel S, Cole R, Alessi C, Chambers M, Moorcroft W, Pollak CP. The role of actigraphy in the study of sleep and circadian rhythms. *Sleep*. 2003;26(3):342-392.
 46. Porcu A, Gonzalez R, McCarthy MJ. Pharmacological manipulation of the circadian clock: a possible approach to the management of bipolar disorder. *CNS Drugs*. 2019;33(10):981-999.
 47. Chen CK, Lee CS, Chen HY, et al. GADL1 variant and medication adherence in predicting response to lithium maintenance treatment in bipolar I disorder. *BJPsych Open*. 2016;2(5):301-306.
 48. Howes OD, McCutcheon R, Agid O, et al. Treatment-resistant schizophrenia: treatment response and resistance in psychosis (TRRIP) working group consensus guidelines on diagnosis and terminology. *Am J Psychiatry*. 2017;174(3):216-229.

49. Scott J, Etain B, Bellivier F. Can an integrated science approach to precision medicine research improve lithium treatment in bipolar disorders? *Front Psychiatry*. 2018;9:360.
50. Scott J, Hidalgo-Mazzei D, Strawbridge R, et al. Prospective cohort study of early biosignatures of response to lithium in bipolar-I-disorders: overview of the H2020-funded R-LiNK initiative. *Int J Bipolar Disord*. 2019;7(1):20.
51. Launer LJ, Wind AW, Deeg DJ. Nonresponse pattern and bias in a community-based cross-sectional study of cognitive functioning among the elderly. *Am J Epidemiol*. 1994;139(8):803-812.
52. Sedgwick P. Bias in observational study designs: prospective cohort studies. *BMJ*. 2014;349:g7731.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Xu N, Shinohara K, Saunders KE, Geddes JR, Cipriani A. Effect of lithium on circadian rhythm in bipolar disorder: A systematic review and meta-analysis. *Bipolar Disord*. 2021;23:445–453. <https://doi.org/10.1111/bdi.13070>