Effects of Lithium on Circadian Rhythm and Cognitive Function in Patients with Bipolar Disorder

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Abstract:

Bipolar disorder (BD) is a highly prevalent group of chronic, debilitating mental disorders. Although lithium has been widely used as the gold-standard treatment for BD, its mechanism of action remains unclear. Additionally, no robust lithium response predictors exist to avoid lengthy and ineffective treatment trials. Therefore, there is a need to investigate the mechanism of action of lithium and to develop biomarkers of lithium response in patients with BD.

Circadian rhythm disruption is one of the hallmarks of BD. However, the effect of lithium on circadian rhythm in clinical cohorts of patients with BD is unclear. **The first objective of this thesis was to examine whether lithium has a direct effect on reversing circadian rhythm abnormalities commonly reported among patients with bipolar disorder**. A systematic review was conducted to examine whether lithium has an impact on circadian rhythm in patients with bipolar disorder. The meta-analysis suggested lithium treatment was associated with greater morningness in patients with BD. The effect of lithium on circadian rhythm was examined further using finer-grained actigraphy data from a double-blind, randomised, placebo-controlled experimental medicine study (Oxford Lithium Trial). No robust evidence supported the hypothesis that lithium might increase the levels of circadian rest-activity, advance the phase of the circadian rest-activity, or reduce the variability of the circadian rest-activity. However, there was some tentative evidence that lithium reduced daytime activity, suggesting that it may have a stabilising effect. In addition, lithium reduced the onset time of daytime activity as well as the variability of circadian rest-activity.

The second objective of this thesis was to examine whether lithium has an adverse impact on cognitive function in patients with bipolar disorder. The subjective cognitive dullness reported by patients with BD treated with lithium has been shown to be a major reason for nonadherence to lithium. Cognitive impairment has also been commonly reported in patients with BD. The methodological limitations of previous studies made it difficult to determine the extent to which cognitive impairments often reported in patients with BD were the result of lithium treatment. In the Oxford Lithium Trial, a modified mobile-based contextual cueing task was applied in patients with BD to monitor daily attentional performance, implicit learning, and memory function after six weeks of treatment. No significant difference between lithium and placebo was found on attention, implicit learning, and memory, suggesting short-term lithium treatment does not impair these cognitive domains in patients with BD.

Overall, these findings provide new insights not only into the effects of lithium on circadian rhythm and cognitive function in patients with BD, but also into the development of novel experimental models for the treatment of BD. Moreover, this thesis demonstrates the potential of real-time, high-frequency mobile assessment techniques to characterise bipolar phenotypes with greater resolution and accuracy, which may provide new insights into the pathogenesis of BD.

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"For our body is like a clock; if one wheel be amiss, all the rest are disordered, the whole fabric suffers: with such admirable art and harmony is a man composed."

-—Robert Burton, The Anatomy of Melancholy (1621)

Declaration:

The systematic review in Chapter 2 as well as a portion of the introduction to Chapter 6 have been published.

Chapter 2

Xu, N., Shinohara, K., Saunders, K., Geddes, J. R., & Cipriani, A. (2021). Effect of lithium on circadian rhythm in bipolar disorder: A systematic review and meta-analysis. *Bipolar disorders*, 23(5), 445–453.

Chapter 6

Xu, N., Huggon, B., & Saunders, K. (2020). Cognitive Impairment in Patients with Bipolar Disorder: Impact of Pharmacological Treatment. *CNS drugs*, 34(1), 29–46.

Based on guidelines, the body of this thesis contains no more than 50,000 words (excluding figures, tables, references, and appendices,) and fewer than 150 figures.

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List of Abbreviation:

Abbreviation	Definition
ANOVA	Analysis of variance
ASRM	Altman Self-Rating Mania Scale
BALM	Basic Language Morningness scale
BD	Bipolar Disorder
BDRN	Bipolar Disorder Research Network
CSM	Composite Scale of Morningness
DALY	Disability-Adjusted Life Years
DLMO	Dim Light Melatonin Onset
DSM	Diagnostic and Statistical Manual of Mental Disorders
GSK	Glycogen Synthase Kinase
HDRS	Hamilton Depression Rating Scale
ICD	International Classification of Disease
IPSRT	Interpersonal and social rhythm therapy
IS	Interdaily Stability
IV	Intradaily variability
L5	The average activity during the least active five-hour period
LMIC	Low-to-Middle-Income Country
M10	The average activity during the most active ten-hour period
MCTQ	Munich Chronotype Questionnaire
MEQ	Morningness-Eveningness Questionnaire

MESOR	Midline Estimating Statistic Of Rhythm
NOS	Not Otherwise Specified
PANAS	Positive and Negative Affect Schedule
PDQ	Perceived Deficits Questionnaire
PSQI	Pittsburgh Sleep Quality Index
QIDS	Quick Inventory of Depressive Symptomatology
RMS	Root Mean Square
RMSSD	Root Mean Squared Successive Difference
SCI	Sleep Condition Indicator
SCID	Structured Clinical Interview for DSM-IV
SCN	Suprachiasmatic nuclei
SMD	Standardised Mean Differences
TKEO	Teager-Kaiser Energy Operator
WASO	Wakefulness After Sleep Onset

Chapter 1: Introduction

"I believe the brain, like any other organ, can get sick and it can also heal"

-Dr John F. Cade

1.1 Background:

Lithium has been widely used as the gold-standard treatment for bipolar disorder, but its mechanism of action remains unclear. A further concern is that less than 30% of patients with bipolar disorder have been shown to respond well to lithium treatment [1], and no robust lithium response predictors have been found. Currently, patients with bipolar disorder commonly undergo a trial and error approach involving taking lithium for several months in order to assess the degree of response to treatment [2]. Therefore, it is imperative to understand the mechanism of action of lithium and to develop biomarkers of lithium response which could facilitate a more rapid assessment of lithium treatment response and avoid lengthy and ineffective treatment trials. Moreover, understanding the mechanism of lithium could provide insights into the development of novel mood stabilisers. Because circadian rhythm disruption has been shown to be one of the hallmarks of bipolar disorder [3] and chronobiological models have suggested circadian rhythm might be central to the pathogenesis of bipolar disorder [4], investigating the effect of lithium on circadian rhythm in patients with bipolar disorder is of great interest.

Patients with bipolar disorder treated with lithium report subjective cognitive dullness, which has been shown to be a major reason for non-adherence to lithium [5]. Cognitive

impairment has also been commonly reported in patients with bipolar disorder [6]. The methodological limitations of previous studies made it difficult to determine the extent to which cognitive impairments often reported in patients with bipolar disorder were caused by lithium treatment [7]. Thus, there is a need to delineate the effect of lithium on cognitive function in a randomised, placebo-controlled trial with higher-resolution cognitive assessments.

1.2 Thesis overview

The first objective of this thesis is to examine whether lithium has direct effects on reversing circadian rhythm abnormalities commonly reported in patients with bipolar disorder. Circadian rhythm disruption has been shown to be one of the prominent features of bipolar disorder [8]. Numerous lines of evidence have suggested that lithium impacts circadian rhythm, including studies using cell lines, animal models, and pharmacogenetic information from patients with bipolar disorder. However, the effect of lithium on circadian rhythm in clinical cohorts of patients with bipolar disorder has not been clear. Therefore, a systematic review was conducted to examine whether lithium has an impact on circadian rhythm in patients with bipolar disorder. The results of the systematic review will be presented in Chapter Two of this thesis.

Using data from a double-blind, randomised, placebo-controlled experimental medicine study (Oxford Lithium Trial) [9], the empirical studies (Chapters Four, Five, and Six) investigated the effects of lithium on circadian rhythm and cognitive function, both of which play crucial roles in bipolar disorder. The trial will be introduced in greater detail in Chapter Three of this thesis. Chapters Four and Five of the thesis will investigate the

effects of lithium on different aspects of circadian rest-activity in participants with bipolar disorder as measured by actigraphy. Chapter Four will examine whether lithium may have a direct effect on increasing circadian rest-activity and Chapter Five will examine whether lithium has a direct effect on advancing the phase of circadian rest-activity and whether lithium reduces the variability of circadian rest activity. The relationship between mood and motor activity and the timing of circadian rest-activity will also be explored in these two chapters.

The second objective of this thesis is to examine whether lithium has an adverse impact on cognitive functioning in patients with bipolar disorder. Using data from the Oxford Lithium Trial, Chapter Six will examine the daily changes in cognitive function in response to lithium treatment compared with a placebo utilising a mobile-based contextual cueing cognitive task. Despite the fact that investigating the relationship between circadian disruptions and cognitive function was not the primary objective of this thesis, some preliminary analyses of the association between these two domains will be discussed in Chapter Six.

The thesis will conclude with Chapter Seven which will summarise the main findings, discuss limitations of the study design, and indicate future directions for this research, including the utility of a real-time, high-frequency monitoring approach to better characterise bipolar phenotypes.

1.3 A brief introduction to bipolar disorder

Bipolar disorder is a group of chronic, debilitating mental disorders characterised by severe, episodic mood swings and disturbed activity levels. Diagnosis of bipolar disorder is exclusively based on comprehensive clinical assessments, and a probable working diagnosis is dependent upon longitudinal assessment [10]. Diagnostic criteria for bipolar disorder are based on the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) and the International Classification of Diseases, 11th revision (ICD-11) [11, 12]. Both DSM-5 and ICD-11 subdivide bipolar disorder into Bipolar I disorder and Bipolar II disorder. Bipolar I disorder is defined by the presence of at least one manic episode, which might be preceded or followed by hypomanic or major depressive episodes. Bipolar II disorder is defined by the presence of at least one hypomanic episode and at least one major depressive episode [10, 12].

For the diagnosis of mania and hypomania, both diagnostic manuals require the presence of both increased energy or activity levels and elevated, expansive or irritable mood. Previous iterations of these diagnostic manuals (DSM-IV-TR and ICD-10) focused predominately on mood symptoms [13]. Mixed episodes (meeting the diagnostic criteria for a manic episode and a major depressive episode concurrently) continues as a diagnosis in ICD-11 but is not maintained in DSM-5. Instead it is replaced with a mixed features specifier which is defined as 'the presence of opposite polarity symptoms during a manic, or major depressive episode' [10].

1.3.1 Epidemiology

Bipolar disorder is highly prevalent globally. The World Mental Health Survey Initiative, a cross-sectional survey of community adults from eleven countries across the Americas,

Europe and Asia, found that bipolar I disorder had a lifetime prevalence of 0.6% and bipolar II disorder of 0.4%; twelve-month prevalence was 0.4 % for bipolar I disorder and 0.3 % for bipolar II disorder [14]. However, the reported prevalence of bipolar disorder varies between higher-income countries and LMICs. A recent China Mental Health Survey, which investigated the prevalence of mental illness using samples from thirty-one provinces including urban and rural populations, reported that the lifetime prevalence was 0.4% for bipolar I disorder and less than 0.1% for bipolar II disorder. In the China Mental Health Survey, twelve-month prevalence was 0.3% for bipolar I disorder and less than 0.1% for bipolar II disorder [15]. In Nigeria and Ethiopia, most community surveys indicated that bipolar disorder's lifetime prevalence was between 0.1% to 0.6% [16]. The prevalence of bipolar disorder may be underestimated in LMICs, especially bipolar II disorder.

A combination of an early age-at-onset and a recurrent course makes bipolar disorder one of the most burdensome conditions in the world. A recent systematic review proposed a trimodal age-at-onset distribution for bipolar disorder: early-onset, mid-onset, and late-onset; the early-onset group had a mean age-at-onset of 17.3 years [17]. Among the early-onset group, higher rates of comorbidity and depressive symptoms were identified, as were longer treatment delays [18]. In all patients with bipolar disorder, the risk of recurrence is high: 40% of patients recovering from first-episode of mania experienced a recurrence within one year [19, 20].

Bipolar disorder is highly disabling, ranking as the 17th leading cause of years lived with disability (YLDs) worldwide [21]. Bipolar disorder also accounted for 9.9 million disability-adjusted life years (DALYs) in 2013 [22]. Depression is the predominant mood

state in both bipolar I disorder and bipolar II disorder [23]. Compared with other mood symptoms, depressive symptoms in patients with bipolar disorder are more debilitating and demonstrate more significant psychosocial impairment [24, 25]. Patients with bipolar I and bipolar II disorder have been found to be euthymic for about half of the year [23]. Beyond the acute phase, patients with bipolar disorder in the euthymic phase also have significant disability and lower quality of life in comparison to healthy individuals [25, 26]. Furthermore, disability status has been identified as a predictor of treatment response and prognosis in bipolar disorder [27]; greater disability and poorer quality of life correlate with worse treatment response and a lower likelihood of recovery. Therefore, uncontrolled symptoms continue to impair the psychosocial functioning of patients, creating a vicious circle.

In addition to impairing psychosocial functioning, bipolar disorder is associated with an increased risk of mortality due to suicide and comorbid general medical illness [28, 29]. In bipolar disorder, suicide is one of the major causes of death, with rates of suicide being 20-to-30-fold higher than in the general population [30]. Cardiovascular disorder, diabetes, and chronic obstructive pulmonary disease are the most common comorbid medical illnesses, leading to increased mortality in bipolar disorder [29]. In a population-based study, cardiovascular disorder was the major cause of increased mortality, accounting for 38% of all deaths among patients with bipolar disorder; the mortality ratios for coronary heart disease and myocardial infarction in patients with bipolar disorder were two times higher than in the general population [31]

Bipolar disorder imposes a significant economic burden on society. One systematic review estimated that the annual economic burden of bipolar disorder in the United States was

more than $195 billion [32]. Limited information is available on the economic impact of bipolar disorder in LMICs. The use of medical care for the treatment of both bipolar disorder and the associated co-morbid medical and psychiatric conditions contributed to about 25% of the national economic burden of bipolar disorder; the rest of the burden was caused by indirect costs, such as poor psychosocial functioning, reduced productivity at work, and unemployment [32]. Therefore, early intervention and effective management of bipolar disorder are vital for the benefit of the individual patient, their family, as well as society as a whole.

1.3.2 Mood instability in bipolar disorder

There is no consensus in the existing literature regarding the definition of mood instability. Several terms related to mood instability have been interchangeably used, including mood swings, mood lability, emotional lability, emotion dysregulation, affective instability and affective lability [33]. Marwaha and colleagues, in an effort to synthesise the definition construct and unify the research area, proposed a definition of mood instability as "rapid oscillations of intense affect, with a difficulty in regulating these oscillations or their behavioural consequences"[33]. Throughout this thesis, mood instability is defined according to the definition proposed by Marwaha et al.

The concept of bipolar disorder has traditionally been considered to represent discrete mood episodes interspersed with normal and stable mood; however, longitudinal mood monitoring tools have revealed mood instability permeates all phases of bipolar disorder [34]. The True Colours system is a digital symptom monitoring tool developed by the University of Oxford over a decade ago for the monitoring of mood symptoms in bipolar

disorder [35]. The True Colours system has revealed that patients with bipolar disorder also experience mood instability during euthymia [36-38].

Mood instability has been reported to be an important characteristic of bipolar disorder, not only because it occurs at all phases of bipolar disorder, but because it occurs in individuals at high risk for bipolar disorder, predicts the onset of bipolar disorder, and it is associated with poor clinical outcomes [34]. Increased mood instability has been noted in unaffected first-degree relatives of newly diagnosed patients with bipolar disorder **[39]**. Mood instability is also a predictor of new-onset bipolar disorder in youth at familial risk of bipolar disorder [40]. Additionally, in patients with bipolar disorder, higher levels of mood instability are closely associated with higher levels of stress, more frequent mood episodes, impaired function, and worse functional recovery [39, 41, 42].

Several implications emanate from the paradigm shift from a model that considered solely discrete mood episodes to one that also focuses on mood instability. Previously, it was challenging to investigate relatively infrequent severe episodes; small-scale and short-term experimental medicine studies were almost impossible [43]. Now, in this new paradigm, short-term experimental medicine studies can focus on core features such as mood instability in patients with bipolar disorder. Moreover, monitoring of mood instability over time promotes longitudinal, frequent monitoring of symptoms, providing finer-grained data which might characterise bipolar phenotypes more accurately than conventional approaches based on retrospective recall. This type of monitoring can also be extended to other features of bipolar disorder, such as circadian rhythm disruptions and cognitive impairments.

1.3.3 Multidimensional view of bipolar disorder

A multidimensional approach to bipolar disorder can better integrate the complex clinical presentations of patient with bipolar disorder and may help unravel the neurobiological basis of the illness. Malhi and colleagues proposed ACE (Activity, Cognition, Emotion) as a multidimensional model to conceptualise bipolar disorder. This model focuses on a group of core symptoms across three domains with equal importance: activity, cognition, and emotion [44]. Additionally, Geoffroy and Gottlieb suggested expanding upon these three domains by incorporating sleep as another crucial pillar of the ACE model. The sleep domain consists of three subdomains: sleep physiology, wakefulness and biological rhythm [45]. One advantage of this multidimensional approach is the ability to assess and describe the highly prevalent clinical phenomenon of mixed states [46] using one coherent model [44]. Furthermore, this multidimensional view of bipolar disorder will contribute to better understanding mood disorder heterogeneity, a significant problem impeding the unravelling of the neurobiological mechanisms underlying bipolar disorder and the development of novel treatments [47].

The multidimensional approach to bipolar disorder encourages continuous tracking of core symptoms, including activity, cognition, emotion, and sleep. For example, Merikangas and colleagues adopted mobile monitoring technology to assess activity, energy, mood and sleep in patients with bipolar disorder in real time [48]; additionally, the dynamic interaction among these domains could also be investigated.

1.4 Circadian rhythm disruption in bipolar disorder

Chronobiological models suggest that disruption of the circadian rhythm might be central to bipolar disorder pathogenesis, as well as one of the hallmarks of the disorder [4].

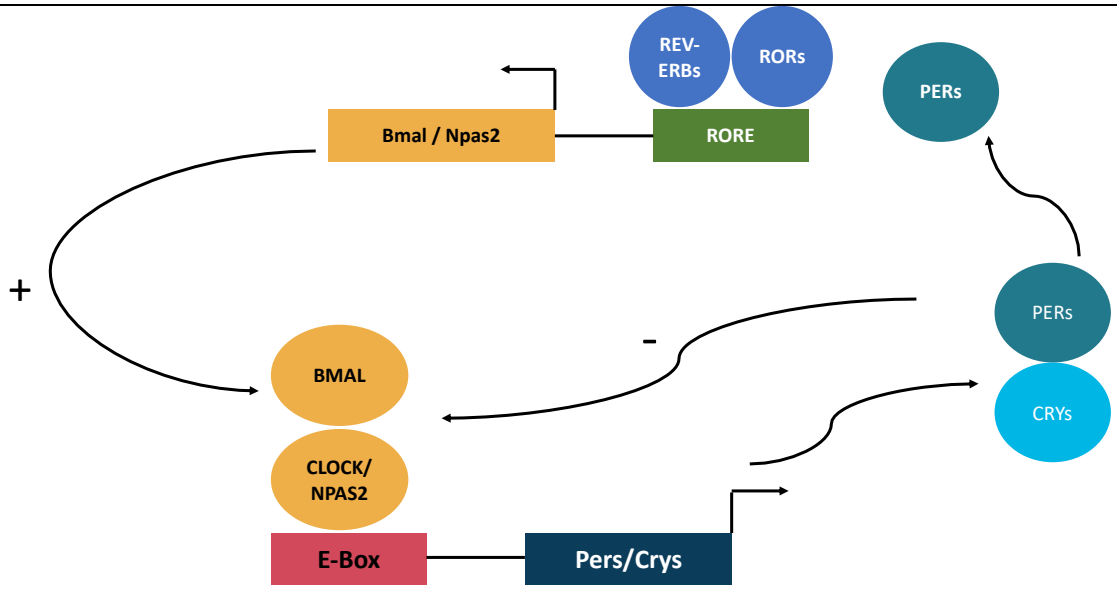
1.4.1 A brief overview of circadian rhythm

Circadian rhythms are biological rhythms with a period of approximately 24 hours in human beings and are generated by an intricate, hierarchical timing system [49]. Autoregulatory molecular clocks serve as the foundation of this internal timing system [50]. Organs and tissues have their own autoregulatory molecular clocks, controlled by the central pacemaker, the suprachiasmatic nuclei (SCN) [51]. Additionally, this internal timing system is entrained to the day-light cycle by external time cues which include light, food, and physical activity. [51, 52].

The molecular clock

Transcriptional-Translational Loops (TTL) serve as the foundation of the molecular clock. The TTL includes one positive arm and one negative arm, with the two being interconnected (see Figure 1). In the negative arm, transcriptional activators CLOCK (NPAS2 in the brain) and BMAL activate the clock genes Period and Cryptochrome. The protein CRYs and PERs inhibit transcription by binding to CLOCK(or NPAS2) and BMAL [50, 51]. In the positive arm, nuclear receptors REV-ERB and ROR regulate the transcription of the genes Bmal and Npas2 [51]. The protein PER2 interacts with REV-ERB receptors, connecting the two arms of the pathway [53]. One cycle of activation and inhibition of clock genes expression takes approximately 24 hours. It is beyond the scope of this chapter to discuss the molecular clock in more detail.

Figure1. 1 Simplified scheme of the molecular circadian clock



This figure is adapted from Landgraf et al. [50] and Albrecht et al. [51]

Suprachiasmatic Nuclei (SCN) and other pacemakers

The SCN are components of intricate neuronal circuits that integrate light, metabolic signals, and reward signals to regulate circadian rhythm [51]. Located in the anterior hypothalamus, SCN cells are not homogeneous, but rather a group of functionally and phenotypically differentiated cells [54]. These cells coordinate with each other through neurochemical signals, including vasoactive intestinal polypeptide, gamma aminobutyric acid, and ghrelin- releasing peptide to regulate the overall circadian rhythm [55]. Additionally, the ventrolateral SCN receives light information through intrinsically

photosensitive retinal ganglion cells (ipRGCs) mediated through the retinohypothalamic tract [51].

Sleep-wake cycle homeostasis

The regular cycle of sleep and wakefulness is the most obvious 24 hour of behaviour. The sleep-wake cycle is governed by the balance between two processes, the circadian process (process C) and sleep-wake homeostasis process (process S). Process C determines the biologically appropriate time to sleep and be awake. As a consequence of process S, sleep pressure increases during waking hours and peaks around bedtime; it then drops during sleep [56]. This two-process model may therefore aid in understanding sleep disturbances in bipolar disorder.

1.4.2 Circadian function measurements

In this thesis, emphasis is placed on circadian rhythm measures with real-world, clinical applicability, as these measures can easily be applied in future clinical research and clinical practice. The most commonly used means of measuring circadian rhythm in patients with bipolar disorder are actigraphy, melatonin assessment, and self-report questionnaires [57]. Actigraphs are wearable accelerometers that measure the timing and the structure of circadian rest-activity patterns [58]. The circadian rest-activity pattern is represented by a sinusodial wave [59]. The term amplitude refers to the difference between the maximum or minimum and the mean of the sinusoidal wave [60]. The term phase is the timing of the reference point (peak or trough) of a sinusoidal wave [60].

Actigraphy and melatonin measures are commonly used to measure the amplitude of circadian rhythm. M10 and L5 are two variables generated from non-parametric analysis of actigraphy data to quantify circadian rest-activity [61]. M10 corresponds to total activity in the most active ten-hour period, a proxy for daytime activity. L5 represents total activity in the least active five-hour period, a proxy for night-time activity. Melatonin is one of the most robust central circadian timing indicators [62]. The amplitude of an individual's 24-hour melatonin profiles can be used as a measure of the amplitude of the circadian rhythm. In addition, the relatively large variations in melatonin synthesis among individuals must be taken into account when using this method .

Dim light melatonin onset (DLMO), sleep midpoint and actigraphy are commonly used to measure circadian phase. The DLMO represents the onset of melatonin synthesis and secretion, which is the most reliable circadian phase marker [57]. Sleep midpoint, defined as (sleep onset time - wakeup time)/2, is another reliable circadian phase marker. Sleep midpoint can be calculated from the Munich Chronotype Questionnaire (MCTQ) and a sleep diary [63]. In addition, M10 onset time and L5 onset time are two phase-markers derived from non-parametric analysis of actigraphy data [57].

Chronotype, also known as Morningness-Eveningness, refers to the preference of individuals for the timing of daily activities, a behavioural manifestation of circadian rhythm [60]. Individuals who show greater morningness tend to be more alert in the morning and prefer morning activities; individuals displaying greater eveningness have an overall preference for evening activities. Chronotype is well correlated with circadian phase. For example, the degree of morningness (as measured by the Morningness-

Eveningness Questionnaire) was correlated with timing of DLMO, a biological marker of circadian phase [63].

Chronotype can be measured by self-report methods, including the Morningness-Eveningness Questionnaire (MEQ), the Composite Scale of Morningness (CSM), and the MCTQ [57]. MEQ is the most commonly used self-report method to measure chronotype, with higher scores indicating greater morningness [64]. CSM focuses on measuring the level of morningness and was developed based on existing chronotype questionnaires such as the MEQ [65]. The MCTQ has been developed to assess the circadian phase based on the timing of sleep; chronotype is calculated from mid-sleep time on days when the subject is not at work [57].

1.4.3 Circadian disruption in bipolar disorder

Circadian disruption is one of the hallmarks of bipolar disorder [3]. The term circadian disruption describes a variety of disturbances in the amplitude and phase of circadian rhythm. In comparison with healthy individuals and patients with bipolar depression, patients with bipolar disorder in a manic state have a higher mean activity level and greater variability of circadian rest-activity [66]. During euthymia and depression, patients with bipolar disorder have a lower mean activity level compared with healthy individuals [67]. In addition, a less stable circadian rest-activity pattern has been found in patients with bipolar disorder [8].

A delayed circadian phase has been found in patients with bipolar disorder. A systematic review concluded that patients with bipolar disorder had an eveningness chronotype [8]. In

another study, one-third of patients with bipolar disorder met criteria for circadian rhythm sleep-wake disorders, the majority of whom meet the criteria for delayed sleep-wake phase disorder [68]. Furthermore, patients with bipolar disorder were found to have a significantly delayed onset of melatonin compared to with patients with unipolar depression [69]. One possible explanation is that patients with bipolar disorder are more sensitive to light at night compared to healthy individuals, which results in a phase delay [70].

1.4.4 Sleep disturbance in bipolar disorder

Sleep disturbance could be an early marker for the development of bipolar disorder. One systematic review suggested individuals at risk for bipolar disorder showed poor sleep quality and circadian rhythm disruption [71]. When children of patients with bipolar disorder were studied, those with poor sleep quality were reported to have a higher risk of developing bipolar disorder than those whose sleep was not disturbed [72, 73].

Sleep disturbances are present at all phases of bipolar disorder and they manifest differently at each phase of the illness [74, 75]. During a manic or hypomanic episode, most patients with bipolar disorder report a reduced need for sleep [12]. Additionally, in manic episodes, a shorter total sleep time has been observed [76], which is not solely due to a reduced need for sleep, but is caused by an increase in energy and activity levels [77]. In euthymia, patients with bipolar disorder have significantly longer total sleep time, longer sleep onset latency, and longer time spent in bed [78]. Insomnia and hypersomnia are both common symptoms in bipolar disorder, and both are present during all phases. A cross-sectional study conducted in Norway found that patients with bipolar II disorder in

depressive episodes were more likely to exhibit insomnia, whereas patients with bipolar I disorder in depressive episodes or euthymia were more likely to report hypersomnia [74].

1.5 Cognitive impairment in bipolar disorder

1.5.1 The type, prevalence, and psychosocial consequences of cognitive impairment in bipolar disorder

Cognitive impairment is another symptom frequently observed in patients with bipolar disorder regardless of their illness phase. In the manic, mixed or depressive state, significant cognitive deficits have been found in domains of attention, executive function, verbal learning, and memory [79]. A systematic review found that approximately 10%-50% of patients with bipolar disorder in euthymia had impairments in attention/working memory, executive function, and verbal and visual memory [80].

In addition, cognitive impairment can also be observed in biological relatives of patients with bipolar disorder. In a recent systematic review, first-degree relatives of patients with bipolar disorder were found to have impaired cognitive functions in areas such as processing speed, verbal fluency and executive function compared with healthy individuals [81].

Cognitive impairment is associated with poor psychosocial functioning and employment outcomes in patients with bipolar disorder. There is considerable evidence indicating that cognitive dysfunction reduced general functioning in patients with bipolar disorder [82, 83]. A longitudinal study assessing cognitive function and psychosocial functioning one

year and two years after baseline assessment suggested that cognitive function and psychosocial functioning were causally related [84]. Additionally, cognitive function was shown to be a significant predictor of favourable employment outcomes [85].

1.5.2 Trajectories of cognitive functioning in bipolar disorder

It is not possible to predict the cognitive trajectory of a patient with bipolar disorder, as current studies demonstrate several trajectories are possible. In cross-sectional studies, more significant cognitive impairments have been found in bipolar patients with a greater number of mood episodes [86, 87]. Additionally, a case-register study found an association between an increased risk of dementia and the number of affective episodes in bipolar disorder [88]. These findings suggest a neuroprogressive cognitive course of bipolar disorder. However, cross-sectional studies do not determine causality. Patients with severely impaired cognition and a greater number of mood episodes may represent a more severe subgroup of patients with bipolar disorder, rather than the result of illness progression. Longitudinal studies in general do not support a neuroprogressive cognitive course of bipolar disorder. A recent systematic review on the longitudinal cognitive performance among recent-onset patients with bipolar disorder and late-life patients with bipolar disorder showed no decline in cognitive function [89]; however, the average follow-up period in this systematic review was less than three years, which may not be long enough to detect cognitive decline. Taken together, these studies suggest repeated episodes may play a role in cognitive decline in patients with bipolar disorder. For example, in a recent longitudinal study with five-year follow-up, cognitive decline was not found in the entire cohort of bipolar disorder patients; a subgroup analysis demonstrated cognitive decline among those who had a greater number of manic episodes [90].

Therefore, there is a need to examine heterogeneity of cognitive outcomes over time, which will enable a better understanding of the cognitive trajectories of bipolar disorder [91].

1.5.3 Cognitive heterogeneity in bipolar disorder

Recent research has sought to identify different cognitive subtypes to understand the cognitive heterogeneity of bipolar disorder and to elucidate potentially different causes, trajectories and correlates of cognitive impairment. Burdick and colleagues identified three distinct cognitive subtypes in patients with bipolar disorder: intact, selectively impaired, and globally impaired [92]. These findings have been supported by other studies [93, 94]. Among euthymic patients, approximately 29%-48% displayed intact cognitive function, 12-40% displayed selective impairments in executive function, verbal learning, and working memory, and 12-40% displayed global impairments [92, 94, 95]. These distinct cognitive subtypes were associated with different premorbid functioning and trajectories of cognitive changes. Therefore, these result might help elucidate reasons for the heterogeneous cognitive trajectories of patients with bipolar disorder [96].

1.6 A brief overview of lithium treatment

1.6.1 Lithium – the gold-standard treatment for bipolar disorder

Lithium is the only true mood stabiliser and has been recognised as the gold-standard treatment for bipolar disorder [43]. Empirical evidence supports the superior effectiveness

of lithium as a treatment for managing bipolar disorder, and particularly in preventing relapses [97]. In addition, lithium has been reported to be effective in treating acute episodes and preventing suicide [98] [99].

Lithium has superior effectiveness in preventing both manic and depressive episode recurrence compared with other mood stabilisers, which is supported by comprehensive and thorough evidence from randomised controlled trials and observational studies [97, 100, 101]. Two other studies demonstrated the effectiveness of lithium in real-world settings, with patients prescribed lithium having the lowest rehospitalisation rate and achieving the longest duration of monotherapy [102, 103].

Lithium is also effective for treating acute episodes. When treating acute mania, the treatment goal is to control symptoms rapidly and avoid a depressive switch [98]. In a systematic review of randomised controlled trials, lithium was superior to placebo in treating acute manic episodes; there was little difference between lithium and other mood stabilisers or most antipsychotics in treating acute mania [104]. In bipolar depression, several international guidelines such as the Royal Australian and New Zealand College of Psychiatrists [105], the American Psychiatric Association [106], and the Canadian Network for Mood and Anxiety Treatments [107] favour lithium as the first-line monotherapy treatment for bipolar depression. Furthermore, the use of lithium in acute episodes has been shown to facilitate successful long-term treatment of bipolar disorder [108].

Robust evidence has demonstrated that lithium is the only mood stabiliser with an anti-suicidal effect [99]. In addition, ecological studies have reported an association between

lithium in drinking water and a reduced risk of suicide in the general population [109]. Further, a systematic review found that lithium's anti-suicidal effect might be independent of its mood-stabilising effect [109].

1.6.2 Adverse effects of lithium

Although the superior efficacy of lithium has been supported by robust empirical evidence, paradoxically, its use in treating bipolar disorder has declined over the last two decades [110]. The underutilisation of lithium can be attributed to a wide range of factors, including adverse effects on renal and thyroid functions, and perceived adverse effects on cognitive function [111]. The effects of lithium on cognitive function in patients with bipolar disorder will be discussed in greater detail in chapter six.

Lithium is known to cause toxicity in the kidney and thyroid. However, the actual risk to patients may be lower since some of the adverse effects can be treated and managed [112]. A systematic review, including both randomised controlled trials and observational studies, found that lithium use was related to hypothyroidism and reduced urinary concentrating ability; there was little evidence of clinically significant impairment of renal function and a low risk of developing end-stage renal failure [113]. Additionally, a nationwide population-based study found that long-term use of lithium was associated with an increased risk of chronic kidney disease, but not with an increased risk of end-stage chronic kidney disease [114]. Further, Kraszewska and colleagues showed no significant difference in thyroid function between patients with bipolar disorder who took lithium for 10-20 years and those who took lithium for more than 20 years; there was no evidence to support an association between lithium use duration and thyroid dysfunction

[115]. In order to minimize the risk of renal and thyroid side effects, regular monitoring and maintaining a lithium serum level at the therapeutic level are crucial [108].

1.6.3 Prediction of lithium response

The response to lithium treatment varies among patients with bipolar disorder. The Consortium on Lithium Genetics reported a trimodal distribution of response to lithium in patients with bipolar disorder, including full, partial, and non-responders [116]. In two studies, only 8.9%-30% of patients with bipolar disorder were considered to be full responders, with complete remission of mood episodes and satisfactory psychosocial functioning [1, 117]. Psychiatrists treating patients with bipolar disorder must take a 'trial and error' approach that requires that their patient take lithium for several months to determine the degree of response [2]. There is a need for reliable and reproducible biomarkers of lithium response in patients with bipolar disorder to avoid prolonged and ineffective treatment trials.

Currently, most of the predictors of lithium response are clinical factors. Patients presenting with ‘classic’ bipolar disorder are likely to respond well to lithium. The ‘classic’ bipolar disorder is characterised by recurrent, recognisable mood episodes with complete remission between episodes [118]. A recent systematic review reported clinical factors associated with good lithium response, including mania-depression-interval sequence, later illness onset, shorter illness duration before taking lithium, family history of bipolar disorder and lithium response, absence of rapid cycling and psychotic symptoms, and fewer mood episodes and hospitalisations before taking lithium [119]. A more recent systematic review limited its findings to high-quality studies and did not find

any robust predictors of good lithium response [2]. Thus, there is a need for reliable clinical predictors of lithium response.

Experimental studies have shed light on lithium response markers. Genome-wide association studies have been used to identify genetic variation associated with lithium response. Song and colleagues identified one genetic variant in SESTD1, a gene involved in regulating phospholipids, which impacted lithium's response [120]. The International Consortium on Lithium Genetics found one locus related to long, non-coding RNAs was associated with lithium response [121]. Polygenic score analysis of psychiatric traits has been used to determine the genetic markers of lithium response. It has been shown that patients with low polygenic loads for major depression or low polygenic loads for schizophrenia respond well to lithium therapy [122, 123]. Epigenetic signatures can also be helpful to identify lithium responders. For example, one study found that different DNA methylation profiles successfully differentiated lithium responders from lithium-non responders [124].

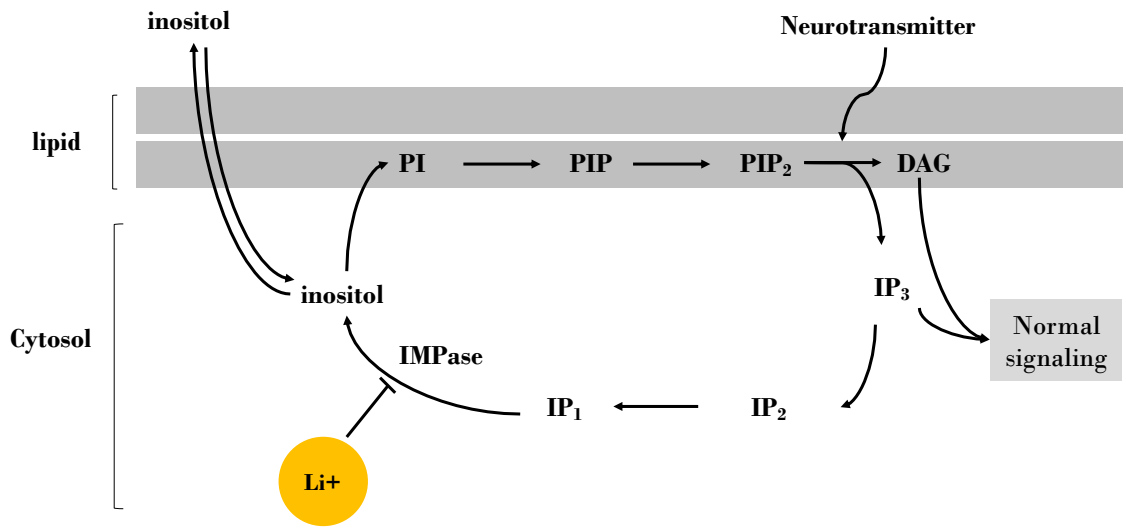
Induced pluripotent stem-cells are also useful tools to investigate the response to lithium. Neurons derived from both fibroblasts and lymphocytes of patients with bipolar disorder displayed a hyperexcitability pattern which was reduced by lithium only in lithium-responsive bipolar patients [125, 126]. In a subsequent study, it was found that downregulation of LEF1, a transcriptional factor, contributed to the inability of lithium to reverse hyperexcitability in neurons from lithium non-responsive bipolar patients [127]. These data from pluripotent stem-cell studies are based on relatively small samples and will require additional replication.

1.6.4 The mechanism of action of lithium

Lithium has the most specific clinical effects in psychiatry; paradoxically, its pharmacological effects are very complex and the mechanism of action of lithium is only partially understood. It is probable that lithium impacts a complex regulatory network with multiple key nodes, including monoaminergic signalling, cAMP signalling pathway, phosphoinositide signalling pathway, glycogen synthase kinase, and intracellular calcium [128].

Among these mechanisms, inositol depletion appears to be the most promising explanation for the clinical effectiveness of lithium. It is hypothesised that phosphoinositide signalling is overactive in patients with bipolar disorder. Lithium inhibits inositol monophosphatase (IMPase), resulting in reduced inositol and impaired IP_3 regeneration (see Figure 2)[29]. In rodent bipolar disorder models, ebselen, an IMPase inhibitor, produced lithium-like behaviours that were reversed by inositol administration [129]. Furthermore, a phase 2a randomised, double-blind, placebo-controlled trial reported some efficacy of ebselen in treating patients with mania or hypomania [130]. While these data provide promising information about the mechanism of action of lithium, phosphoinositide signalling studies in patients with bipolar disorder using magnetic resonance spectroscopy do not consistently demonstrate overactive signalling and reduced inositol after lithium treatment; additional studies are needed to probe this hypothesis [131].

Figure1. 2 A simplified diagram of the phosphoinositide cycle.



Abbreviation: PI: phosphatidylinositol; PIP: phosphatidylinositol phosphate; PIP2: phosphatidylinositol-4,5-bisphosphate; DAG: diacylglycerol; IP_s: inositol phosphates, with subscript numbers indicate the number of attached phosphate groups; IMPase: inositol monophosphatase. Two arrows indicate the movement of inositol across the plasma membrane. This figure is adapted from Geddes et al. chapter 69 [29] and Saiardi et al. [132].

A major limitation of current studies on the mechanism of action of lithium is that most of the findings have been generated from studies of animal models, healthy participants, and post-mortem brains of patients with bipolar disorder. Animal models for bipolar disorder have faced several challenges that reduce their validity. The recurrent nature of bipolar disorder has not been able to be reproduced in animal models [133]. In addition, studies using animal models do not replicate the conditions in which lithium is used in clinical settings with patients: the dose of lithium administered in animal models has been much higher than the therapeutic range for lithium and the treatment durations were much shorter in animal studies than in clinical cohorts of patients with bipolar disorder. Findings from healthy participants may not be relevant for the mechanism of action of lithium in patients with bipolar disorder. Studies on the mechanism of action of lithium using post-

mortem brain tissue are complicated to analyse because they contain many samples from patients who were lithium non-responders and who have other psychiatric comorbidities. In addition, these studies may be compromised by incomplete clinical information [128]. As such, the field requires more prospective, longitudinal studies conducted in clinical cohorts of patients with bipolar disorder.

1.7 Digital phenotyping

The rapid development of information science and technology has made digital phenotyping a valuable tool for characterising phenotypes of psychiatric illness [134]. Digital phenotyping is a method of quantifying individual human phenotypes moment-to-moment by analysing data from digital devices [135]. There are two major methods of collecting data, passive monitoring and active assessment. Passive monitoring automatically acquires data on the physical state and behaviour of an individual. As an example, a wrist worn device known as an actigraph has been widely used for analysing motor activities and assessing circadian rhythm and sleep patterns [136]. Active assessments are used to supplement passive assessments by examining mood symptoms, subjective experience, and cognitive function. For example, the ecological momentary sampling method is the most common technique for assessing day-to-day mood changes and other psychological states [136]. With both methods of assessment, high-resolution phenotypes, using physical and psychological data pertinent to psychiatric disorders, can be elucidated.

In experimental medicine studies, digital phenotyping can be used to track real-time changes in circadian rhythms, mood symptoms, and cognitive function, all of which are

important to measure when considering the multi-dimensional view of bipolar disorder. In addition, the interrelationships between these different domains can be examined. In this thesis, digital phenotyping was applied to patients with bipolar disorder treated with either lithium or placebo. The short-term impact of lithium on circadian rhythms, mood, and cognitive functions of patients with bipolar disorder was evaluated using multimodal, time-stamped data generated from actigraphy, ecological momentary sampling, and interactive cognitive tasks.

Chapter 2: Effect of lithium on circadian rhythm in bipolar disorder: a systematic review and meta-analysis

"How this, the sparkler in the night's black field, lighting up my brain with love"- Erlichman, Shira. Odes to Lithium

This chapter has been published in the *Bipolar Disorders* "Effect of lithium on circadian rhythm in bipolar disorder: A systematic review and meta-analysis"[137]

2.1 Introduction

As discussed in chapter one, lithium is a first-line treatment for bipolar disorder. However, not every patient with bipolar disorder responds well to lithium. One recent naturalistic observation study found that less than one-third of bipolar patients who took lithium showed a full response to the treatment [1]. Few proposed predictors of individual responsiveness based on clinical profiles have been identified [119]. However, these predictors lack robustness and are not applicable to clinical practice. As a result, patients with bipolar disorder are frequently forced to take a 'trial and error 'approach, which involves a commitment to take lithium for several months to discover the degree of individual's treatment response. To avoid prolonged and ineffective treatment trials in bipolar patients with a low chance of benefit from lithium treatment, reliable and reproducible biomarkers of lithium response are needed [2].

Circadian biomarkers are prime candidates for predictors of lithium response [138]. As discussed in chapter one, disrupted circadian rhythms play pivotal roles in the onset, symptom expression, and course of bipolar disorder. There is copious evidence from cell lines, animal models, and human studies to support a link between lithium and circadian rhythm.

2.1.1 Evidence from cell lines

Circadian rhythm in mammals is organised by a hierarchy of circadian oscillators in many different tissues throughout the body, with a master clock located in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus (more detail in chapter 1 section 1.2.1). SCN coordinate the inputs from the internal circadian timing system and environmental signals and entrain the circadian rhythm to the solar day [49]. Abe and colleagues showed that lithium acted directly on the mice SCN tissue to lengthen the circadian period of individual neurons [139]. Johansson and colleagues investigated the effect of lithium on rhythmic expression of PERIOD 2, the clock gene protein, in the SCN tissues obtained from transgenic PERIOD2::LUCIFERASE (PER2::LUC) knock-in mice. Lithium delayed the phase and lengthened the period of the PER2::LUC rhythm in mice [140].

Fibroblast cell line cultures can be utilized to investigate cellular circadian rhythm as fibroblasts can pass circadian timing to daughter cells [141]. Utilizing skin fibroblasts provides an additional advantage as they can be easily harvested from biopsies taken from patients. In skin fibroblasts from bipolar patients, lithium lengthened the period of PER2::LUC rhythm at a concentration ten times higher than its use in clinical practice [142]. Two recent studies using fibroblast cultures added additional support the hypothesis

that lithium responsiveness and the cellular circadian phenotype are linked. The period-changing effect of lithium was associated with the underlying circadian phenotype and patients with a longer period of the cellular circadian rhythm at baseline showed poorer responsiveness to lithium treatment [143, 144]

2.1.2 Evidence from animal models

Animal models have been widely used to investigate mood disorders because the behaviour profiles of the animal models have been shown to be comparable to the symptoms of patients with mood disorders [50]. Thus, animal models can be a valuable tool to elucidate the mechanism of action of lithium treatment. In mammalian cells, autoregulatory transcriptional-translational feedback loops (TTLs), which regulate rhythmic expression of core clock genes, constitute the foundation for circadian rhythm. CLOCK, the transcriptional activators, is one essential component of the core TTLs [50]. Clock- Δ 19 transgenic mice are created by N-ethyl-N-nitrosourea (ENU)-induced point mutation in exon 19 of the circadian gene Clock, producing a dominant-negative CLOCK protein [145, 146]. Clock- Δ 19 mice display a series of behaviour phenotypes including disrupted circadian rhythm, decreased sleep, hyperactivity, increased cocaine preference; these symptoms are very similar to patients with bipolar disorder in the manic state [147]. Chronic lithium treatment reversed these manic-like behaviours to wild-type levels [147, 148]. In another transgenic mouse model, forebrain-specific defects of mitochondrial DNA are created. The mice demonstrated disrupted circadian rhythm, which was ameliorated by lithium treatment [149]. Lastly, Sawai and colleagues adopted an innovative in vivo study design to continuously monitor the peripheral clock gene expression rhythms. Lithium was found to prolong the period of the peripheral clock gene expression rhythms in mice [150].

2.1.3 Evidence from human studies

In patients with bipolar disorder, studies investigating genetic influences on circadian rhythm have demonstrated the essential role of circadian rhythm regulation on the mechanism of action of lithium and on lithium responsiveness. Despite the lack of reproducibility and power in some of the studies, these early pharmacogenomic studies reveal the role of circadian genes including NR1D1, GSK3b, CRY1, ARNTL, TIM, PER2 on patient's responsiveness to lithium [151-154]. Papiol and colleagues conducted formal gene set enrichment analyses for circadian clock genes in the context of psychiatric traits and clinical response to lithium (both continuous and dichotomous). Significant enrichment of a set of circadian clock genes was found in the dichotomous lithium response phenotype, but not in any other psychiatric traits [155]. These circadian biomarkers could potentially serve as predictors of lithium response in humans.

2.1.4 Major limitations in the field

Although studies from cell lines, animal models, pharmacogenomics studies in patients with bipolar disorder have given credence to the effect of lithium on circadian rhythm, there are three major limitations in this field. First, knowledge obtained from cell lines, animal models and human studies has not been translated to bipolar patients. For example, Moreira and Geoffroy conducted a systematic view examining the impact of lithium on circadian rhythm and found few studies included bipolar patients [156]. Second, pharmacogenetic findings have not been translated into circadian phenotypes [157]. Third, circadian measurement tools with real-world applicability have been underused. The

International Society for Bipolar Disorders Chronobiology Task Force recommends actigraphy, self-report methods, and melatonin measurements [57].

Therefore, we have conducted a systematic review to answer the question of whether lithium has an impact on circadian rhythm in bipolar patients. We included both experimental and observational studies where the primary outcome was circadian rhythm measurement using validated tools with real-world applicability. The findings of this chapter foreshadow further exploration of lithium's effect on circadian rest-activity in chapter four and chapter five.

2.2 Method

This review is reported in accordance with PRISMA guideline [158] and the study protocol was registered on PROSPERO (CRD42018109790)

2.2.1 Search strategy

We searched electronic databases including Cochrane Library, EMBASE, MEDLINE, PsycINFO, clinicaltrials.gov website for published and unpublished trials from the inception of the databases until Sep 28th, 2018. We also searched PubMed from Sep 28th, 2018 to Sep 17th, 2020. No restrictions of language were imposed. The reference lists of included studies and systematic reviews in the field were screened for additional eligible studies.

The following search terms were used in databases mentioned above:

("Bipolar Disorder" OR "Bipolar Depression" OR "Manic Depression" OR "Bipolar Affective Disorder" OR "Bipolar Mood Disorder")

AND

(Lithium OR Calith OR Camcolit* OR Carbolit* OR Ceglution OR Duralith OR Durolith OR Eskalith OR Hypnorex OR Hynorex OR Hyponrex OR Lentolith OR Licab OR Licarb OR Licarbium OR Lidin OR Lilipin OR Li?liquid OR "Li-liquid" OR Lilitin OR Limas OR Liskonum OR Litarex OR Lithan OR Lithane OR Litheum OR Lithicarb OR Lithionate OR Lithizine OR Lithobid OR Lithocarb OR Lithocap OR Lithonate OR Lithosun OR Lithotabs OR Litheril OR Litilent OR Manialit* OR Maniprex OR Phanate OR Phasal OR Plenur OR Priadel OR Quilonium OR Quilonorm OR Quilonum OR Teralithe OR Theralite)

AND

("Circadian Rhythm*" OR "Circadian Clock" OR Sleep OR "Sleep Disorder*" OR Chronotype OR "Biological Rhythm*" OR "Chronobiology Disorder*" OR Chronotherapy OR "Chronobiology Phenomena" OR "Biological Clock" OR "Sleep Wake Disorder*" OR "Sleep Wake Cycle*")

2.2.2 Inclusion and exclusion criteria

Participants:

We included patients with a primary diagnosis of bipolar disorder according to standardised 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, sex, country,

phase of illness, subtype (type I, type II, rapid cycling, not otherwise specified) and clinical setting.

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 [159].

Comparators:

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

Types of studies：

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

Primary outcomes：

1. Circadian rest-activity measured by actigraphy, considering the following ten measures: (i) Intradaily variability (IV), (ii) Interdaily stability (IS), (iii) the average activity during the most active ten-hour period (M10), (iv) the average activity during the least active five-hour period (L5), (v) M10 onset time, (vi) L5 onset time, (vii) Relative amplitude. The following three parameters generated by Cosinor rhythmometry analyses, an approach fit a sinusoidal wave with a period of 24 hours to the actigraphy data [160]. (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 [59].

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[161]. 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[162].
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)[163] .

2.2.3 Data extraction and quality assessment

Two review authors (Ni Xu and Kiyomi Shinohara) 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 (Andrea Cipriani). If data were unavailable from published reports, authors were contacted.

The quality of each included study was evaluated by two independent review authors (Ni Xu and Kiyomi Shinohara). When disagreements occurred, the two review authors had a discussion and formed a consensus. We used AXIS tool for cross-sectional studies. The AXIS is a critical appraisal tool with 20 questions about study design, potential bias, quality of reporting and transparency [164]. Since cut-offs for study quality have not been established for the AXIS tool, we decided that a study with four or less "No" criteria represented a high-quality study; this protocol is similar to one utilised in previous study [165]. The quality of cohort studies was assessed utilizing the Newcastle-Ottawa scale [166] on a scale from zero to nine stars, with a high-quality cohort study represented by eight or nine stars [167]. For randomized controlled trials, the Cochrane Risk of Bias Tool was used to assess risk of bias [168]

2.2.4 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, standardised 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 [169]. Expecting substantial heterogeneity among studies, we decided to pool the data using random-effects model,

which assumes the effects being examined are not identical in different studies, but follow certain distribution [170]..

2.2.5 Changes to protocol

We changed one of the secondary outcomes 'Changes on 24-hr melatonin and cortisol concentration of patients from baseline' into 'Daily profiles of cortisol and melatonin levels in order to be consistent with the literature. We did not conduct the literature search on World Health Organization International Clinical Trials Registry Platform (WHO ICTRP): www.who.int/ictrp .

2.3 Results

2.3.1 Study selection

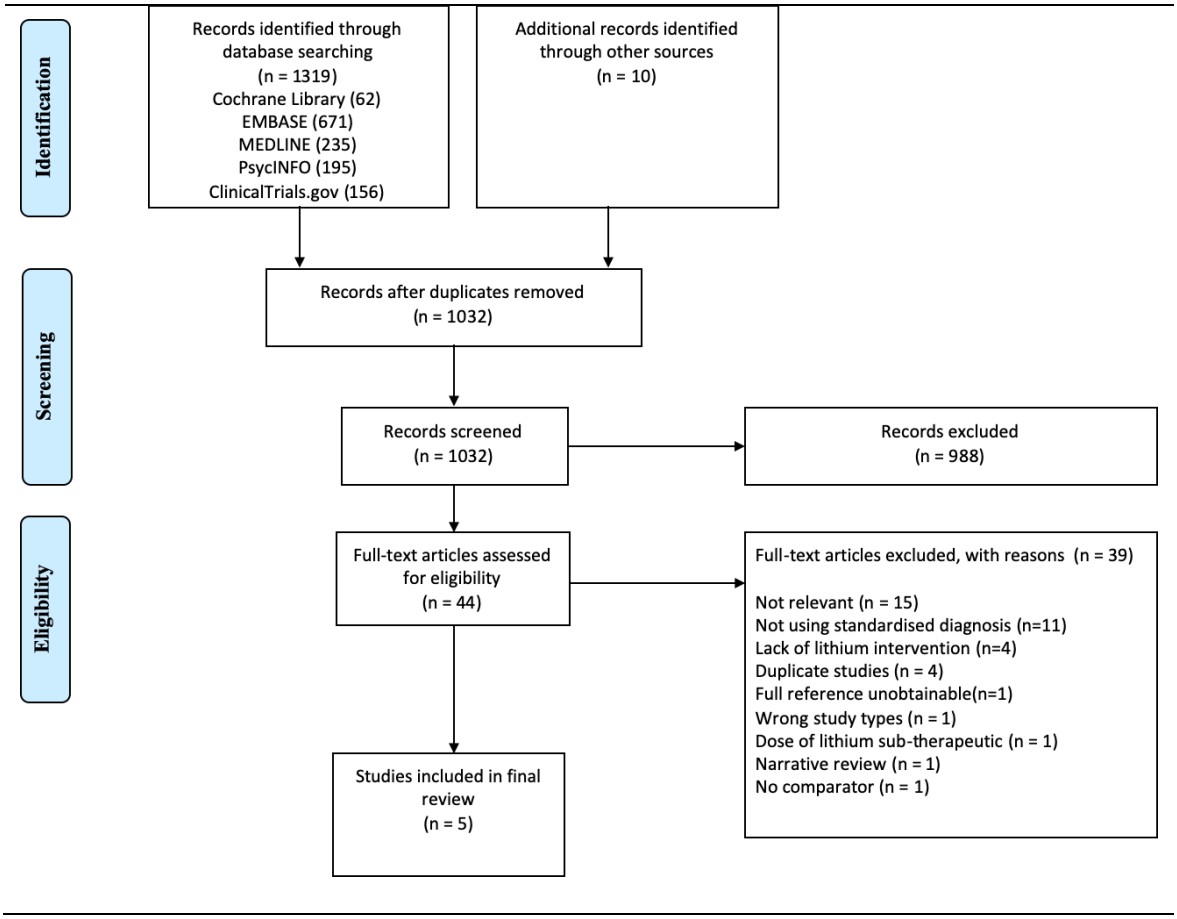
Our initial electronic searches, together with screening the reference lists of relevant records, yielded 1319 potentially relevant studies (Figure 1). After removing duplicates, we screened the title and abstracts of 1032 studies. Of these, 44 full texts were retrieved and assessed. After excluding 39 studies that did not fully meet the eligibility criteria, we included 5 independent studies, described in 9 published articles. Kim et al and Hwang et al [171, 172] are reports from the same study, each reporting different outcome measurements with Hwang selected on patients with BD II for its final analysis.

2.3.2 Description of included studies

All included studies were published from 2014 to 2018. Four of the included studies were observational studies (three cross-sectional studies [173-175] and one cohort study [176]) and the fifth was an 8-week, non-blind randomised controlled trial [172]. 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 euthymic[174-176]; the other two studies recruited patients who were experiencing a current mood episode[172, 173]. Four studies recruited from outpatient settings and a fifth from both outpatient and inpatient settings[172]. Five studies had between 29 and 525 participants, and only one study recruited more than 100 participants[174]. Hwang et al and Benizri et al compared lithium monotherapy with another mood stabiliser [172, 176], whereas the other three studies compared two groups with multiple medications, one took lithium, the other did not[173-175].

Figure 2. 1 PRISMA flow diagram



Study (Author, Year)	Methodology (Type of study)	Follow-up	Diagnosis & Mood state & Setting	Mean Age (SD)	Gender (%	Treatment （dose）	Number of	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	Tot: 46.6 (not reported	Tot: 43%	Lithium Other medication except lithium	Li: 13 Other: 40	MEQ scores
Dopierała 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)	Li: 27 Other: 27	CSM scores
Hwang 2017	RCT	8 weeks	Inpatients and outpatients with a DSM-IV diagnosis of bipolar II disorder and a current depressive episode (Hamilton Depression Rating Scale 17-item score [HDRS-17] ≥	Li: 32.7 (8.7) Que: 37.2	Tot: 52% Que: 70%	Lithium monotherapy (serum lithium level was maintained at 0.8 to 1.2 mM)	Li: 15	Actigraphy measures: acrophase, amplitude, mesor
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	Li: 52% Other:61	Lithium No lithium (with other mood	Li: 149 Other:	CSM total scores PSQI total scores
Benizri2015	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
Kim2014	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 mM)	Li: 17	PSQI scores

Table 2. 1 Characteristics of included studies.

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

2.3.3 Quality assessment

No included studies were scored as high quality using the Cochrane Risk of Bias Tool, AXIS tool, and Newcastle-Ottawa scale. Using the Cochrane Risk of Bias Tool, it was determined that the randomised control trial has a high risk of bias due to blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and other sources of bias like sponsorship bias (see Table 2). The cohort study reported unclear information about the follow-up (Table 3) and in all three cross-sectional studies there were limited measures undertaken to address and categorise non-responders which were susceptible to reporting bias (see Table 4).

Table 2. 2 Cochrane risk of bias

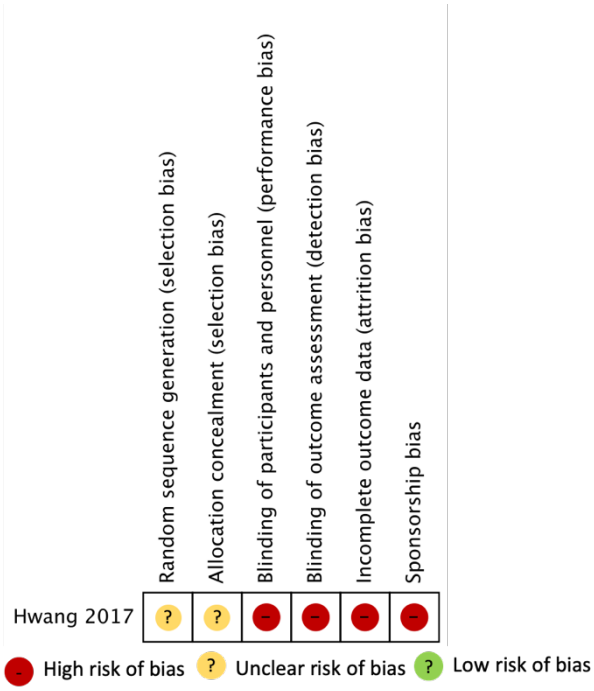


Table 2. 3 Quality assessment based on the Newcastle-Ottawa Scale of cohort study included in this systematic review

Studies	Selection	Comparability	Outcome	Total stars
Benizri 2015	★★★	★	★★	6

Table 2. 4 Quality assessment based on the AXIS tool for cross-sectional studies included in this systematic review

Introduction	Kanagarajan 2018	Dopierała 2017	Geoffroy 2016
1. Were the aims/objectives of the study clear?	√	√	√
Method			
2. Was the study design appropriate for the stated aim(s)?	√	√	√
3. Was the sample size justified?	×	×	×
4. Was the target/reference population clearly defined? (Is it clear who the research was about?)	√	√	√
5. Was the sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation?	√	√	√
6. Was the selection process likely to select subjects/participants that were representative of the target/reference population under investigation?	×	√	√
7. Were measures undertaken to address and categorise non-responders?	×	×	×
8. Were the risk factor and outcome variables measured appropriate to the aims of the study?	√	√	√
9. Were the risk factor and outcome variables measured correctly using instruments/measurements that had been trialled, piloted or published previously?	√	√	√
10. Is it clear what was used to determined statistical significance and/or precision estimates? (eg, p values, CIs)	×	√	√
11. Were the methods (including statistical methods) sufficiently described to enable them to be repeated?	√	√	√
Results			

12. Were the basic data adequately described?	√	√	√
13. Does the response rate raise concerns about non-response bias?	×	×	×
14. If appropriate, was information about non-responders described?	√	×	×
15. Were the results internally consistent?	√	√	√
16. Were the results for the analyses described in the methods, presented?	√	√	√
Discussion			
17. Were the authors' discussions and conclusions justified by the results?	√	√	√
18. Were the limitations of the study discussed?	√	√	√
Other			
19. Were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results?	×	×	×
20. Was ethical approval or consent of participants attained?	√	√	√

2.3.4 Circadian rest-activity

Only two studies evaluated the impact of lithium on circadian rest-activity using actigraphy. In the randomised 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 [172], 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.

2.3.5 Sleep quality

Polysomnography (PSG) is widely considered as the gold standard of measuring sleep objectively[161]. All included studies adopted the Pittsburgh Sleep Quality Index (PSQI) rather than PSG[171, 174]. The randomised 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[171]. 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) [176]. 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 [174].

2.3.6 Chronotype

Four observational studies reported data about chronotype and we meta-analysed the results [173-176]. Three of included studies adopted CSM scale[174-176], the other one used the MEQ questionnaire[173]. Benizri et al. , a cohort study with 21-day actigraphy recording, measured chronotype using CSM questionnaire at one point in time [176]. 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 [173]. The meta-analysis provides 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).

Figure 2. 2 Morningness as a continuous measure on a validated chronotype rating scale in observational studies comparing lithium with other mood stabilizers except for lithium.

SD = standard deviation; CI = confidence interval; I^2, percentage of the variability in effect estimates due to heterogeneity.

2.4 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 are included, four of which are observational studies. The quality of evidence ranges from low to moderate. Bearing in mind these limitations, the main finding is that lithium treatment may be associated with greater morningness. We cannot confirm the potential beneficial effect of lithium on sleep quality. Lithium treatment may increase amplitude of circadian rest-activity rhythm.

2.4.1 Lithium is associated with greater morningness

Although substantial heterogeneity was found, the meta-analysis shows a potential association between lithium and greater morningness. The heterogeneity is not unexpected because the type of study and mood state are not the same between studies. Nevertheless, the direction of effect between lithium and greater morningness was consistent across studies. Most of the included studies are cross-sectional, precluding any valid conclusions about cause and effect. Thus, 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 stabilisers. 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 the Basic Language Morningness scale (BALM) for chronotype analysis, found that lithium-responsive BD patients showed higher levels of morningness compared with lithium non-responders [144]. Fibroblasts cells from lithium-responsive bipolar patients showed a short period of the cellular circadian rhythm [143, 144]. A higher level of morningness was found to be associated with a shorter period [177]. With a similarly long period, phase advance was

observed in lithium-responsive cells in comparison with lithium-nonresponsive cells [144]. 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 [144]. Another study showed that shifts towards morningness were related to reductions in depression, increases in positive affect and improvements in sleep quality in military veterans receiving brief behavioural treatment for insomnia [178]. 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 [144]. The shorter period was associated with an increased level of morningness [177]. Furthermore, lithium displayed more substantial period-shortening effect in bipolar patient fibroblasts with shorter periods [143]. 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 and changes in clinical practice. 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, randomised, placebo-controlled trials with a larger sample of bipolar patients treated with lithium, better control for mood symptoms and sleep quality are required to allow causal inferences to be made. Patients were followed at least six months to identify lithium-responsive bipolar patients. chronotype can be measured by self-report methods including Morningness-Eveningness Questionnaire (MEQ), Composite Scale of Morningness (CSM), Munich chronotype questionnaire (MCTQ) [57]. For more accurate circadian timing measurements, the dim light melatonin onset (DLMO) measurement, actigraphy together with daily diary measures can be used [57]. The ecological momentary sampling enables us to better control for mood symptoms and sleep quality [179].

Measurement of chronotype should also be considered as a part of the clinical assessment in bipolar disorder. First, eveningness increases the relative risk of lithium non-responsiveness [144]. Second, evening chronotype might be considered as a sub-phenotype in bipolar disorder, which was associated with an early age of onset, more prior mood symptoms, more comorbidities and past suicide attempt [180]. Finally, self-report chronotype measurements can be valuable tools for psychoeducation [57]. The content of psychoeducation and related intervention can be centred upon the results of the self-report measurements.

2.4.2 The effect of lithium on sleep quality is uncertain

While sleep dysregulation is well-documented in bipolar disorder [181], no consistent results on the effect of lithium on sleep quality were found in this systematic review. One included study Geoffroy et al. found significant lower PSQI scores in patients with BD I, women, but not men, receiving lithium treatment[174]. 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 [182]. In Kim et al. study [171], 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.

2.4.3 The effect of lithium on circadian rest-activity has not been well studied

There are limited studies exploring the effect of lithium on circadian rest-activity patterns 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 [176]. The effect of lithium on amplitude have 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 [142]. 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 [142, 183, 184].

2.4.4 Future directions for research

Three out 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[185, 186]. Thus, it is advisable to use both

subjective and objective measurements to assess the circadian rhythm in BD patients[187]. Actigraphy, as one of the objective measurements, has increasingly been used in assessing circadian rhythm in mood disorder[181, 188]. Actigraphy provides continuous objective measurement of movement over time, which could provide more details of circadian rhythm changes, improve assessment by reducing recall bias[58]. 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 [156, 189]. 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 [190, 191]. Moreover, the translational potential of lab studies were hampered by the fact that few studies have integrated prospective longitudinal monitoring of illness activity, assessing clinically relevant phenotype with the biomarker research [192]. 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 [193].

2.4.5 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 randomised controlled trial, so causal inferences cannot be made. Studies have small sample size. Except for Geoffroy et al, included studies had between 29 to 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 [194, 195].

2.4.6 Conclusions

There is a growing interest in the effect of lithium on circadian rhythm. Our meta-analysis suggests a possible association between lithium and greater morningness in bipolar patients. Chronotype could be a potential target of further exploration of the mechanism of action of lithium treatment and biomarkers or biosignatures of lithium responsiveness. 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 comprehensive circadian rhythm measurements to monitor daily changes of circadian rest activity. In chapter four and chapter five, further investigation on the effect of lithium on motor activity, the timing and variability of circadian rest-activity pattern using data from Oxford Lithium Trial will be discussed.

Chapter 3: Dataset: Oxford Lithium Trial

"What do my organs think of your soft arrival each day Who unlocks the door to let you in, like a wet cat How did you lift the heaviest season from my eyelids, sweeping away a whole cloud"

-Erlichman, Shira. Odes to Lithium

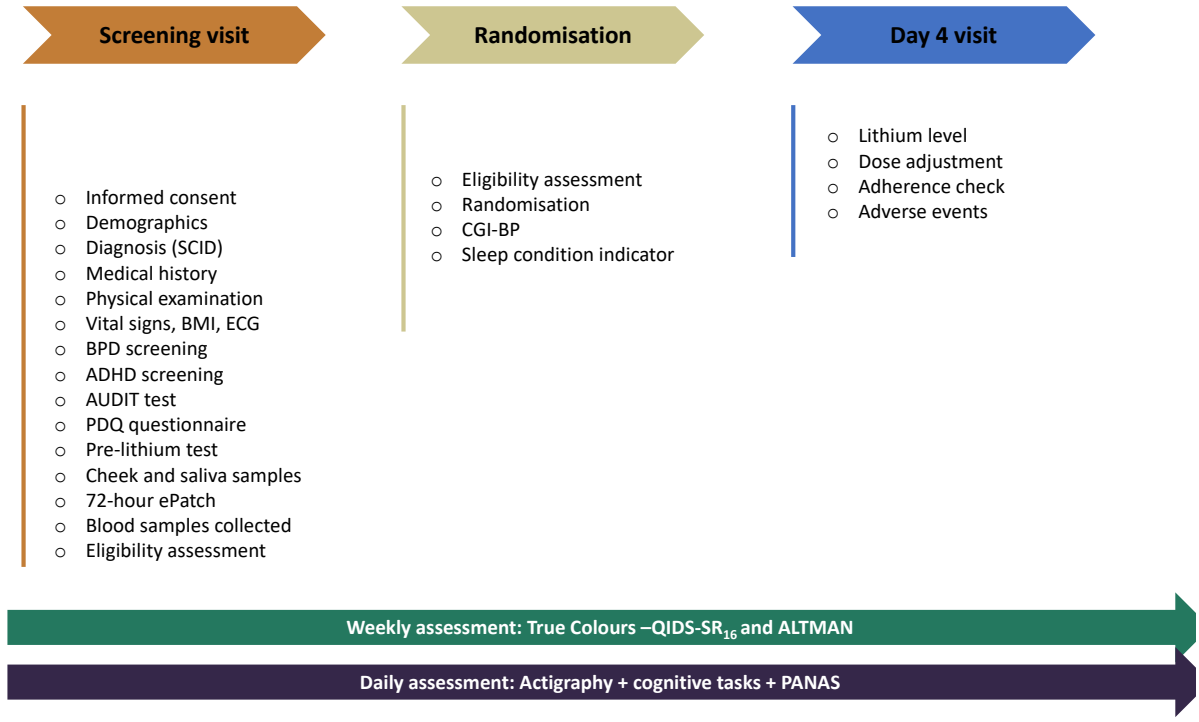
The purpose of this chapter is to introduce the Oxford Lithium Trial (Oxlith), a study that was developed to evaluate early affective, cognitive, neural, and biochemical effects of lithium among patients with bipolar disorder and current mood instability. Participants underwent deep phenotyping following short-term treatment with lithium or a placebo, including assessments related to mood, circadian function, and cognitive function. The primary outcome of Oxlith was mood severity and stability over the 6-week randomised period. This thesis contains empirical studies (chapters 4-6) that are secondary analyses of Oxlith data with two primary objectives: the first is to investigate whether lithium can reverse the circadian rhythm abnormalities commonly reported in patients with bipolar disorder, and the second is to examine whether lithium has an adverse effect on cognitive functioning in patients with bipolar disorder.

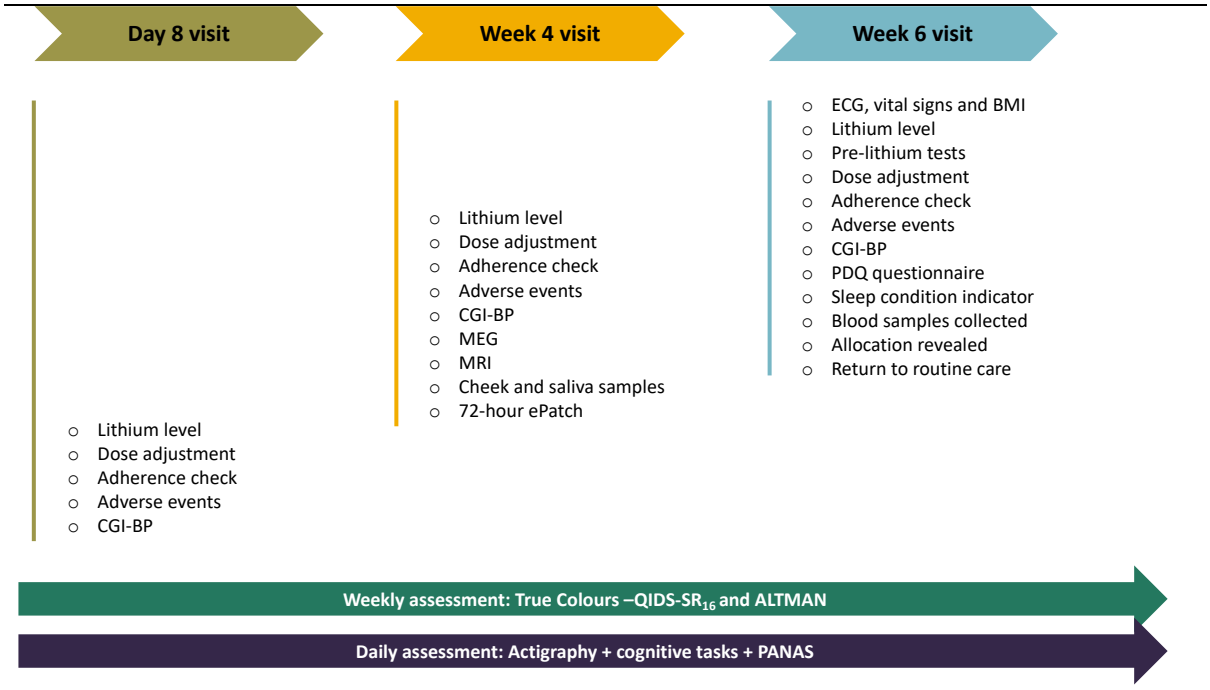
3.1 Study design

The Oxlith is a randomised, placebo-controlled, double-blind, six-week experimental study of lithium treatment in patients with bipolar disorder and mood instability [9]. During the trial,

routine psychiatric care was provided. Every participant had an intensive battery of multi-modal investigations including circadian rest-activity monitoring, cognitive testing, remote monitoring of mood, neuroimaging (fMRI and magnetoencephalography) as well as biochemical and genetic testing (Figure 1). At the end of the trial, participants returned to routine care.

Figure 3. 1 The Oxford Lithium Trial (Oxlith) study design





Abbreviations:

AUDIT, Alcohol Use Disorders Identification Test

BMI, Body Mass Index

CGI-BP, Clinical Global Impressions-Bipolar Scale

MEG, Magnetoencephalography.

PDQ, Perceived Deficits Questionnaire

SCID, Structured Clinical Interview for DSM-IV

3.1.1 Pre-randomisation phase

Participants who met the eligibility criteria entered the pre-randomisation phase, which lasted for approximately two weeks. The pre-randomisation phase enabled participants to be familiar with the daily and weekly digital symptom monitoring tools. At the screening visit, every participant completed the perceived deficits questionnaire (PDQ), True Colours registration and received an activity monitor and an iPad where cognitive tasks and daily

mood assessment were installed. In addition, demographic data, medical history, blood samples were collected.

3.1.2 Randomisation visit

At the end of the pre-randomisation phase, every participant attended a randomisation visit when they were randomly allocated to either the lithium or placebo group (see 3.1.2 for more details). Before the randomisation, each participant completed the sleep condition indicator questionnaire, and the psychiatrist assessed the severity of illness using Clinical Global Impression-Bipolar Disorder (CGI-BP).

3.1.3 Randomised phase visits

During the six-week randomised phase (including titration phase), participants attended four assessment visits at four days, eight days, fourth week (day 21-28), sixth week (day 35-42) post-randomisation. Lithium serum level, reported treatment adherence, and adverse events were checked at each visit. At the 8-day visit, the 4-week visit and the 6-week visit, the psychiatrist completed CGI-BP. At the 6-week visit, each participant completed PDQ and SCI. In addition, the psychiatrist opened the code-break envelop after finishing all necessary assessments and knew the allocated treatment. Then the psychiatrist discussed future treatment options with patients.

3.2 Randomisation and allocation concealment

Participants were randomised by a central web-based computer algorithm that minimised separately on two variables related to prognosis: age (<25 and >25) and gender (male and female). Each participant was randomised to either lithium or placebo group. All individuals involved in trial recruitment and assessment visits, including patients, clinicians and researchers were blind to allocation.

Central randomisation ensured complete allocation concealment [196]. The computer-generated randomisation algorithm was designed by the software development team based at the University of Oxford, Department of Psychiatry.

3.3 Participant identification

The participants were initially recruited from primary care and community mental health teams. General practitioners in Oxford referred patients with mood instability who were willing to participate in research directly to the Bipolar Disorder Research Clinic (BDRC) for a diagnostic assessment. Psychiatrists at Oxford Health NHS Foundation Trust referred patients who were interested in participating in research directly to the BDRC. The BDRC is located at the National Institute for Health Research-Clinical Research Facility (NIH-CRF) at Warneford Hospital, Oxford.

Psychiatrists met with participants referred to the BDRC and identified those who met the broad eligibility criteria and were willing to take part in the trial. Following this, the psychiatrist presented the participant with the Participant Information Sheet, which detailed

the exact nature of the trial, what it involved, and what potential adverse effects and risks could be associated with taking part in the trial.

The participants were given as much time as they needed to consider the information and given the opportunity to ask questions of the psychiatrist, NIHR-CRF staff, and their general practitioner before deciding whether they would like to participate in the study. Upon deciding to enrol in the trial, participants signed an informed consent form with their dated signature and a signature from a trial psychiatrist.

The participants who provided informed consent attended a screening visit (further details can be found at 3.1.1), and their eligibility was evaluated at the screening visit in accordance with inclusion and exclusion criteria.

3.4 Inclusion criteria

Participants were required to meet the following inclusion criteria [9]:

(1) Willing and able to consent to participate in the trial

(2) Age 18 or over

(3) Male or female

(4) Diagnosis of bipolar disorder (I, II, not otherwise specified) based on DSM-IV (bipolar patients with co-morbid anxiety or borderline personality disorder are not excluded)

(5) Clinical complaint of significant mood instability

Psychiatrists considered several factors during the screening visit, including the participant's history, their past experiences, and their mental status examination, to make an overall

clinical judgment regarding the clinical complaint of significant mood instability. Prior to randomisation, psychiatrists reviewed the frequency and intensity of changes in mood symptoms, which had been monitored in the pre-randomisation phase in order to re-assess mood instability.

(6) Clinical uncertainty of benefit of lithium treatment

(7) Not on lithium at trial entry

(8) No clear indication for immediate treatment with lithium

(9) No clear indication for alternative treatment

(10) Pre-treatment renal, cardiac, thyroid, and parathyroid function testing is acceptable for lithium initiation

(11) Willing and able to comply with all trial requirements over an eight-week period, as assessed by a psychiatrist

3.5 Exclusion criteria

Participants were excluded if they met the following criteria [9]:

(1) Any contraindication to lithium

(2) Presenting a need for treatment of an acute mood episode where placebo would be inappropriate

(3) Currently taking any psychotropic medication that cannot be withdrawn (e.g. antidepressants, antipsychotics, other mood stabilisers, benzodiazepine, non-benzodiazepine sleeping tablets)

(4) Clinically significant substance abuse

(5) Participation in another medication trial in the past 12 weeks

(6) Immediate risk of suicide and self-harm

(7) Pregnant, lactating or planning pregnancy over the next 12 weeks

3.6 Interventions

3.6.1 Allocated treatment

Lithium carbonate was provided as Priadel 200mg prolonged-release tablets. Priadel is one of the formulations commonly supplied by the Oxford Health NHS Foundation Trust Clinical Pharmacy Support Unit. Matched placebo tablets were manufactured by The Guy's and St Thomas NHS Foundation Trust Pharmacy Manufacturing Unit. Each bottle of Priadel and placebo contained 28 tablets and was assigned a unique randomisation number to ensure the concealment of randomisation.

3.6.2 Lithium titration schedule

Every participant started lithium at 400 mg/day taken as a single dose at night. The target lithium serum level was 0.7 mmol/L (range from 0.4 to 1.0 mmol/L). The dose of lithium was adjusted to maintain the serum lithium levels within the therapeutic range by following the schedule below (Table 1).

Table 3. 1 Lithium dose adjustment scheme

Lithium level	Titration/dose adjustment
⩽ 0.3 mmol/L	Increase dose to 800mg/day
>0.3 and <0.6 mmol/L	Increase dose to 600 or 800mg/day as appropriate

0.6-1.0 mmol/L	Continue current dose
⩾ 1.0 mmol/L	Decrease dose by 200 mg/day or 400 mg/day as appropriate

3.6.3 Lithium blood tests

Serum lithium levels were taken for each participant as close as possible to four different time points: day 4, day 8, week 4 and week 6 after the initiation of treatment. Additional blood tests were arranged if required. Blood samples for participants on lithium were analysed by John Radcliffe Hospital (JR), Oxford. An un-blinded nurse informed the trial psychiatrist of the serum lithium levels, and the related information including reported adherence, time since most recent dose and adverse events. For participants on placebo, the un-blinded nurse gave the trial psychiatrist a sham lithium level considering the reported adherence, time since most recent dose and adverse events. Recommended sham lithium level is presented in Table 2.

3.6.4 Adverse event monitoring

After randomisation, participants were asked whether they had experienced any adverse events at every visit. Lithium has been widely used for decades with a well-documented safety profile [197]. Therefore, non-serious adverse events were not routinely recorded. Only non-serious adverse events with a longer duration, or with greater severity, than expected were reported. Any serious adverse event should be reported to the research team within 24 hours of becoming aware of it.

3.7 Adherence assessment

During each visit after randomisation, participants were asked to report adherence to trial treatment and returned any unused medication. Counting returned pills, and lithium serum levels provided further evidence of adherence.

Table 3. 2 Recommended sham lithium serum levels for patients allocated to placebo group

Current dose	Reported adherence	Level reported to trial psychiatrist (mmol/L)
2 tablets (400 mg/day)	More than 65%	0.4
	Between 50 and 65%	0.3
	Between 25 and 49%	0.2
	Less than 25%	0.1
3 tablets (600 mg/day)	More than 65%	0.6
	Between 50 and 65%	0.4
	Between 25 and 49%	0.2
	Less than 25%	0.1
4 tablets (800 mg/day)	More than 65%	0.8
	Between 50 and 65%	0.6
	Between 25 and 49%	0.4
	Less than 25%	0.2
5 tablets (1000 mg/day)	More than 65%	1.0
	Between 50 and 65%	0.7
	Between 25 and 49%	0.4
	Less than 25%	0.2

3.8 Sample size and power analysis

This study was designed with a target sample size of 40 participants, of whom 20 were allocated to the lithium group and 20 to the placebo group. The sample size and power analysis were calculated based on the main mood outcome. Variability was calculated as the square root of the number of transitions (ND) between integer scores on the QIDS-SR16 and on the ALTMAN per week. In a previous study, OXTEXT-6, the mean ND was 1.98 and the standard deviation was 1.73 [198]. Taking a 25% reduction in ND as a minimum clinically meaningful change over a period of six weeks, two post-randomisation assessments and a target sample size of 40 randomised participants could provide over 90% power to detect differences between groups on the primary mood outcomes with a significance level of 0.5% [9].

3.9 Ethical statements

Initiating lithium treatment is a commitment because it is a long-term treatment for at least years, and it requires constant medical monitoring [199]. Patients with uncertain benefits of lithium were recruited. For instance, an individual might receive their diagnosis recently or has had relatively few major mood episodes. Thus, it was justified to allocate placebo to participants in this trial.

The study protocol was approved on 14 April 2015 by the National Research Ethics Service Committee South Central – Oxford A (reference number 15/SC/0109) and on 10 July 2015 by Oxford Health NHS Foundation Trust. Written consent was obtained from every participant.

3.10 Measures

3.10.1 Measuring circadian rest-activity using actigraphy

Every participant received an actigraph on the screening day visit. Participants were asked to continuously wear these devices on their non-dominant wrist from the beginning of the study to the end of the randomised phase. Due to limitation of data storage and battery life of each device, three actigraphs were given to every participant during the study; replacements were planned for day eight and week four visits. Five participants received an extra actigraph because of a prolonged run-in phase.

GENEActiv Original actigraphs (ActivInsights Ltd., UK) were used for measuring the timing and the structure of circadian rest-activity patterns. GENEActiv Original actigraph is a triaxial, ±8g seismic acceleration sensor (1 g = 9.81 m/s^2). Actigraph measurement frequency was set at 25 Hz to facilitate battery life for the recording period. The autocalibration method was used to minimize the calibration error in the actigraph [200].
The raw data of the actigraph were summarized into a gravity-subtracted signal magnitude vector given by the following equation [201]:

$$\text{SVM} = \sum|\sqrt{x^2 + y^2 + z^2} - g|$$

x,y,z represent the acceleration signals from x, y, z axes and the correction for gravity was conducted to account for the acceleration signals due to gravity.

GENEActiv software (ActivInsights Ltd., UK) was used to extract raw data from the GENEActiv actigraph. The raw data are in .bin files and .csv epoch files form, which can be further analysed using R packages (R Core Team, Vienna) and MATLAB (version 9.8.0 (R2020a). Natick, Massachusetts: The MathWorks Inc.; 2020.). The data converter function in GENEActiv software allowed us to convert .bin files, the default data format, into .csv files which Excel can read. An Excel macro (GENEActiv_Sleep_Macro_5.1.xltm) acquired from the open-access site (open.geneactiv.org) was used to visualise and clean the data.

3.10.2 Measuring cognitive function

Both perceived deficits questionnaire (PDQ) and contextual cueing task were adopted to measure cognitive function. The methodology is described in detail in Chapter 6.

The PDQ is commonly used as a measure of subjective cognitive dysfunction in patients with a neurological or psychiatric disorder [202]. The PDQ consists of 20 items, each with a score ranging from 0-4. A higher score indicates greater impairment of cognitive function. As a result, the total score can range from 0-80. Twenty items of the PDQ can be categorised as four 5-item subscales, including attention/concentration, prospective memory, retrospective memory, and planning/organization. Each subscale has a score range of 0-20 [203]. Participants in the Oxlith study completed this questionnaire twice, once at the randomisation visit and again at the week six visit.

As part of the Oxlith trial, each participant had an iPad with the contextual cueing task installed and were instructed to complete the task daily until the end of the study. Participants

completed 60 trials a day in which the participant had to identify a target letter "T" among distractor letters. The program recorded the search reaction time for each trial. Two conditions were presented in 60 trials. The novel condition was a set of configurations generated for every day of the trial and were not repeated. The repeated conditions were the following configurations repeated at a different frequency.

3.10.3 Measuring mood

The Positive and Negative Affect Schedule Short Form (PANAS-SF) was used to assess day-to-day variations of mood. PANAS-SF is a self-reported questionnaire with 10 items [204]. The ten items describe the participant's mood over the day, including feeling afraid, nervous, upset, hostile, ashamed, active, determined, attentive, inspired, alert. The first five items are categorised as negative affect; the latter five are categorised as positive affect. Each item is rated on a five-point scale from never to always ("never" corresponds to 1, and "always" corresponds to 5). Participants rated their mood over that day using an iPad.

When analysing daily mood, we calculated two variables (positive affect and negative affect) by summing the five corresponding items. Thus, positive affect and negative affect each range from five to twenty-five points.

3.10.4 Measuring manic and depressive symptoms

True Colours is a digital symptom monitoring tool developed by the University of Oxford. This tool allows registered patients to report a wide range of health measures in an agreed personal schedule [205]. Every participant was instructed to score each item based on their

symptoms over the last seven days. After the screening visit, every participant was registered on True Colours and received weekly prompts by emails or text to complete two self-report questionnaires. Participants chose the time of the day and the day of the week to receive the prompts.

In Oxlith, the Quick Inventory of Depressive Symptomatology (QIDS-SR_{16}) and the Altman Self-Rating Mania Scale (ASRM) were used to capture the weekly manic and depressive symptoms changes. QIDS-SR_{16} is a 16-items self-report rating scale that covers nine DSM-IV diagnostic symptoms of the major depressive episode, including sleep disturbance (Q1-Q4), depressed mood (Q5), increased or decreased appetite/weight (Q6-9), impaired concentration and decision making (Q10), self-blaming (Q11), suicidal ideation (Q12), anhedonia (Q13), fatigue (Q14), psychomotor agitation/retardation (Q15-16). The score on each item ranges from 0-3. The total score is the sum of the highest score on any sleep items (Q1-Q4), the highest score on any appetite/weight items (Q6-9), the highest score on either of the two psychomotor items (Q 15-16) and the scores on the individual rest items. The total scores range from 0-27 [206]. A total score of less than 5, between 6 and 10, between 11 and 15, between 16 and 20, more than 21 is considered no depression, mild depression, moderate depression, severe depression, and very severe depression, respectively [207].

The ASRM is a 5-items self-report questionnaire that assesses the severity of manic symptoms. These five items encompass positive mood, self-confidence, sleep patterns, speech and motor activity levels. Scores on each item range from 0 to 4. The total scores range from 0 to 20 [208].

3.11 Statistical analysis

3.11.1 Data processing

Baseline data from the two weeks closest to the randomisation date were utilised, which is consistent with the research protocol. The post-randomisation data from six weeks after the randomisation date were used. Actigraphy data affected by the daylight-saving time transition were excluded [209, 210].

3.11.2 True colour data pre-processing

Although participants were instructed to report the True Colour symptoms on a weekly basis, some did not adhere to this regimen. Data from the participant report that best covered the week after randomization was utilized. For example, if May 18, 2017 would have been the date to report symptoms for week four, and a participant reported symptoms on May 17, 2017, and May 20, 2017, the data reported on May 17, 2017 was selected.

3.11.3 Fisher's exact test

Fisher's exact test was used to determine whether the proportions of one variable were different depending on the value of the other variable when there were two nominal variables. When the sample size is small, Fisher's exact test is more accurate than the chi-square test [211]. Fisher's exact test was carried out using R (R Core Team, Vienna). If $p < 0.05$, the differences were considered to be statistically significant.

3.11.4 Student's t-test

Two-tailed student's t-test was used when there were one measurement variable and one nominal variable. The test examines whether the means of the measurement variable are different between the two groups [211]. Levene's test was completed first to compare the variances of two groups. Student's t-test and Levene's test was carried out using R (R Core Team, Vienna). If $p < 0.05$, the differences were considered to be statistically significant.

3.11.5 Mann–Whitney U test:

The Mann-Whitney U test is a rank-based test used to determine whether there are differences between two groups without regard to the distribution of the groups [212]. Due to the non-normal distribution of some of the circadian variables, the Mann–Whitney U test was used to compare these variables at baseline between the lithium and placebo groups. If $p < 0.05$, the differences were considered to be statistically significant.

3.11.6 Two-way ANOVA

Two-way ANOVA was used when there were one measurement variable and two nominal variables. This test assesses three null hypotheses [211]:

(1) the means of the measurement variable are not different among different values of the first nominal variable.

(2) the means of the measurement variable are not different among different values of the second nominal variable.

(3) There is no interaction.

Two-way ANOVA was carried out using R (R Core Team, Vienna). If $p < 0.05$, the differences were considered to be statistically significant.

3.11.7 Linear mixed effect model

To compare the circadian rest-activity patterns and cognitive function between treatment groups, the data were fitted to the linear mixed-effect model using lme4 package (version 1.1-23) because this model is suitable for analysing data that are correlated, longitudinal and hierarchical [213]. Also, when dealing with missing data in the repeated-measures design, this model can estimate parameters with the available data. While the lme4 package and nlme package are both commonly used for the linear mixed-effect model, the lme4 package was chosen because of its built-in parametric bootstrapping function.

The assumptions for this model are [214]:

- Linearity: the predictor variables are related linearly to the outcome variables
- Normally distributed errors: The residuals of the model are random, normally distributed with a mean of zero.
- Homoscedasticity: the residuals have similar variance at each level of the predictor variables
- No perfect multicollinearity: the predictor variables are not perfectly correlated

Most of the circadian rest-activity data were skewed, and bootstrapping procedures were conducted to circumvent distribution assumptions of the linear mixed-effect model and to produce estimates of the model parameters. A study showed that applying bootstrap procedure in the original skewed data had better estimates of the true latent moderator effect

and less type-II error compared with applying regression analysis in a log-transformed dependent variable [215].

An analysis of between-group differences was the primary analytical strategy and the primary focus of this thesis. Within-group comparisons were merely exploratory and supplementary. The circadian rest-activity variables were dependent variables, the allocation × time interaction was an independent variable, and gender and age were introduced as covariates in the analysis. Participants were included as a random effect. Variance inflation factor (VIF) was used to ensure the no perfect multicollinearity assumption and exclude the highly correlated variables. If a VIF is larger than 10, then the model has a collinearity problem (car package in R, version 3.0-7) [216].

When comparing different models, maximum likelihood (ML) method was used. Whereas restricted maximum likelihood (REML) was adopted for estimating the parameters in other situations [214]. Akaike's information criterion (AIC) was used for comparing models. The smaller values indicate better-fitting models [214].

The lme4 package did not provide p-values. However, 95% confidence intervals were calculated using bootstrapping procedures, which have been considered to be a better alternative than a p-value. The confidence interval gives a better estimation of the effects existing in the population, allows a direct evaluation of clinical significance [217]. If the 95% confidence interval does not contain 0, the results are statistically significant.

3.11.8 Mediation analysis

To determine whether lithium had a direct effect on circadian rest-activity, the influence of affect changes was adjusted for as a mediator in the linear mixed-effect model. Specifically, this analysis focused on the direct effects of lithium on circadian rest-activity, not on the indirect effects of lithium on circadian rest-activity mediated by modulating affect: changes in circadian rest-activity following the administration of lithium may be attributed to altered affect.

The criteria for mediation are: 1) the potential mediator is associated with the predictor of interest as well as a causal consequence of the predictor, and 2) the potential mediator and the predictor are both associated with the outcome [218]. Numerous studies have reported the association between mood and physical activity [219-221]. Therefore, positive affect or negative affect, as measured by PANAS, could be a mediator.

Using the traditional or statistical approach for performing a mediation analysis developed by Baron and Kenny [222, 223], the effect of lithium on positive and negative affect was examined using a linear mixed-effect model as a first step. If the relationship between lithium and affect was significant, then the variable significantly affected by lithium was adjusted for in the second linear mixed-effect model, in which Allocation × Week interaction was the independent variable and the circadian rest-activity outcome was the dependent variable. This approach leverages the linear mixed-effects model's ability to estimate parameters from the available data and is insensitive to missing data, providing more power to detect the differences between lithium and placebo groups. In addition, the effect sizes of other covariates are also available.

For the purposes of supplementing the traditional method and estimating direct, indirect, and total effects, R-package mediation (version 4.5.0) was utilised [224]. This package includes the mediation() function, which can be used to conduct casual mediation analyses using simulations. Two models were fitted the same way as the traditional approach. Following this, the mediation() function was used to estimate the total effects of lithium on circadian rest-activity outcomes, the average direct effects (ADE) of lithium on circadian rest-activity outcomes, and the average causal mediation effects (ACME) which represents indirect effects. By bootstrapping, this function obtained the 95% confidence interval of the above-mentioned effects (1000 bootstrap samples).

The causal mediation analysis using the mediation R package has the following drawbacks. First, this approach has less power than the traditional approach to detect differences between the lithium and placebo groups. Using the mediation () function, the same number of observations were required as for mediators and outcomes variables. The listwise deletion approach was used to remove all missing values from the mediator and outcome variables. Second, the medsens () function was not used for sensitivity analysis in this thesis. The medsens () function in this package can be used to examine the robustness of findings to potential unmeasured mediator-outcome confounders through simulations. However, the linear mixed-effects model was not compatible with the current version of medsens () function.

3.12 My role in the Oxford Lithium Trial

The Oxford Lithium Trial was not designed by me and I was not involved with the data collection. I was part of the study meetings and in charge of the data cleaning, data analysis and some follow up work.

The Oxford Lithium Trial data was used by me to explore the effects of lithium on circadian rhythm and cognitive functions in patients with bipolar disorder. The findings will be presented in chapters four to six. These empirical studies do not aim to provide definitive answers regarding the effects of lithium on patients with bipolar disorder, but rather to generate new insights and ideas for developing new experimental medicine models for bipolar disorder. In chapter seven, the implications of the research and future directions will be discussed in depth.

Chapter 4: The effect of lithium on motor activity in patients with bipolar disorder

"No attacks, no hospitalizations, but even, and perhaps most, health itself is different, freer and out of the shadow." – Robert Lowell

Excerpt From: Kay Redfield Jamison. "Robert Lowell, Setting the River on Fire".

Acknowledgement:

Dr Oliver Carr developed the cosinor method MATLAB algorithm used in this analysis [225, 226].

4.1 Introduction

4.1.1 The importance of motor activity in bipolar disorder

The significance of motor activity disturbance in bipolar disorder has been acknowledged since the 19th century when the modern definition of bipolar disorder was developed. In the nineteenth century, psychiatrists adopted a descriptive and longitudinal approach to conceptualising bipolar disorder [44]. In Kraepelin's original description and formulation of mood disorders, he assigned equal importance to the disturbances in mood, cognition and motor activity [227].

In contemporary psychiatric practice, motor activity disturbance has regained its importance in diagnosing bipolar disorder. DSM-V and International Classification of Diseases 11th Revision (ICD-11) included increased activity or energy as a cardinal symptom [228]. Several previous iterations of the Diagnostic and Statistical Manual of Mental Disorders

(DSM) had psychomotor disturbance as one of the seven criterion B symptoms for the diagnosis of bipolar disorder [67].

Numerous studies have further highlighted the importance of motor activity in bipolar disorder. In the U.K. Bipolar Disorder Research Network program, overactivity was present in the context of manic or hypomanic episodes in 94% of patients with a lifetime DSM-IV diagnosis of bipolar I disorder (N=2801) and 93% of patients with a lifetime DSM-IV diagnosis of bipolar II disorder (N=1192) [229]. In a network analysis of symptoms in adolescents with bipolar disorder, symptoms like fatigue and hyperactivity, which belong to the activity domain, were central symptoms that highly correlated with other symptoms [230]. A recent systematic review supported the increase in motor activity and energy levels as one of the central symptoms of bipolar disorder [67].

Circadian rest-activity abnormalities have been found in patients with bipolar disorder and in individuals at a high risk of developing bipolar disorder as measured by actigraphy. Patients with bipolar disorder in a manic state have a higher mean activity level than healthy individuals and those with bipolar depression [66]. Patients with bipolar disorder have a lower activity level during euthymia and depression than healthy individuals [67]. In addition, lower amplitudes of motor activity have been observed in individuals at risk for bipolar disorder compared with healthy controls [231, 232].

4.1.2 The effect of lithium on motor activity

Evidence from cell lines

Although lithium has been widely used as a first-line treatment for bipolar disorder [233], its impact on motor activity is only partially understood. Recent studies conducted in cell lines have found that lithium had an impact on the amplitude of cellular circadian rhythm. However, the findings were not consistent across different cell lines. In mouse SCN neurons, lithium had no effect on the amplitude of firing rate rhythms [139]. Skin fibroblast cells obtained from patients with bipolar disorder have been used in circadian rhythm studies; Per2::luc, a rhythmically expressed, bioluminescent circadian rhythm reporter gene was adopted to indicate circadian rhythm changes [142]. At a therapeutic dose, lithium was found to increase the amplitude of the circadian rhythm in fibroblast cells extracted from healthy participants [142]. However, lithium failed to achieve this effect in fibroblast cultures obtained from patients with bipolar disorder [142, 183, 184]. Therefore, it is unclear whether lithium has an impact on the amplitude of circadian rhythm in patients with bipolar disorder

Evidence from clinical cohorts

Very few studies have investigated the effect of lithium on motor activity in bipolar patients. In chapter 2, the updated systematic review included one study investigating the effect of lithium on the amplitude of the circadian rest-activity as measured by actigraphy. The study revealed that lithium significantly increased amplitude compared with anticonvulsants in patients with euthymic bipolar disorder [176]. In a second study, seven of ten remitted bipolar patients receiving lithium maintenance treatment relapsed into hypomania or mania within three months after discontinuation of lithium; under lithium treatment, the daytime activity of patients who relapsed was significantly higher than those who remained stable after lithium discontinuation [234]. However, the results need to be interpreted with caution due to the limited sample size.

The importance of motor activity in characterising bipolar disorder, the motor activity abnormalities observed in patients with bipolar disorder, and the limited research on the effect of lithium on motor activity, suggest a strong imperative for further investigation of the effect of lithium on motor activity. **This chapter sought to investigate whether lithium may have a direct effect on increasing circadian rest-activity in patients with bipolar disorder using actigraphy data as well as self-reported mood data.**

4.2 Methodology

4.2.1 Measuring circadian rest-activity using actigraphy

The methodology is described in chapter 3 (section 3.9.1)

4.2.2 Quantifying circadian rest-activity

Cosinor method

The cosinor method is a curve-fitting method that attempts to fit a sinusoidal wave with a period of 24 hours to the circadian rest-activity data through least square procedures [59, 235]. While the cosinor method was initially developed to analyse short data series [235], this analysis has also been extended to longer-term signals [225].

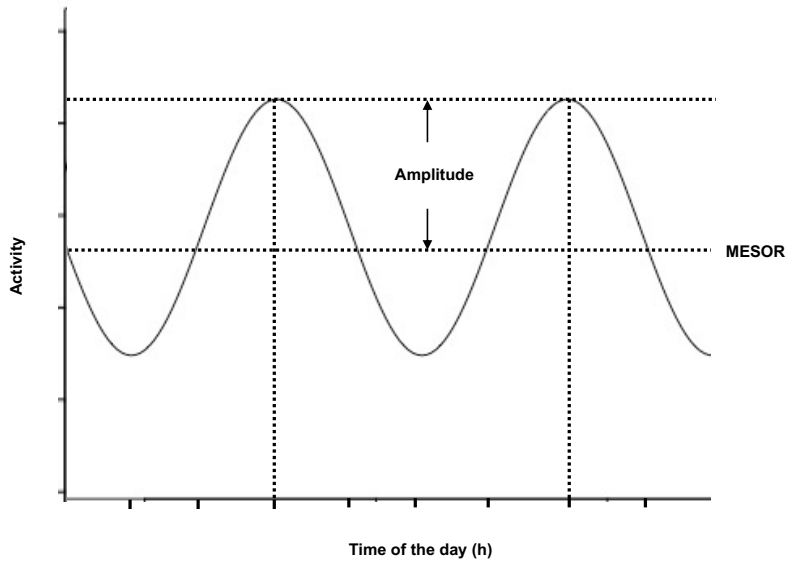
The following integration method was applied to the raw acceleration data to show the sinusoidal patterns of the actigraph acceleration data. First, the mean of the signal was

subtracted from the whole signal to centre the signals on zero. 8-hour windows were utilised, which shifted by one data point along the entire signal to find the area under the signal curves. For example, when the 8-hour window overlapped with the most active time of the day, almost all signals should be above the mean, so areas under the signal would be the largest [225].

Only activity data between the first and the last midnight of each participant were included. We applied the cosinor analysis to each one-week section of the signals, which required at least four-day effective activity recording each week to represent the circadian rest-activity patterns of its week. Within every week, the fitting of the 24-hour sinusoidal wave started from midday to midday.

Two measurements were utilised to quantify the motor activity of every participant on a weekly basis. The first measurement, midline estimating statistic of rhythm (MESOR) represents the rhythm-adjusted mean of the sinusoidal wave. The second measurement, Amplitude, corresponds to the distance between the MESOR and the peak of the sinusoidal wave (Figure 1) [59]. Both MESOR and Amplitude were extracted from the circadian rest-activity patterns using the cosinor method applied to the *weekly* actigraphy data.

Figure 4. 1 Schematic representation of parameters (Amplitude and Mesor) which characterise the circadian rest-activity patterns using cosinor method.



Adapted from Refinetti 2007 [59] .

Non-parametric analysis

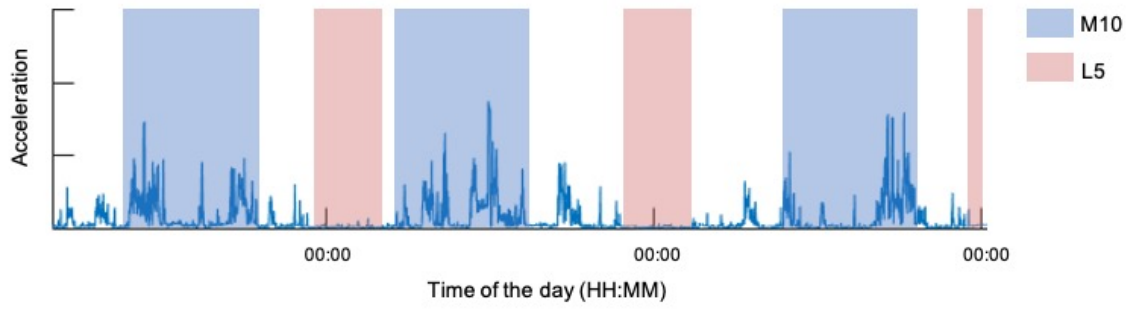
A non-parametric analysis was utilised to quantify the circadian rest-activity patterns. In contrast to the cosinor method, the non-parametric analysis does not follow the assumption that the circadian rest-activity patterns behave similarly to sinusoidal waves [61]. The non-parametric analysis uses *daily* actigraphy data, which has more power to detect the differences between lithium and placebo groups.

GGIR package (version 1.11-0) [236] was used to perform non-parametric analysis of the raw data extracted from the GENEActiv software. Actigraphy non-wear time was detected by

a default function of the GGIR algorithm. If more than 3 hours of non-wear time were detected for a single day, the data of this particular day would be excluded for further analysis [237].

M10 and L5 are two variables generated by the non-parametric analysis to quantify motor activity [61]. M10 corresponds to total activity in the most active ten-hour period, a proxy for daytime activity. L5 represents total activity in the least active five-hour period, a proxy for night-time activity or nocturnal arousal (see Figure 2). Thus, higher M10 means elevated activity in the daytime, and higher L5 denotes disturbed sleep. The relative amplitude is represented by (M10-L5)/(M10+L5) with a value ranging from 0 to 1. The lower the value, the more disturbed the circadian rhythm is [61]. To compare the amount of circadian rest-activity disturbance between the lithium and placebo groups, the relative amplitude was calculated at baseline.

Figure 4. 2 Colour coded regions highlight the most active ten-hours periods and the least active five-hours periods over three-days of acceleration data for one participant



4.2.3 Evaluating sleep quality

Nocturnal arousal (L5) can be an indicator of sleep quality. One study reported a significant correlation between sleep quality and the mean activity of sleep active epochs [187].
The Sleep Condition Indicator (SCI) is a brief scale with eight items to screen for an insomnia disorder in clinical practice. This scale is strongly correlated with the Pittsburgh Sleep Quality Index (PSQI) [238]. The eight questions assess sleep latency, ability to remain asleep, sleep quality, duration of the sleep problem, daytime performance, and the extent to which the patient is troubled by sleep problems. Each item is scored on a 0-4 scale, with the lower scores representing worse sleep problems (see Appendix for the full details of SCI). In the Oxlith study, every participant was screened using the SCI at the randomisation visit and at the week six visit.

The total score of four subitems of the QIDS-SR_{16} questionnaire was adopted to evaluate the sleep symptoms weekly after randomisation. The first four subitems assess the disturbances in falling asleep (Q1), sleep during the night (Q2), waking up early (Q3), sleeping too much (Q4) [206]. Each item scores from 0 to 3. Higher scores represent more severe sleep disturbances. A linear mixed-effects model was used to compare the weekly sleep symptoms changes between lithium and placebo groups.

4.2.4 Measuring mood

The Positive and Negative Affect Schedule Short Form (PANAS-SF) was used to assess day-to-day variations of mood. The methodology is described in detail in Chapter 3 (section 3.9.3).

4.2.5 Statistical analysis

Student's t-test

A two-tailed independent t-test was conducted to compare sleep quality between the lithium and placebo groups at baseline. The sleep quality was evaluated based on the total scores of the SCI questionnaire. The Shapiro-Wilk test was used to determine the normality of the total scores of the SCI questionnaire. The assumption of homogeneity of variance was examined using Levene's test. All data were analysed with R (R Core Team, Vienna). If $p < 0.05$, the differences were considered to be statistically significant.

Two-way analysis of variance (Two-way ANOVA)

For each question and the total scores of the sleep condition indicator, we compared the group mean values between lithium and placebo groups using two-way analysis of variance to detect the significant effect of allocation, time and allocation × time interaction. All data were analysed with R (R Core Team, Vienna). If $p < 0.05$, the differences were considered to be statistically significant.

Linear mixed-effects model

The methodology is described in detail in chapter 3 (3.11.7 statistical analysis）

Mediation analysis:

The methodology is described in detail in chapter 3 (3.11.8 Mediation analysis)

Correlation analysis

Pearson correlation was used to examine the association between non-parametric circadian variables and self-reported sleep quality measurements at baseline. Data from each variable were tested for normality using the Shapiro-Wilk test. All data were analysed with R (R Core Team, Vienna). If $p < 0.05$, the differences were considered to be statistically significant.

4.2.6 Missing data analysis

Finalfit (version 1.0.2) R package was used to check for associations between missing and observed data. The missing_compare function was adopted to compare missing data in the dependent variable across independent variables. Continuous data were compared with the Kruskal Wallis test, a rank-based non-parametric test [211]. To use the available data to its full, a linear mixed-effect model was used to accommodate missing data points.

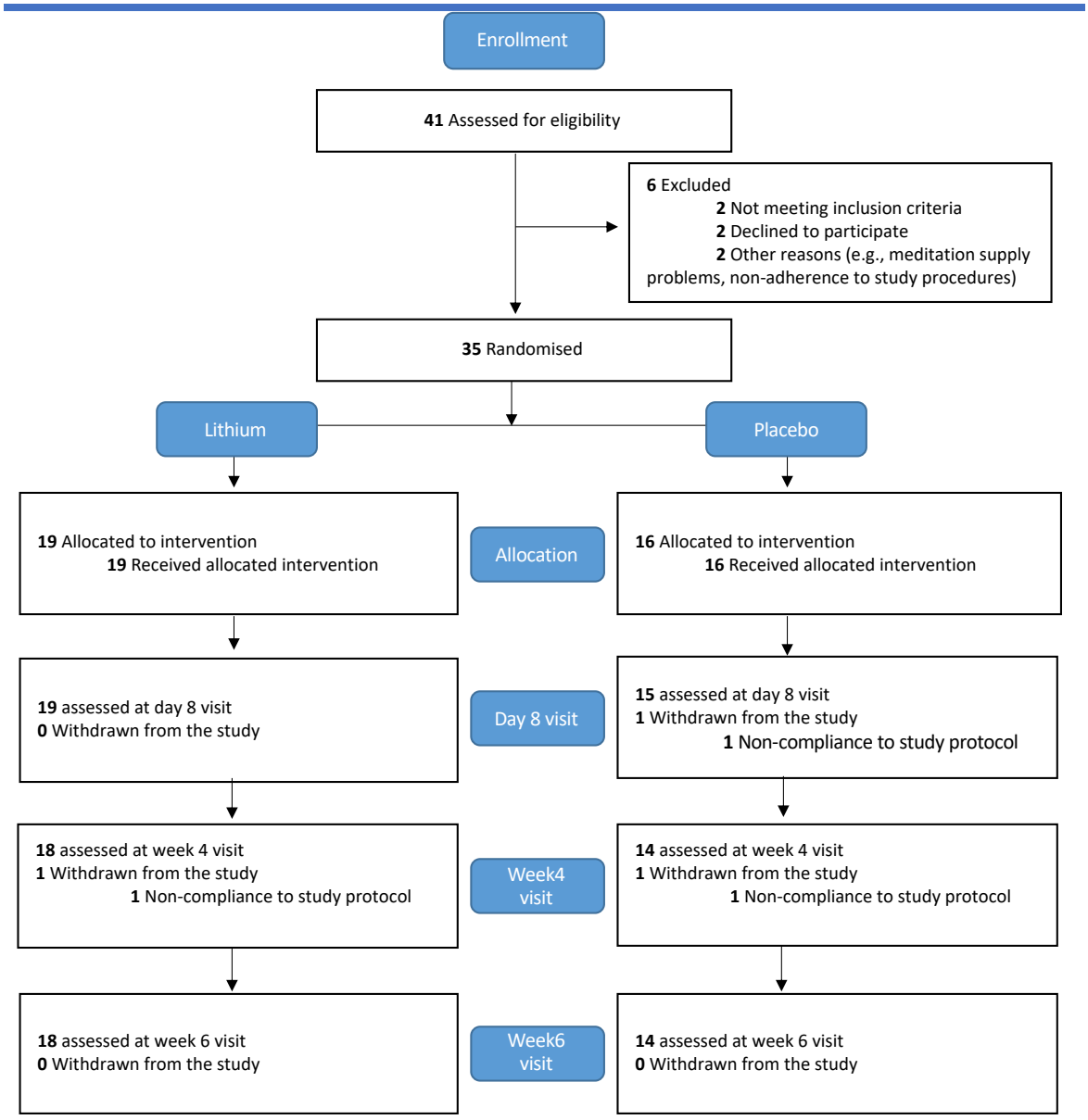
The reasons for missing data in actigraphy were placed in four categories: (1) files missing, (2) technical problems, (3) recording less than 21 hours within a day, (4) recording less than required days.

4.3 Results

4.3.1 Participant Flow

From August 2015 to Jan 2018, forty-one participants were screened for eligibility and six were excluded. Thirty-five participants were randomised and initiated treatment; nineteen received lithium and the other sixteen received placebo. Of the nineteen participants randomised to lithium, eighteen (95%) completed the study. Of the sixteen participants randomized to placebo, fourteen (88%) completed the study (Figure 4.3).

Figure 4. 3 CONSORT Flow Diagram



4.3.2 Baseline demographic characteristics

Participants had various lengths of pre-randomisation phases ranging from 10 days to 45 days. More than 74% of participants had greater than or equal to 14 days of run-in phase. Baseline demographic characteristics are presented in Table 4.1. Most of the recruited participants (77%) were diagnosed with bipolar II disorder. No significant differences were

found between those randomised to lithium or placebo on any of the baseline demographic variables (all p-value > 0.1). Additionally, there were no significant differences between the two groups on seasonal distribution (p = 0.57).

Table 4. 1 Demographic details of study participants.

	Randomised treatment		
	Lithium (N=19)	Placebo (N=16)	p-value
Gender: n (%)			>0.99
Male	8 (42%)	7 (44%)	
Female	11 (58%)	9 (56%)	
Age (years): mean (SD)			0.14
	28 (10)	35(14)	
BMI: mean (SD)			0.58
	25.4 (6.3)	26.5 (5.0)	
Subjective mood: mean (SD)			
Positive mood	11.9 (5.4)	10.8 (4.0)	0.41
Negative mood	9.5 (4.7)	11.5 (5.7)	0.23
ASRM total scores: mean (SD)			0.56
	2.83 (3.81)	3.63 (3.93)	
QIDS total scores: mean (SD)			0.39
	9.56 (6.25)	11.25 (4.95)	
Bipolar disorder subtype: n (%)			0.53
BD I	3 (16%)	4 (25%)	
BD II	16 (84%)	11 (69%)	
BD NOS	0 (0%)	1 (6%)	
Seasons: n (%)			0.57
Spring	3(16%)	3(19%)	
Summer	3(16%)	5(31%)	
Autumn	4(21%)	4(25%)	
Winter	9(47%)	4(25%)	

Abbreviation: ASRM: Altman Self-Rating Mania Scale; BD, bipolar disorder; BMI, body mass index; NOS, not otherwise specified; QIDS-SR16: Quick Inventory of Depressive Symptomatology.

Percentage has been rounded.

4.3.3 Adherence to lithium treatment

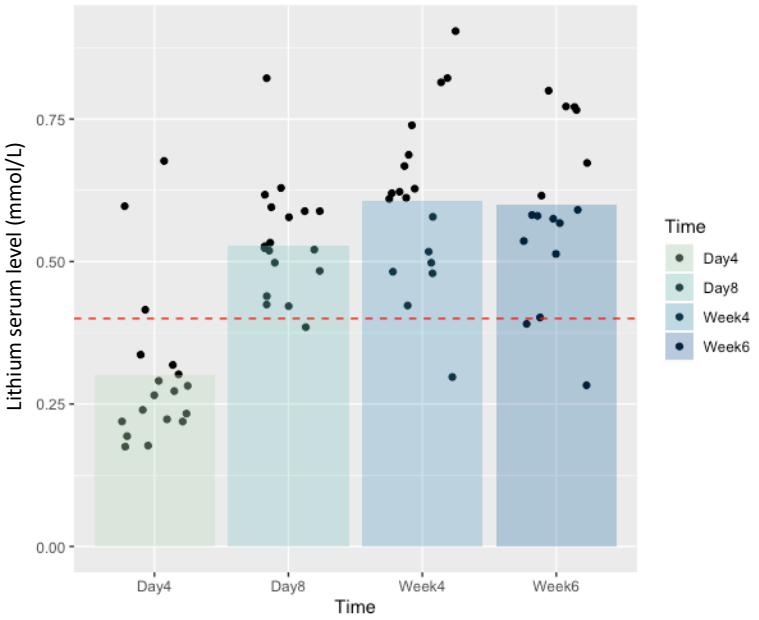
Nearly all participants were adherent to lithium treatment throughout the trial (Table 4.2). The serum level of lithium of all participants reached the targeted therapeutic range at Day 8

visit, and fifteen out of seventeen remained within the therapeutic range (Figure 4.4). The lithium serum level of one participant fell to 0.3 mmol/L at week 4 visit and returned to the target level after the dose was increased. Another participant had a 0.3 mmol/L lithium serum level at week 6 even though this participant was receiving a large dose (1000mg/day) and was highly adherent to lithium treatment; an inaccurate lithium assay result was suspected.

Table 4. 2 Reported adherence to lithium treatment through the trial

Reported adherence:	Day 4 visit	Day 8 visit	Week 4 visit	Week 6 visit
More than 65%: n (%)	19 (100%)	19 (100%)	18 (95%)	17 (94%)
Between 50-65%: n (%)	0	0	1 (5%)	1 (6%)
Between 25-49%: n (%)	0	0	0	0
Less than 25%: n (%)	0	0	0	0

Figure 4. 4 Lithium serum level reported at each visit.

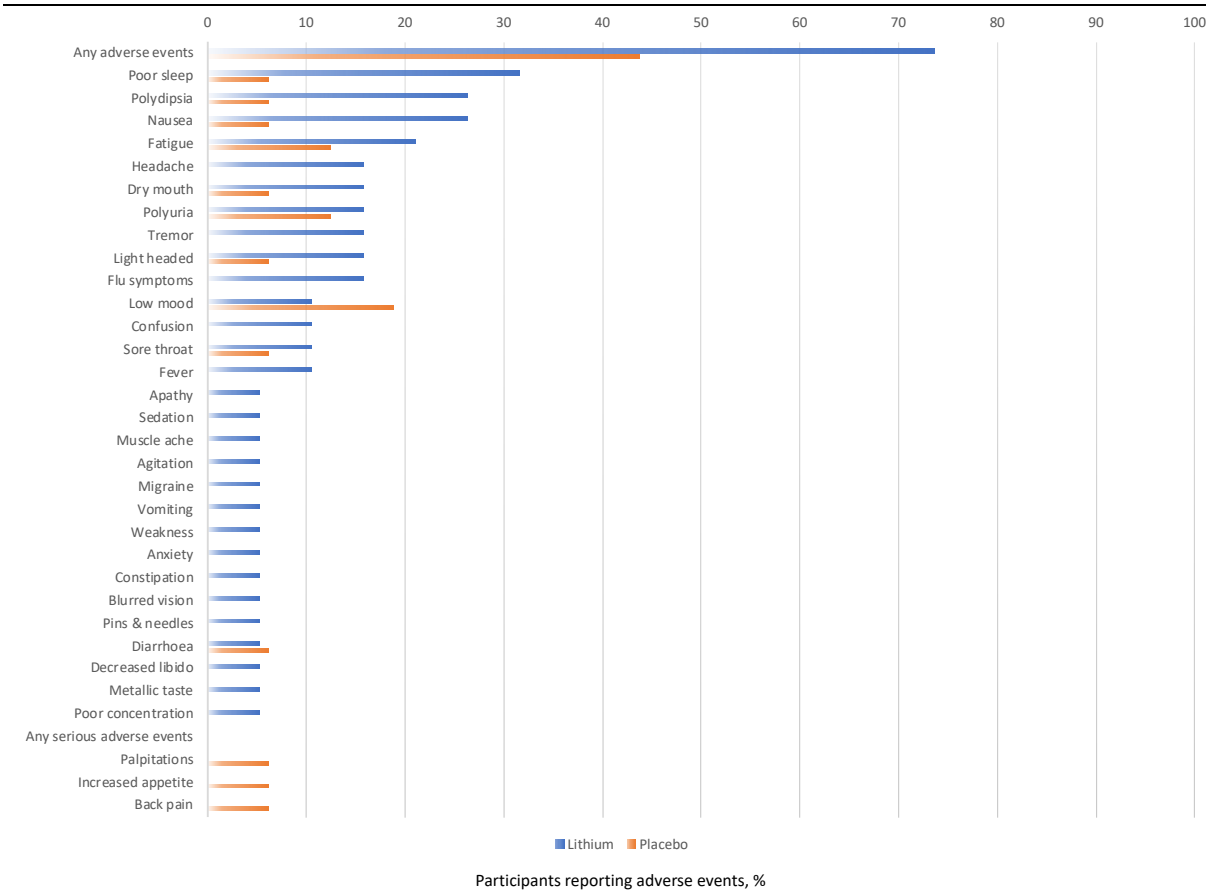


Each black point represents the lithium serum level of each participant. The red dotted line denotes the minimal lithium serum level (0.4 mmol/L) of our targeted lithium therapeutic range (0.4-1.0 mmol/L).

4.3.4 Adverse events

There were no serious adverse events reported during the study (Figure 4.5). In the lithium group, fourteen (74%) participants reported adverse events. The most common adverse events in the lithium group were poor sleep (32%), polydipsia (26%), nausea (26%), and fatigue (21%). Of the participants in the placebo group, seven (44%) reported adverse events. In the placebo group, the most commonly reported adverse events were low mood (19%), fatigue (13%), and polyuria (13%).

Figure 4. 5 Adverse events by allocation



Percentage of participants reporting adverse events in each group. The participants were able to report more than one adverse event. The denominator represents the number of participants in each group.

4.3.5 Missing data

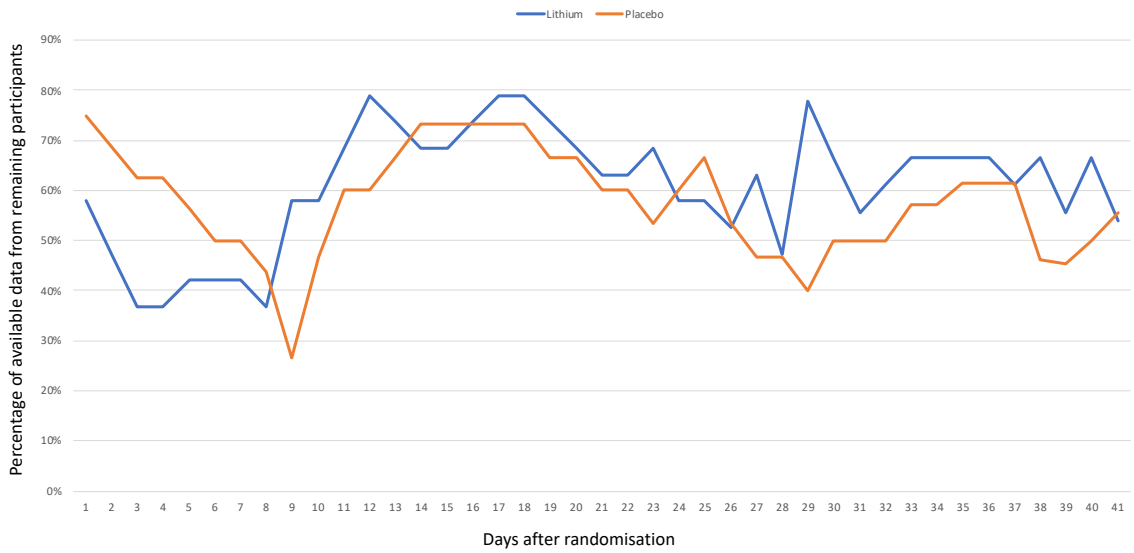
When comparing the lithium and placebo groups, no significant differences in the amount of missing data in the circadian rest-activity data stream were found ($p = 0.55$, Table 4.3). Reasons for missing data in actigraphy are presented in Table 4.4. Less circadian rest-activity data in the first eight days were noted in both groups (see Figure 4.6). In the first eight days after randomisation, there were more participants susceptible to the problem of recording less than required days (the few-days recordings after randomisation were the last few days of recordings for the first actigraph every participant received). Twenty-four days of actigraphy data, from four participants, were excluded due to the daylight-saving time transition (Supplementary Table 2)

Table 4. 3 Missing data in circadian rest-activity data stream.

	Not missing	Missing	P value
Placebo: N (%)	438 (62.3)	265 (37.7)	0.55
Lithium: N (%)	580 (60.7)	375 (39.3)	

N represents the number of data points.

Figure 4. 6 Changes in the amount of available data in circadian rest-activity data streams after randomisation.



Percentage of available data from remaining participants was calculated as the number of participants recording satisfactory data divided by the number of participants attempting to record. Circadian rest-activity data refers to the data generated from actigraphy.

Table 4. 4 Summary of missing data with reasons

Missing data with reasons:	**Day 8 visit**		**Week4 visit**		**Week6 visit**		**Additional visit**	
	Lithium	Placebo	Lithium	Placebo	Lithium	Placebo	Lithium	Placebo
Recording less than required: N	8	4	4	1	1	1	0	0
Recording less than 21 hours within a day: N	2	2	0	1	1	1	1	0
Technical problems: N	1	1	2	2	3	5	0	0
File missing: N	1	0	0	1	0	0	0	0

There are 5 participants who had additional visit because the prolonged run-in phase or there was a problem happened.

4.3.6 The effect of lithium on manic and depressive symptoms

Table 4.5 presents results of the linear mixed-effect analysis comparing the effect of lithium on manic symptoms and depressive symptoms over six weeks after randomisation. We did not detect any significant differences between lithium and placebo group. Male bipolar patients tended to have lower ASRM total scores (β = -2.11, 95% confidence interval: -3.62, -0.50).

Table 4. 5 Results of linear mixed-effects models evaluating the changes of ASRM total scores and QIDS-SR$_{16}$ six weeks after randomisation

	ASRM total scores		QIDS-SR$_{16}$ total scores	
	Coefficient estimates	95% CI	Coefficient estimates	95% CI
(Intercept)	5.51	(2.45, 8.46)	12.19	(6.45, 17.73)
Gender (Male)	-2.11	(-3.63, -0.50) *	-1.05	(-4.18, 2.11)
Age	-0.03	(-0.09, 0.037)	-0.01	(-0.14, 0.12)
Allocation (Lithium)	-1.08	(-3.74, 1.38)	-1.84	(-5.56, 1.91)
Week1 vs BL	-1.25	(-3.48, 1.03)	0.42	(-2.09, 3.17)
Week2 vs BL	-0.83	(-3.15, 1.67)	0.59	(-2.41, 3.36)
Week3 vs BL	0.13	(-2.40, 2.38)	-2.58	(-5.56, 0.29)
Week4 vs BL	-0.85	(-3.24, 1.50)	-0.12	(-2.74, 2.63)
Week5 vs BL	-0.79	(-3.37, 1.65)	-1.33	(-4.24, 1.68)
Week6 vs BL	-0.34	(-2.66, 2.14)	-2.08	(-4.87, 0.58)
Allocation × (Week1 vs BL)	1.09	(-1.84, 4.02)	-0.14	(-3.63, 3.28)
Allocation × (Week2 vs BL)	1.80	(-1.50, 4.85)	-1.38	(-5.23, 2.64)
Allocation × (Week3 vs BL)	0.08	(-3.04, 3.32)	1.69	(-2.01, 5.50)
Allocation × (Week4 vs BL)	1.72	(-1.41, 4.68)	-1.72	(-5.27, 2.11)
Allocation × (Week5 vs BL)	0.76	(-2.44, 3.92)	0.06	(-4.01, 3.76)
Allocation × (Week6 vs BL)	-0.17	(-3.41, 2.94)	2.23	(-1.57, 5.88)

Data from one participant was excluded from analysis because of unidentified ID. ASRM total scores or QIDS-SR$_{16}$ was included as the dependent variable. Age, gender, allocation, week and allocation × week interaction were included as independent variables (* represents statistically significant).

Abbreviations: BL: Baseline. ASRM: Altman Self-Rating Mania Scale. QIDS-SR$_{16}$: Quick Inventory of Depressive Symptomatology.

4.3.7 The effect of lithium on positive affect and negative affect

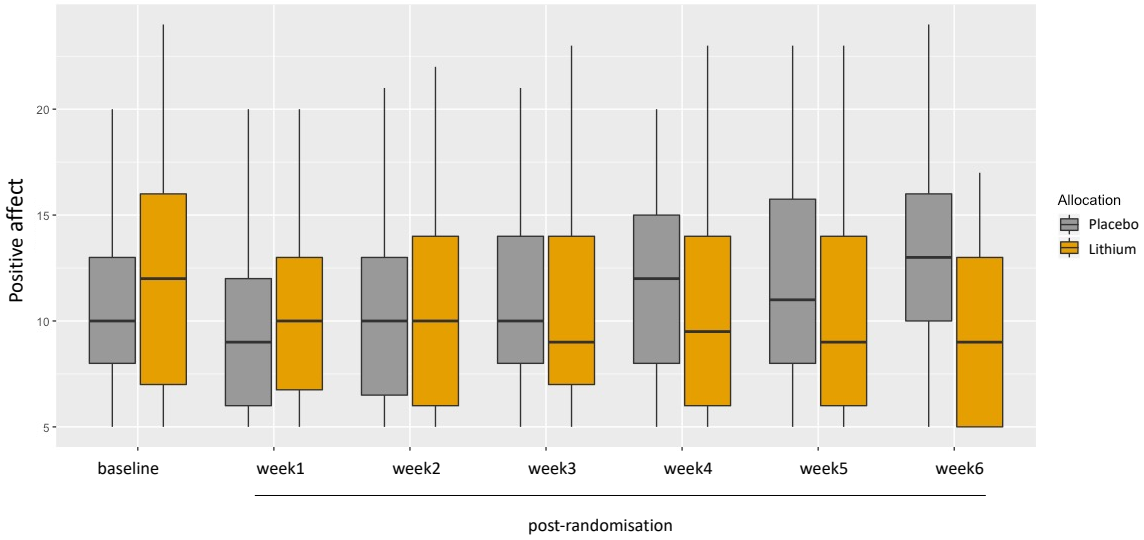
Table 4.6 shows the results of two linear mixed-effect models. A trend towards lower positive affect from week one to week six was found in the lithium group compared to the placebo group; the size of the effect increased over time and the difference was statistically significant from week three to week six. Lithium treatment and week six interaction was a significant predictor of negative affect ($\beta = 2.06$, 95% CI: 0.68, 3.45) (see Figure 4.7 for observed weekly positive affect and negative effect).

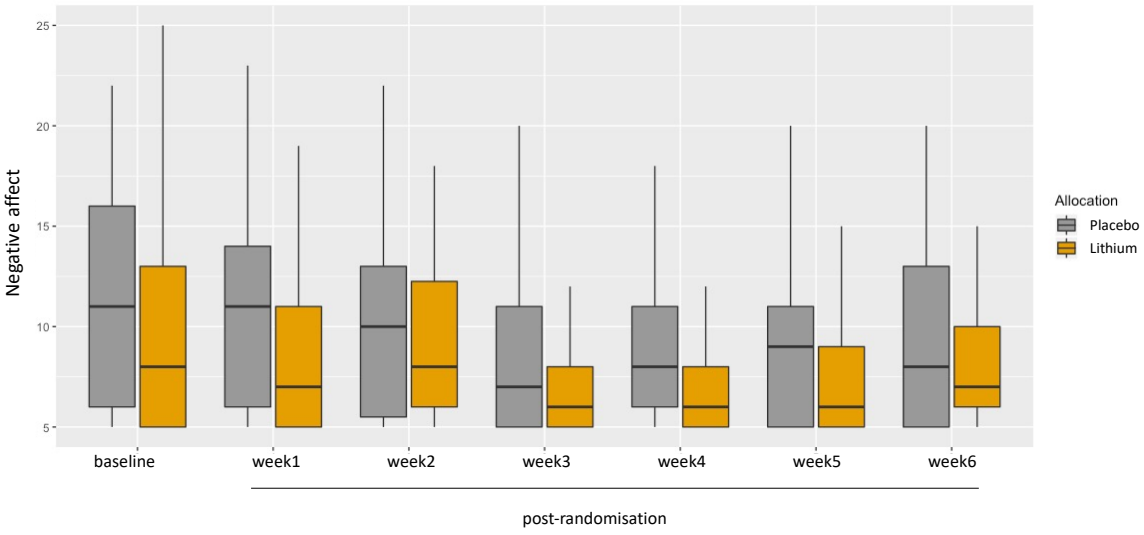
Table 4. 6 Results of linear mixed-effects models evaluating the changes of positive affect and negative affect six weeks after randomisation

	Positive affect		Negative affect	
	Coefficient estimates	95% CI	Coefficient estimates	95% CI
(Intercept)	11.85	(8.06, 15.56)	12.70	(8.09, 17.13)
Gender (Male)	-3.25	(-5.38, -1.11) *	-2.13	(-4.72, 0.47)
Age	0.00	(-0.09, 0.09)	-0.01	(-0.12, 0.11)
Allocation (Lithium)	1.29	(-1.14, 3.76)	-2.34	(-5.11, 0.28)
Week1 vs BL	-1.22	(-2.14, -0.29) *	-0.32	(-1.19, 0.61)
Week2 vs BL	-0.19	(-1.13, 0.73)	-0.78	(-1.63, 0.10)
Week3 vs BL	0.34	(-0.63, 1.25)	-2.15	(-2.96, -1.32) *
Week4 vs BL	0.55	(-0.39, 1.40)	-1.85	(-2.70, -1.03) *
Week5 vs BL	1.16	(0.11, 2.17) *	-1.82	(-2.72, -0.87) *
Week6 vs BL	1.50	(0.38, 2.56) *	-2.22	(-3.23, -1.18) *
Allocation × (Week1 vs BL)	-0.19	(-1.47, 1.09)	-0.22	(-1.39, 0.85)
Allocation × (Week2 vs BL)	-1.12	(-2.31, 0.20)	0.55	(-0.56, 1.67)
Allocation × (Week3 vs BL)	-1.43	(-2.65, -0.08) *	0.93	(-0.33, 2.16)
Allocation × (Week4 vs BL)	-2.10	(-3.39, -0.76) *	0.43	(-0.80, 1.59)
Allocation × (Week5 vs BL)	-2.74	(-4.11, -1.31) *	0.79	(-0.56, 2.04)
Allocation × (Week6 vs BL)	-3.51	(-5.04, -1.89) *	2.06	(0.68, 3.45) *

Positive affect or negative affect was included as the dependent variable. Age, gender, allocation, week, and allocation × week interaction were included as independent variables (* represents statistically significant). Abbreviations: BL: Baseline.

Figure 4. 7 Boxplots showing weekly positive affect (upper) and negative affect (lower) in patients with bipolar disorder randomised to lithium treatment or placebo.





	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Placebo (N)	15	15	14	14	14	12	11
Lithium (N)	18	19	19	17	18	17	16

Above is a table showing the number of participants who recorded satisfactory PANAS data each week

4.3.8 The effect of lithium on motor activity level in patients with bipolar disorder

From week one to week six in the linear mixed-effects model, a non-significant trend towards lower Amplitude was observed in the lithium group compared with placebo (Table 4.7 and Figure 4.8). In addition, there was a non-significant trend towards smaller MESOR after randomisation in the lithium group (Table 4.7 and Figure 4.8). The lithium × week six interaction was a significant predictor of MESOR (β = -5.03, 95% CI: -9.40, -0.26). However, the significant interaction could be the result of a limited sample size in week six. In week six, only five participants in the placebo group had satisfactory data analysed using the cosinor method.

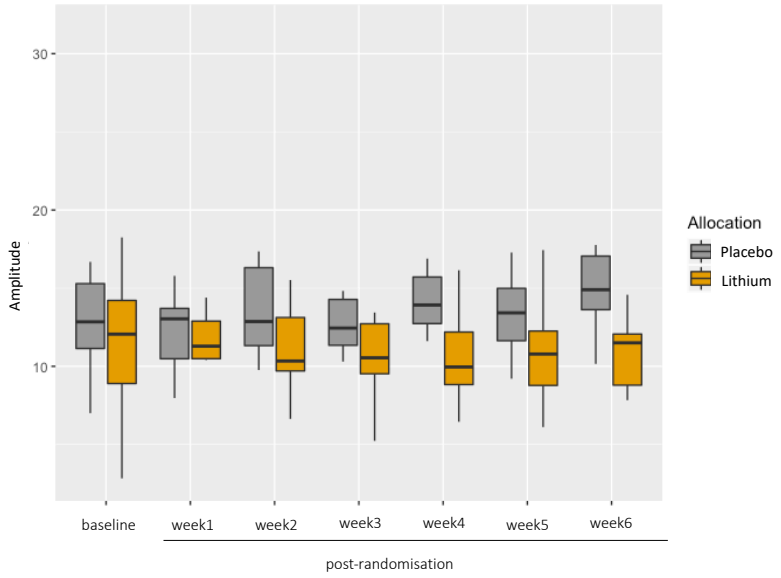
Table 4. 7 Results of linear mixed-effects models evaluating the changes of Amplitude and MESOR during six weeks after randomisation

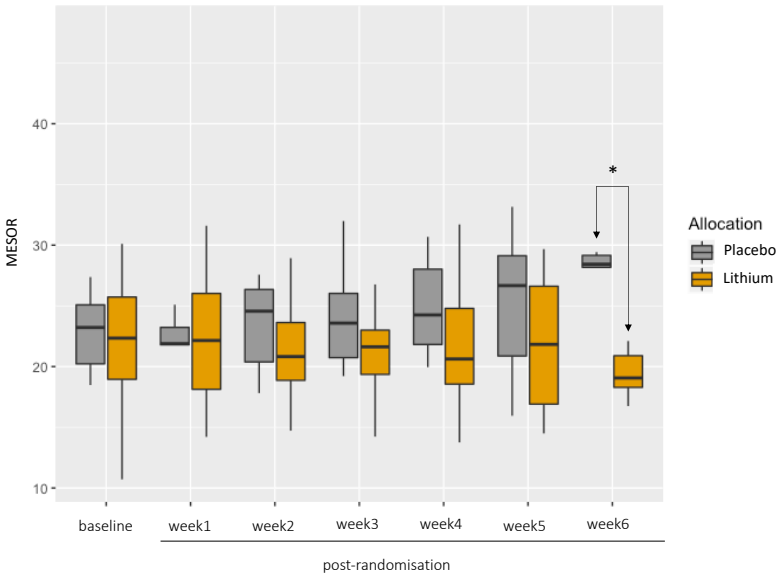
	Amplitude		MESOR	
	Coefficient estimates	**95% CI**	**Coefficient estimates**	**95% CI**
(Intercept)	14.34	(9.82, 18.71)	24.74	(19.30, 30.43)
Gender (Male)	0.88	(-1.61, 3.05)	2.07	(-1.18, 5.16)
Age	-0.04	(-0.14, 0.07)	-0.07	(-0.20, 0.07)
Allocation (Lithium)	-1.76	(-4.69, 1.26)	-2.24	(-6.06, 1.68)
Week1 vs BL	-0.03	(-2.31, 2.21)	0.00	(-2.74, 2.66)
Week2 vs BL	1.79	(-0.57, 4.09)	2.00	(-0.81, 4.95)
Week3 vs BL	0.32	(-1.76, 2.51)	1.79	(-0.77, 4.43)
Week4 vs BL	1.36	(-1.11, 3.75)	2.93	(-0.20, 5.91)
Week5 vs BL	-0.30	(-2.77, 2.14)	2.34	(-0.52, 5.54)
Week6 vs BL	1.38	(-1.61, 4.35)	3.03	(-0.57, 6.32)
Allocation* (Week1 vs BL)	-1.87	(-5.16, 1.59)	-0.47	(-4.38, 3.22)
Allocation* (Week2 vs BL)	-2.82	(-5.77, 0.06)	-1.76	(-5.92, 1.89)
Allocation* (Week3 vs BL)	-1.75	(-4.55, 1.04)	-1.89	(-5.42, 1.52)
Allocation* (Week4 vs BL)	-3.00	(-6.15, 0.08)	-2.63	(-6.52, 1.54)
Allocation* (Week5 vs BL)	-0.93	(-4.33, 2.35)	-2.27	(-6.43, 1.40)
Allocation* (Week6 vs BL)	-2.72	(-6.39, 0.64)	-5.03	(-9.40, -0.26) *

Amplitude or MESOR was included as the dependent variable. Age, gender, allocation, week and allocation × week interaction were included as independent variables (* represents statistically significant).

Abbreviations: BL: Baseline.

Figure 4. 8 Boxplots showing weekly Amplitude (upper) and MESOR (lower) in patients with bipolar disorder randomised to lithium treatment or placebo





	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Placebo (N)	13	9	8	11	7	7	5
Lithium (N)	16	7	12	13	11	12	9

* represents statistically significant). Above is a table showing the number of participants with satisfactory data analysed using the cosinor method each week

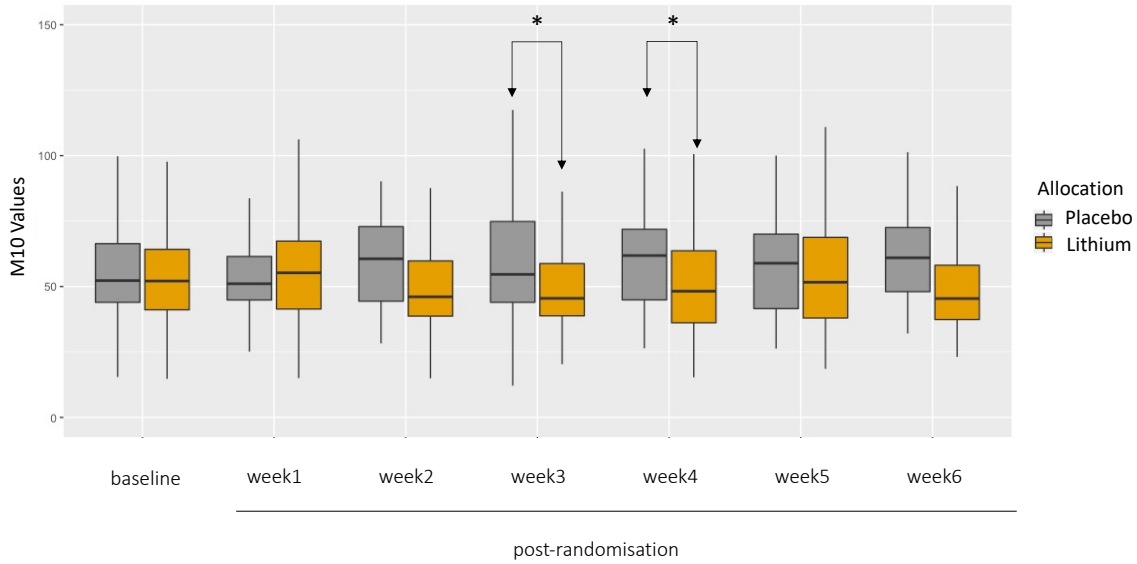
4.3.9 The effect of lithium on daytime activity in patients with bipolar disorder

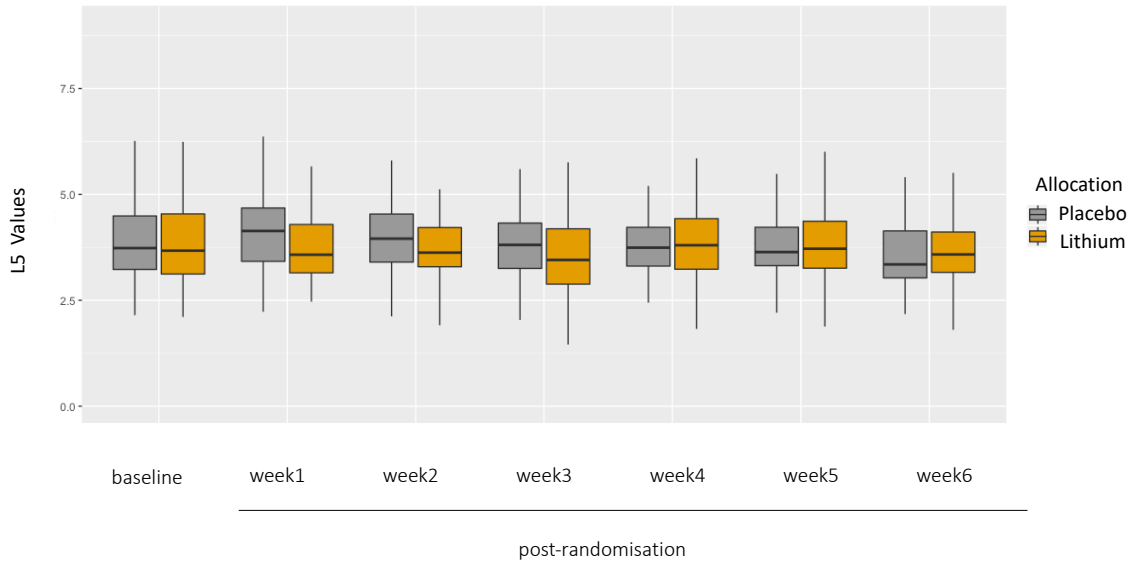
No significant differences were found between the lithium and placebo groups on the M10 and relative amplitude at baseline (Table 4.10). The direct effect of lithium on daytime activity was examined with daily actigraphy data using non-parametric analysis. Table 4.8 presents the results of the linear mixed-effects analysis comparing the direct effects of lithium and placebo on M10, adjusting for the effect of positive affect. Positive affect significantly predicted M10 (β = 0.86, 95% CI: 0.35, 1.41). Lithium had a significant effect on reducing M10 on week 3 (β= -11.62, 95% CI: -22.35, -1.04) and week 4 (β=-13.56, 95% CI: -24.63, -1.79) compared to placebo (Figure 4.9).

Causal mediation analysis was conducted to estimate direct and indirect effects of lithium on M10 during the six weeks after randomisation (Supplementary Figure 1 and Supplementary Table 3). Lithium had a significant direct effect on reducing M10 in week 3 (β= -14.35, 95% CI: -27.21, -2.95) and week 4 (β= -15.94, 95% CI: -29.88, -2.23) when compared with the placebo group. The positive affect did not significantly mediate the effect of lithium on M10.

Next, the daytime activity changes within each treatment group was analysed. In patients with bipolar disorder treated with lithium, there were no significant changes in M10 after randomisation. However, M10 in patients with bipolar disorder who took placebo significantly increased in week 4 (β = 8.08, 95% CI: 0.93, 15.12) (Table 4.9).

Figure 4. 9 Boxplots showing weekly M10 (upper) and L5 (lower) in patients with bipolar disorder randomised to lithium treatment or placebo





	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Placebo (N)	14	13	12	11	11	9	8
Lithium (N)	17	12	16	15	16	14	14

(* represents statistically significant). Above is a table showing the number of participants with satisfactory data analysed using the non-parametric method each week

Table 4.8 Results of linear mixed-effects analysis of M10 between lithium and placebo group, adjusting for mood changes six weeks after randomisation.

M10	Coefficient estimates	95% CI
(Intercept)	51.34	(32.39, 70.64)
Gender (Male)	9.21	(-1.80, 19.17)
Age	-0.20	(-0.65, 0.22)
Positive affect	0.86	(0.35, 1.41) *
Allocation (Lithium)	-2.36	(-14.56, 9.34)
Week1 vs BL	3.17	(-4.61, 10.57)
Week2 vs BL	6.68	(-0.83, 14.64)
Week3 vs BL	5.54	(-2.26, 13.23)
Week4 vs BL	7.97	(-0.12, 15.97)
Week5 vs BL	-0.87	(-9.46, 7.72)
Week6 vs BL	2.15	(-7.48, 12.66)
Allocation* (Week1 vs BL)	-6.92	(-18.23, 4.28)
Allocation* (Week2 vs BL)	-7.70	(-18.36, 3.18)
Allocation* (Week3 vs BL)	-11.62	(-22.35, -1.04) *
Allocation* (Week4 vs BL)	-13.56	(-24.63, -1.79) *
Allocation* (Week5 vs BL)	-1.11	(-12.45, 11.64)
Allocation* (Week6 vs BL)	-8.29	(-22.48, 4.08)

M10 was the dependent variable. Age, gender, positive affect, and week × allocation interaction were independent variables (* represents statistically significant). Abbreviations: BL: Baseline.

Table 4. 9 Results of linear mixed-effects analysis evaluating M10 changes within each treatment group six weeks after randomisation.

M10	Lithium		Placebo	
	Coefficient estimates	95% CI	Coefficient estimates	95% CI
(Intercept)	62.80	(42.03, 85.02)	42.19	(12.19, 70.57)
Gender (Male)	7.35	(-2.64, 17.98)	9.82	(-11.23, 29.34)
Age	-0.51	(-1.07, 0.05)	-0.03	(-0.73, 0.70)
Positive affect	0.52	(-0.27, 1.32)	1.12	(0.45, 1.81) *
Week1 vs BL	-4.60	(-13.72, 3.95)	3.80	(-3.22, 10.65)
Week2 vs BL	-1.73	(-10.63, 7.26)	6.73	(-0.09, 14.06)
Week3 vs BL	-6.83	(-15.23, 1.52)	5.64	(-0.79, 12.32)
Week4 vs BL	-6.74	(-16.28, 1.87)	8.08	(0.93, 15.12) *
Week5 vs BL	-3.22	(-12.28, 6.40)	-1.50	(-9.72, 6.93)
Week6 vs BL	-7.35	(-17.20, 1.61)	1.02	(-7.08, 9.95)

M10 was the dependent variable. Age, gender, week, and positive affect were independent variables (* represents statistically significant). Abbreviations: BL: Baseline.

4.3.10 The effect of lithium on nocturnal arousal and sleep quality in patients with bipolar disorder

There was no significant difference between the lithium and placebo groups on the L5 at baseline (Table 4.10). The linear mixed-effects model which compared the direct effects of lithium and placebo on L5 after adjusting for the impact of positive affect as a mediator (Table 4.11) revealed that positive affect (β = 0.00, 95% CI: -0.02, 0.02) did not predict L5. Neither lithium (β = 0.03, 95% CI: -0.43, 0.48) nor lithium × week interaction over six weeks predicted L5 (Figure 4.9). Causal mediation analysis was conducted to estimate direct and indirect effects of lithium on L5 during the six weeks after randomisation (Supplementary Figure 2 and Supplementary Table 4). Lithium did not have a significant

direct effect on L5 when compared with the placebo group. The positive affect did not significantly mediate the effect of lithium on L5.

The sleep quality of bipolar patients was investigated using both the total score and sub-item scores of the SCI questionnaire. Twenty-three participants (thirteen of them took lithium) completed both questionnaires. A comparison of the total scores of the SCI questionnaire was conducted at baseline between the lithium (Mean = 19.6, SD = 6.2, N=15) and placebo groups (Mean = 13.6, SD = 3.7, N=10). The total scores of the SCI in the lithium group were significantly higher than those in the placebo group ($t(23) = -2.74$, $df = 23$, $p = 0.01$, 95% confidence interval: -10.53, -1.47).

Lithium had no significant impact on sleep quality (all $p > 0.05$) (Table 4.12). Pearson correlation analysis showed no association between SCI total score and non-parametric circadian variables at baseline: L5 and M10 (all $p>0.05$, Figure 4.10). There was no association between L5 and related individual items on SCI (Supplementary Figure 5). Table 4.13 presents the results of the linear mixed-effects analysis comparing the changes in sleep symptoms measured by QIDS-SR_{16}. No significant differences between lithium and placebo were found in sleep symptoms over six weeks.

Table 4. 10 Results of Mann-Whitney U tests comparing actigraphy parameters in the lithium and placebo groups at baseline.

Outcome	Lithium			Placebo			p-value
	Median	**IQR**	**N**	**Median**	**IQR**	**N**	
M10	52.8	(41.5, 64.8)	17	52.4	(44.0, 66.5)	14	0.45
L5	3.7	(3.1, 4.5)	17	3.7	(3.2, 4.5)	14	0.39
Relative Amplitude	0.87	(0.82, 0.90)	17	0.87	(0.83, 0.89)	14	0.85

Abbreviation: IQR, Interquartile range.

Table 4. 11 Results of linear mixed-effects analysis evaluating changes in L5 adjusting for mood changes six weeks after randomisation.

L5	Coefficient estimates	95% CI
(Intercept)	3.73	(3.04, 4.46)
Gender (Male)	0.18	(-0.25, 0.58)
Age	0.00	(-0.01, 0.02)
Positive affect	0.00	(-0.02, 0.02)
Allocation (Lithium)	0.03	(-0.43, 0.48)
Week1 vs BL	0.10	(-0.19, 0.39)
Week2 vs BL	-0.08	(-0.38, 0.24)
Week3 vs BL	-0.17	(-0.46, 0.10)
Week4 vs BL	-0.18	(-0.51, 0.12)
Week5 vs BL	-0.15	(-0.49, 0.23)
Week6 vs BL	-0.24	(-0.62, 0.13)
Allocation* (Week1 vs BL)	0.03	(-0.39, 0.48)
Allocation* (Week2 vs BL)	-0.15	(-0.58, 0.26)
Allocation* (Week3 vs BL)	-0.27	(-0.69, 0.18)
Allocation* (Week4 vs BL)	0.05	(-0.42, 0.53)
Allocation* (Week5 vs BL)	0.17	(-0.35, 0.67)
Allocation* (Week6 vs BL)	0.04	(-0.48, 0.60)

L5 was the dependent variable. Age, gender, positive affect, and week × allocation interaction were the independent variables (* represents statistically significant). Abbreviations: BL: Baseline.

Table 4. 12 Allocation × time interaction effects on sleep latency, remaining asleep, sleep quality, duration of the sleep problem, daytime performance, and extent troubled by sleep problems measured by individual question and overall sleep quality measured by total scores in the SCI questionnaire

	Two-way ANOVA (Allocation × time interaction)		
	F values	df	P values
Q_1. ... how long does it take you to fall asleep?	0.056	1	0.814
Q_2...if you then wake up during the night ... how long are you awake for in total?	0.046	1	0.832
Q_3 ... how many nights a week do you have a problem with your sleep?	1.854	1	0.180
Q_4 ... how would you rate your sleep quality?	0.237	1	0.629
Q_5 ... affected your mood, energy, or relationships?	2.128	1	0.152
Q_6 ... affected your concentration, productivity, or ability to stay awake	2.261	1	0.113
Q_7 ... troubled you in general	3.461	1	0.070
Q_8 ... how long have you had a problem with your sleep?	0.122	1	0.728
Total scores	1.803	1	0.186

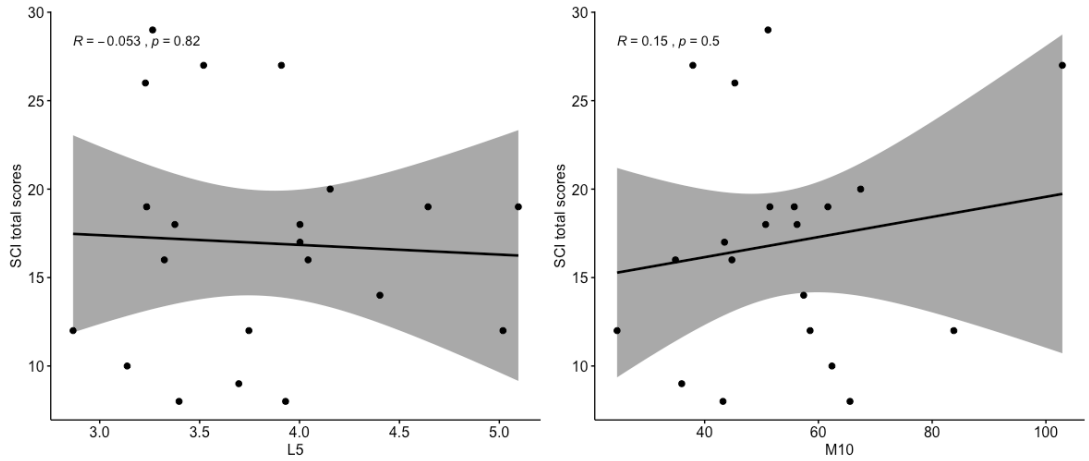
Table 4. 13 Results of linear mixed-effects analysis evaluating the changes in sleep symptoms during six weeks after randomisation.

Sleep symptoms	Coefficient estimates	95% CI
(Intercept)	5.44	(3.37, 7.65)
Gender (Male)	-0.81	(-2.00, 0.36)
Age	-0.03	(-0.08, 0.021)
Allocation (Lithium)	-0.79	(-2.33, 0.82)
Week1 vs BL	-0.13	(-1.45, 1.21)
Week2 vs BL	0.27	(-1.20, 1.69)
Week3 vs BL	-1.13	(-2.34, 0.12)
Week4 vs BL	-0.33	(-1.65, 1.04)
Week5 vs BL	-0.71	(-2.16, 0.68)
Week6 vs BL	-1.18	(-2.55, 0.18)
Allocation* (Week1 vs BL)	0.24	(-1.66, 2.06)
Allocation* (Week2 vs BL)	-1.02	(-2.87, 0.93)
Allocation* (Week3 vs BL)	0.72	(-1.05, 2.35)
Allocation* (Week4 vs BL)	-0.43	(-2.26, 1.34)
Allocation* (Week5 vs BL)	0.56	(-1.20, 2.49)
Allocation* (Week6 vs BL)	0.65	(-1.24, 2.48)

The total score of four subitems of the QIDS-SR_{16} questionnaire was included as the dependent variable. Age, gender, week, allocation and week × allocation interaction were included as independent variables (* represents statistically significant). Abbreviations: BL: Baseline.

Figure 4. 10 Pearson correlation between SCI total score and non-parametric circadian variables at baseline.

A. Correlation of L5 with SCI total score. B. Correlation of M10 with SCI total score



R represents correlation coefficient; shaded area represents 95% CI; dots show individual data points.

4.4 Discussion

The effect of lithium on motor activity in bipolar patients and the interaction between mood and motor activity was examined using fine-grained actigraphy data and daily self-reported mood data. The main findings of this chapter do not support the hypothesis that lithium has a direct effect on motor activity in patients with bipolar disorder when compared with a placebo. Despite this, lithium had a significant direct effect on reducing daytime activity in two of the weeks, suggesting that lithium might stabilise daytime activity in patients with bipolar disorder by preventing the significant elevation of daytime activity observed when using a placebo. Lithium did not impact nocturnal arousals and sleep quality. In addition, results revealed a significant association between daytime activity and positive affect. These findings should be interpreted with caution because of the limited sample size. Future experimental medicine studies in bipolar patients should enrol larger numbers of participants and adopt multi-modal recording mapping of both motor activity and mood.

4.4.1 Investigating the effect of lithium on motor activity in patients with bipolar disorder

The findings of this chapter do not support the hypothesis that lithium has direct effect on increasing motor activity in patients with bipolar disorder compared with placebo. There was, however, a significant direct effect of lithium on reducing daytime activity in two of the weeks. There may be different interpretations of this finding.

First, lithium might stabilise daytime activity in patients with bipolar disorder by preventing the significant elevation of daytime activity observed when using a placebo. In between-

group analysis, lithium significantly reduced the daytime activity measured by M10 in week three and week four compared with placebo. This result was further supported by the causal mediation analysis which showed that lithium had a significant direct effect on reducing M10 during weeks 3 and 4. In addition, there was a consistent trend towards lower Amplitude and MESOR from week one to week six in the lithium group. The findings that positive affect did not significantly mediate the effect of lithium on M10 and lithium did not significantly impact manic and depressive symptoms compared to the placebo further support the direct impact of lithium on reducing daytime activity. According to within-group analysis, there were no significant changes in daytime activities within the lithium group. In contrast, a significant increase in daytime activity was observed in week four in the placebo group. Therefore, this effect of reducing daytime activity might be interpreted as a stabilising effect on daytime activity.

However, these results are not robust or consistent and should be interpreted with caution. The significant effect of lithium on reducing daytime activity did not last through week six. Potential reasons for this effect not being significant after week four were less statistical power in week five, and particularly in week six where some participants finished recording early in the week. Additionally, it should be noted that the within-group analysis was not the primary analysis and was carried out mainly for supplementary and exploratory purposes. Studies that make conclusions solely on the basis of within-group comparisons within randomised groups have been found to have higher type I error rates and may lead to false-positive findings [239, 240]. Overall, the findings should be replicated in larger cohorts.

The motor-activity stabilising effect of lithium has been reported in animal models. For example, lithium reduced the voluntary activity of rats by inhibiting the initiation of

voluntary activities without affecting their muscle strength [241, 242]. Lithium also attenuated d-amphetamine-induced hyperactivity in rats and mice [243, 244].

There are very few studies investigating lithium's effect on motor activity in patients with bipolar disorder. These studies were heterogeneous in terms of the comparators, diagnosis of bipolar disorder subtype, mood state, length of recording period and study design. Therefore, it is challenging to compare studies directly. In a randomised controlled trial with patients meeting diagnostic criteria for bipolar II disorder and a current depressive episode, Hwang et al. found no significant changes in Amplitude in patients who took lithium [172]. This study is subject to a high risk of bias, and the study quality is relatively low.

Two observational studies compared lithium with active comparators. Both studies were limited by their study design; the detected differences between groups may be pre-existing differences rather than changes induced by pharmacological treatments. Benizri et al. showed that euthymic patients with bipolar disorder who took lithium had a significantly larger amplitude of circadian-rest-activity than patients taking anticonvulsants. Limitations included the absence of data on bipolar disorder subtype, mood state, and other affective symptoms [176]. In another cohort study, Scott et al. found lithium responders had higher levels of motor activity measured by M10 and Amplitude. This study enrolled patients with bipolar I disorder and compared the circadian rest-activity variables between lithium responders and lithium non-responders. A higher level of activity might result from more successful symptom alleviation because lithium responders had fewer residual symptoms and better functional recovery than lithium non-responders [245].

The effect of lithium on reward processing and impulse control may be an underlying mechanism of lithium's motor activity stabilising effect. Disturbances in reward processing have been considered to be a component of bipolar disorder pathophysiology [246]. Lithium has shown significant impacts on the reward system. In patients with bipolar disorder comorbid with pathological gambling, lithium effectively reduced gambling behaviour [247]. In healthy participants, lithium stabilised reward processing by increasing responsiveness to reward anticipation and dampening reward outcome-related activity [248]. Future research should investigate the effect of lithium on the fronto-striatal neural circuit, which has been considered the central component of the reward system [246].

Second, the adverse reaction to lithium may explain the lower level of daytime activity in the lithium group. It has been reported that lithium therapy has several acute adverse effects, including fatigue, lethargy, and gastrointestinal disturbances, including nausea, vomiting, and diarrhoea [249, 250]. A direct or indirect result of these adverse events could be a reduction in daytime activity. In this study, the lithium group reported a greater number of adverse events and more frequent complaints of fatigue, poor sleep, nausea, headache, and light-headedness compared with the placebo group. In addition, a significant reduction in daytime activity was observed during weeks three and four and did not last through week six. Therefore, it should be aware of the possibility that the reduction in activity observed during the early and middle phases of the trial could reflect an acute adverse effect of lithium. Ideally, future studies with a larger sample size could compare the activities of participants with or without these abovementioned adverse reactions to lithium. This would assist in the understanding of lithium's therapeutic effect.

4.4.2 Lithium had no significant impact on nocturnal arousal and sleep quality

Despite the utilisation of three different methods to assess nocturnal arousal and sleep quality, no evidence was found that lithium had an impact on sleep quality. There are several potential reasons why Oxlith did not detect any significant differences in sleep quality between groups. First, sleep quality was not a primary outcome of the Oxlith and so the methods utilised may not have been sensitive enough to detect the differences in sleep disturbances between groups. Two of the most commonly used and sensitive methods for assessing sleep disturbances are presented below. The Pittsburgh Sleep Quality Index is a self-report questionnaire evaluating the sleep disturbances over one month [162]. Polysomnography is the gold-standard objective measurement of sleep [251]. Second, the sample size of this study is relatively small and so the effects may have been too small to be detected.

Third, the sleep quality of participants in the lithium group was significantly better than that of the comparison group at baseline. As suggested by Espie and colleagues [238], a score of 16 on the SCI is considered the threshold for clinically significant insomnia. Participants in the lithium group had a much lower risk of being diagnosed with insomnia disorder than participants in the placebo group. Therefore, the finding that no significant differences in sleep quality between two groups can be explained in two ways. On the one hand, lithium may have reached a ceiling effect to improve sleep quality. On the other hand, the baseline imbalance of sleep quality could reduce the statistical power to detect differences between two groups if lithium were to negatively affect sleep quality. In this study, six of the nineteen participants who took lithium reported poor sleep as an adverse event, compared with one of sixteen participants taking placebo. Fourth, six weeks after the treatment may not long

enough to detect significant sleep quality changes; a study with a longer-term follow-up would be needed to test this possibility. Lastly, participants in the Oxlith were heterogeneous in terms of diagnosis of bipolar disorder subtypes and different levels of depressive symptoms and sleep concerns; the effect of lithium may not have been detected because of the heterogeneity of the sample.

It is essential to incorporate sleep measures in bipolar disorder research. Studies have found that bipolar patients who had poor sleep quality were associated with greater symptoms and worse long-term treatment outcomes [252, 253]. Our systematic review found that the effect of lithium on sleep quality was uncertain (Chapter 2). Due to methodological limitations, no evidence was found indicating that lithium had any impact on sleep quality in this chapter. Thus, it is imperative that future studies adopt sleep-specific measures and have a large, well-characterised cohort to investigate the effect of mood stabilisers on sleep quality in bipolar disorder.

4.4.3 An association between mood and motor activity

Our results revealed a significant association between positive affect and daytime activity, which aligns with previous findings in healthy participants and bipolar patients. In previous studies involving healthy individuals, an association between physical activity and positive emotion style was observed; an increase in physical activity predicted a higher level of positive affect. [219, 220, 254]. Another study revealed a bidirectional relationship between these two domains [221]. In patients with bipolar disorder, a positive association between mood and activity was found by a smartphone-based monitoring system over six to nine months [255]. Another study found a prospective association between motor activity and

subsequent mood changes, with increased motor activity in the previous period predicting increased mood in the subsequent period [179]. These findings suggest that changing physical activity can serve as an intervention to improve positive mood.

Both the association between mood and motor activity and the effect of lithium on positive affect suggest that mood is a mediator that needs to be adjusted for in the regression models when examining the direct effects of lithium on motor activity. The results showed that lithium directly affected daytime activity, and that positive affect did not significantly mediate this effect. These results reveal the complex nature of physiological and psychological changes induced by lithium treatment in bipolar disorder. This association between mood and activity domains underscores the need for tracking multimodal subjective and objective data of motor activity and mood changes in real-time to investigate the mechanisms of action of lithium treatment.

The emergence of digital phenotyping technology offers new possibilities for mental health research [256]. For example, Merikangas et al. demonstrated the feasibility of real-time, simultaneous, multimodal acquisition of objective and subjective parameters of motor activity, energy, sleep, and mood changes in patients with bipolar disorder [179]. Our proof-of-concept study extends use of these digital phenotyping techniques to an experimental medicine paradigm and to exploration of the mechanism of a pharmacological treatment. However, compared with lab-based studies where conditions are better controlled, digital phenotyping studies adopting ecological assessments were susceptible to more variability [256]. A randomised controlled, double-blind study design could help circumvent this problem.

4.4.4 Limitations

The study had several limitations. First, this proof-of-concept study had a limited sample size. These results need to be replicated in a larger sample. Second, three actigraphy devices were used for each participant, which led to more missing data. To increase the maximum period of recording, we could lower the frequency of measurement or choose another product with longer battery life. Third, there may be hidden, unmeasured confounding factors between the mediator (positive affect) and the outcome that can bias the mediation analysis. Since Oxlith is a randomised controlled trial, participants were randomly assigned to intervention groups, so it may be possible to assume that intervention-outcome and intervention-mediator effects are unconfounded. However, the mediator-outcome effect might be confounded [257]. The robustness of findings has not been examined with respect to potential unmeasured mediator-outcome confounding factors using sensitivity analysis because the medsens() function in the mediation package was not compatible with the linear mixed-effect model [224]. Finally, limited by this short-term study design, we did not differentiate between lithium responders and lithium non-responders. Lithium responders had distant clinical features and fewer comorbidities [258]. The heterogeneous response to lithium may undermine the power to detect differences between lithium and placebo groups.

4.4.5 Conclusion

Motor activity in bipolar disorder has received increasing research attention. In this study, the direct effect of lithium on motor activity was investigated using digital devices to simultaneously record daily mood changes and motor activity. The findings do not support the hypothesis that lithium may have a direct effect on increasing motor activity in patients

with bipolar disorder. Even though the results were not robust or consistent, lithium was found to directly reduce daytime activity, which may indicate that lithium stabilises daytime activity levels. In addition, lithium did not affect nocturnal arousal and sleep quality. The significant association between mood and motor activity highlighted the need for a multimodal acquisition of mood and activity data in future studies. While interpretation of the results was limited by a small sample size, this high-intensity, randomised, double-blind, placebo-controlled experimental medicine study coupled with digital phenotyping technology provided a methodological framework for understanding the therapeutic target of current mood stabilisers and contributing to the development of novel mood stabilisers.

Chapter 5: The effect of lithium on the timing and variability of circadian rest-activity patterns in patients with bipolar disorder

“日出而作，日入而息，逍遥于天地之间而心意自得”

-《庄子·让王》

“When the sun comes up, I work; when the sun goes down, I rest. I wander free and easy between heaven and earth, and my mind has found all that it could wish for.”

-《Zhuangzi· Giving Away a Throne》Translated by Burton Watson

5.1 Introduction

5.1.1 The importance of stable and synchronised circadian rhythm

Rhythmicity is a characteristic shared by all living things and circadian rhythm is one of the most common biological rhythms in humans [56]. The circadian rhythms of healthy individuals are regular, stable, and synchronised both within the body and with the external environment, particularly with light/dark cycles [56]. Circadian disruption is an umbrella term, which denotes a range of disturbances in the amplitude and phase of circadian rhythm. As introduced in chapter one, circadian disruption is one of the leading features of bipolar disorder, including an unstable or delayed circadian rhythm as well as other patterns of disruption [3].

Unstable or delayed circadian rhythm in patients with bipolar disorder are associated with worse clinical outcomes. Euthymic patients with bipolar disorder and unstable circadian rest-activity had more mood variability and delayed and more variable circadian phase [259]. Conversely, increased circadian rest-activity stability and robustness were associated with fewer manic symptoms in bipolar I patients [260]. Chronotype, also known as Morningness-Eveningness, is the individual preference for the daily timing of activity, a behavioural manifestation of circadian rhythm [60]. Eveningness represents a general preference for evening activity and is also a proxy marker of circadian rhythm disruption [261]. Romo-Nava et al. suggested eveningness as a distinctive sub-phenotype of bipolar disorder [180]. Patients with bipolar disorder with a higher level of eveningness had an early age-at-onset, more prior mood episodes, more disordered eating behaviours, higher rates of suicide attempts, substance abuse and somatic comorbidities [180, 261]. Individuals who show more morningness have more alertness in the morning and prefer a morning activity. Their circadian rhythms tend to synchronise better with external light/dark cycles. In patients with bipolar disorder, a higher level of morningness was associated with better clinical outcomes, milder depressive and manic symptoms, and fewer past suicide attempts [144]. Esaki et al. found that a higher level of morning light exposure was associated with a lower risk of depressive episode relapse in patients with bipolar disorder [262].

5.1.2 Chronotherapies in bipolar disorder

Treatment modalities targeting the circadian phase and the regularity of behavioural activity have shown efficacy in improving affective symptoms. Melatonin is one of the major outputs of the circadian clock and the onset of melatonin secretion is a marker of the circadian phase

[8]. Ramelteon, the melatonin receptor agonist, was found to improve depressive symptoms in bipolar I patients with manic symptoms and insomnia [9] and to prevent relapse in euthymic bipolar patients [10]. Sleep phase advance as a chronotherapy not only showed an antidepressant effect [11] but also produced a synergic treatment effect with lithium in patients with bipolar disorder [12]. Interpersonal and social rhythm therapy (IPSRT) is a manualised treatment targeting interpersonal difficulties and disrupted social rhythms and daily routines. The goal of IPSRT is to improve the regularity of daily routines [263]. Randomised controlled trials supported the effectiveness of IPSRT in achieving faster recovery from depression [264] and more extended time in remission [265].

5.1.3 Limited evidence of the effect of lithium on circadian rhythm in patients with bipolar disorder

Because cellular and animal research support the role of lithium in modifying circadian rhythm [156, 189], it is tempting to speculate that the phase regulation and increase of circadian rest-activity regularity could be lithium's therapeutic mechanism of action in patients with bipolar disorder. Despite growing evidence has shown that lithium has an impact on circadian rhythm [43, 156, 189], very few studies of the effect of lithium on circadian phase and variability have been conducted in patients with bipolar disorder. Therefore, the effects of lithium on the timing and variability of circadian rhythm in patients with bipolar disorder are still open questions.

A recent systematic review suggested that lithium stabilised circadian rhythm by lengthening the period and delaying the phase of circadian rhythm. These conclusions were based on findings from mice, rats, hamsters, and healthy human participants [156]. The systematic

review included nineteen studies of patients with bipolar disorder; however, methodological limitations precluded definitive conclusions regarding lithium's effect on circadian phase and period. Five of these studies did not adopt standardised 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. Two of the studies involved total sleep deprivation that can perturb circadian rest-activity. The other studies enrolled patients with bipolar disorder but primarily investigated the association between circadian genes polymorphism and lithium treatment response [156]. These pharmacogenetic studies gave credence to the role of circadian genes in lithium therapeutic response. However, some of the findings did not appear to be reproducible and would require replication in a larger sample. While the preponderance of the evidence suggested that lithium lengthened the period and delayed the phase of circadian rhythm in animal models and healthy individuals, this has not yet been conclusively established in patients with bipolar disorder.

The updated systematic review in chapter 2 included five studies published from 2014 to 2018. Only one study investigated the effect of lithium on the variability of circadian rest-activity in patients with bipolar disorder. Benizri et al. found that lithium treatment was associated with smaller intradaily variability than anticonvulsants [176]. None of the included studies explored the stability of circadian rest-activity over a 24-hour period. The meta-analysis revealed that lithium was associated with a greater morningness. However, all included studies were observational studies and adopted self-report questionnaires to measure chronotype. Thus, the causal relationship between lithium treatment and the advance of circadian timing is still unclear.

The purpose of this chapter was to examine the effect of lithium on the timing and variability of circadian rest-activity in patients with bipolar disorder. Two hypotheses were investigated in this chapter (1) whether lithium has a direct effect on advancing the phase of circadian rest-activity in patients with bipolar disorder and (2) whether lithium reduces the variability of circadian rest activity in patients with bipolar disorder.

5.2 Method

5.2.1 Study design

The Oxlith study design is described in full in chapter 3 (3.1.1 section)

Relevant to this chapter, participants who met the eligibility criteria entered the pre-randomisation phase, which lasted for approximately two weeks. The pre-randomisation phase enabled participants to be familiar with the actigraphy and daily digital symptom monitoring tools. Every participant received an actigraph on the screening day visit. Participants were asked to continuously wear these devices on their non-dominant wrist from the beginning of the study to the end of the randomised phase. Due to limitation of data storage and battery life of each device, three actigraphs were given to every participant during the study; replacements were planned for day eight and week four visits. Following the screening visit, each participant began reporting mood daily using the Positive and Negative Affect Schedule Short Form (PANAS-SF).

5.2.2 Measuring circadian rest-activity

This methodology is described in Chapter 4

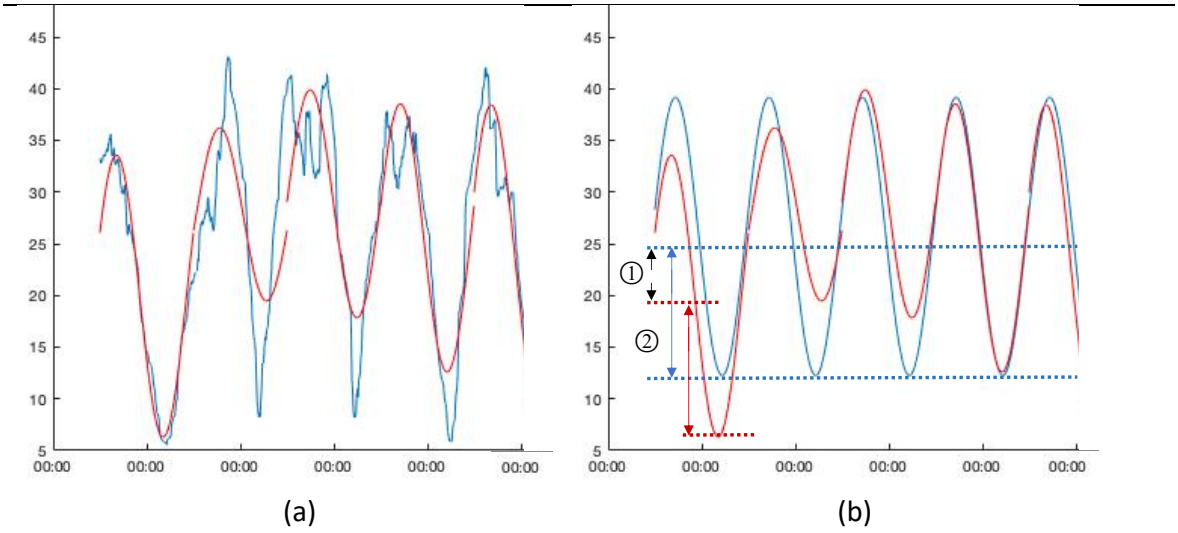
5.2.3 Quantifying the timing of the circadian rest-activity patterns

The cosinor method was adopted to calculate the Phase of the circadian rest-activity patterns. Phase corresponds to the timing of the peak of the sinusoidal wave [59]. Non-parametric circadian rhythm analysis was also performed to quantify the timing of the rest-activity rhythm. M10 onset time denotes the onset time of the most active ten-hour period of the day. L5 onset time corresponds to the onset time of the least active five-hour period of the day [61].

5.2.4 Quantifying the variability of the circadian rest-activity patterns

The variability of circadian rest-activity patterns was characterised by comparing the Cosinor fit for each day and the average fit for the week [225]. The variability of circadian rest-activity patterns each week was calculated and compared between the lithium and placebo groups. For each week, Amplitude and MESOR of the daily sinusoid fit and the weekly average sinusoid fit were extracted. stdMesor and stdAmplitude corresponded to the standard deviation of the differences between the daily fit and the weekly sinusoid fit [225] (Figure 1). In addition, the root mean square error (RMS error) between the daily and total sinusoid was also calculated [225]. Larger RMS error represents more significant variability.

Figure 5. 1 A demonstration of quantifying the variability of the circadian rest-activity



(a) the integrated acceleration signals (blue) with a sinusoid fit each 24-hour period (red). (b) the comparison between daily (red) and weekly (blue) sinusoids with the difference between MESORs ① and Amplitudes ② shown.

5.2.5 Measuring mood

The Positive and Negative Affect Schedule Short Form (PANAS-SF) was used to assess day-to-day variations of mood. The methodology is described in detail in Chapter 3 (section 3.9.3).

5.2.6 Statistical analysis

Missing data analysis

Missing data analysis for non-parametric circadian rhythm analysis is described in chapter 4. The Fisher's exact test was used to determine whether the proportion of missing data was different depending on the allocation in the datasets analysed by the cosinor method [211]. The Fisher's exact test was carried out using R (R Core Team, Vienna). If $p < 0.05$, the differences were considered to be statistically significant.

Linear mixed-effects model:

The methodology is described in detail in chapter 3 (3.11.7 Linear mixed-effects model)

Mediation analysis:

The methodology is described in detail in chapter 3 (3.11.8 Mediation analysis)

5.3 Results

5.3.1 Baseline demographic characteristics and missing data analysis

The demographic characteristics of the participants were described in Chapter 4 (section 4.3.2). Missing data analysis for non-parametric circadian rhythm analysis was described in chapter 4. When comparing the lithium and placebo groups, no significant differences in the amount of missing data in the circadian rest-activity data stream were found (section 4.3.4).

In the datasets analysed by the cosinor method, no significant differences were found in the proportion of missing data between the lithium and placebo groups (p=0.69, Table 5.1).

Table 5. 1 Missing data analysis for datasets analysed by the cosinor method

	Not missing	Missing	P value
Placebo: N (%)	60 (57.1)	45 (42.9)	0.64
Lithium: N (%)	80 (60.2)	53 (39.8)	

N represents the number of data points.

5.3.2 The effect of lithium on the timing of circadian rest-activity in patients with bipolar disorder

The effect of lithium on the phase of circadian rest-activity was investigated with *weekly* actigraphy data. Table 5.2 shows the linear mixed-effects analysis comparing the effect of lithium and placebo on phase over six weeks. Neither lithium treatment (β = -0.43, 95% CI: -1.66, 0.87) nor the lithium × time interaction over six weeks significantly predicted the phase of circadian rest-activity. Age was a significant predictor of the phase of circadian rest-activity. Older patients tended to start their daily activity earlier than younger patients.

Next, the effect of lithium on M10 onset time and L5 onset time was examined with *daily* actigraphy data using non-parametric analysis. At baseline, no difference in M10 onset time

was observed between the lithium and placebo groups (Table 5.5). The linear mixed-effects analysis was used to compare the direct effects of lithium and placebo on M10 onset time, adjusting for positive affect as a mediator. Lithium numerically reduced the M10 onset time from week one to week six after randomisation (Table 5.3) but this trend over six weeks was not statistically significant. Lithium significantly reduced M10 onset time in week 4 (β = -1:46h, 95% CI: -3:41h, -0:06h) compared with placebo. Positive affect significantly predicted M10 onset time of the circadian rest-activity (β = -0:05h, 95% CI: -0:10h, -0:00h).

Causal mediation analysis was conducted to estimate direct and indirect effects of lithium on M10 onset time during the six weeks after randomisation (Supplementary Figure 3 and Supplementary Table 5). Lithium had no significant direct effect on M10 onset time in comparison with the placebo group. Positive affect did not significantly mediate the effect of lithium on M10 onset time.

M10 onset time changes within each treatment group were examined as an exploratory and supplementary analysis. In patients with bipolar disorder treated with lithium, lithium significantly reduced M10 onset time in week one (β = -1:28h, 95% CI: -2:52h, -0:01h), week two (β = -1:52h, 95% CI: -3:11h, -0:34h), week three (β = -1:42h, 95% CI: -3:02h, -0:25h), and week six (β = -1:40h, 95% CI: -3:11h, -0:05h). However, there were no significant changes in M10 onset time in the placebo group over the six weeks after randomisation (Table 5.4).

At baseline, no difference in L5 onset time was observed between the lithium and placebo groups (Table 5.5). It was found that the effect of time on reducing L5 onset time was

statistically significant in weeks two, five, and six following randomisation. No significant differences on L5 onset time were found between the lithium and placebo groups six weeks after randomisation. Positive mood was a significant predictor of L5 onset time (β = -0:04h, 95% CI: -0:06h, -0:01h) (Table 5.3). To estimate the indirect and direct effects of lithium on L5 onset time during the six weeks following randomisation, a causal mediation analysis was performed (Supplementary Figure 4 and Supplementary Table 6). In comparison with the placebo group, lithium did not have a significant direct effect on L5 onset time. Positive affect did not significantly mediate the effect of lithium on L5 onset time.

Table 5. 2 Results of linear mixed-effects models evaluating the changes of phase during six weeks after randomisation.

Phase	Coefficient estimates	95% CI
(Intercept)	17.03	(15.23,18.74)
Gender (Male)	0.64	(-0.37, 1.68)
Age	-0.05	(-0.09, -0.01) *
Allocation (Lithium)	-0.43	(-1.66, 0.87)
Week1 vs BL	-0.60	(-1.47, 0.22)
Week2 vs BL	-0.39	(-1.31, 0.52)
Week3 vs BL	-0.39	(-1.29, 0.44)
Week4 vs BL	0.14	(-0.79, 1.07)
Week5 vs BL	0.02	(-0.91, 0.96)
Week6 vs BL	-0.94	(-2.01, 0.19)
Allocation* (Week1 vs BL)	0.26	(-1.00, 1.56)
Allocation* (Week2 vs BL)	-0.47	(-1.67, 0.67)
Allocation* (Week3 vs BL)	-0.22	(-1.37, 1.04)
Allocation* (Week4 vs BL)	-0.32	(-1.65, 0.91)
Allocation* (Week5 vs BL)	-0.47	(-1.73, 0.73)
Allocation* (Week6 vs BL)	0.77	(-0.67, 2.17)

Phase was the dependent variable. Age, gender, allocation, week and allocation × week interaction were independent variables (* represents statistically significant). Abbreviations: BL: Baseline.

Table 5. 3 Results of linear mixed-effects analysis of M10 onset time and L5 onset time between lithium and placebo group, adjusting for positive and negative affect changes six weeks after randomisation.

	M10 onset time		L5 onset time	
	Coefficient estimates	**95% CI**	**Coefficient estimates**	**95% CI**
(Intercept)	14.27	(12.04, 16.70)	27.50	(25.67, 29.47)
Gender (Male)	0.23	(-0.99, 1.46)	-0.13	(-1.16, 0.92)
Age	-0.04	(-0.09, 0.01)	-0.03	(-0.08, 0.01)
Positive affect	-0.08	(-0.17, -0.00) *	-0.06	(-0.10, -0.02) *
Allocation (Lithium)	0.67	(-0.80, 2.46)	-0.42	(-1.60, 0.72)
Week1 vs BL	-0.82	(-1.96, 0.29)	-0.44	(-0.97, 0.06)
Week2 vs BL	-0.59	(-1.83, 0.65)	-0.58	(-1.18, -0.03) *
Week3 vs BL	-0.10	(-1.21, 1.00)	-0.51	(-1.04, 0.01)
Week4 vs BL	0.84	(-0.36, 2.13)	-0.52	(-1.14, 0.06)
Week5 vs BL	-0.02	(-1.30, 1.37)	-0.76	(-1.43, -0.09) *
Week6 vs BL	-1.26	(-2.73, 0.29)	-1.07	(-1.78, -0.35) *
Allocation* (Week1 vs BL)	-0.55	(-2.30, 1.13)	0.45	(-0.42, 1.22)
Allocation* (Week2 vs BL)	-1.20	(-2.96, 0.62)	0.17	(-0.67, 1.02)
Allocation* (Week3 vs BL)	-1.57	(-3.37, 0.18)	0.22	(-0.58, 1.03)
Allocation* (Week4 vs BL)	-1.76	(-3.68, -0.10) *	-0.17	(-1.04, 0.65)
Allocation* (Week5 vs BL)	-0.63	(-2.60, 1.19)	0.45	(-0.44, 1.38)
Allocation* (Week6 vs BL)	-0.27	(-2.56, 1.88)	0.82	(-0.14, 1.81)

M10 onset time or L5 onset time was the dependent variable. Age, gender, positive affect, and allocation × week interaction were independent variables (* represents statistically significant).

Abbreviations: BL: Baseline

Table 5. 4 Results of linear mixed-effects models evaluating M10 onset time changes within each treatment group six weeks after randomisation.

	Lithium		Placebo	
M10 onset time	**Coefficient estimates**	**95% CI**	**Coefficient estimates**	**95% CI**
(Intercept)	15.36	(12.17, 18.84)	13.94	(10.72, 17.09)
Gender (Male)	0.06	(-1.66, 1.70)	0.33	(-1.74, 2.32)
Age	-0.04	(-0.13, 0.05)	-0.05	(-0.13, 0.02)
Positive affect	-0.12	(-0.23, -0.01) *	-0.04	(-0.15, 0.08)
Week1 vs BL	-1.46	(-2.86, -0.01) *	-0.74	(-1.85, 0.32)
Week2 vs BL	-1.86	(-3.19, -0.56) *	-0.55	(-1.68, 0.61)
Week3 vs BL	-1.70	(-3.04, -0.41) *	-0.09	(-1.17, 0.97)
Week4 vs BL	-0.98	(-2.42, 0.38)	0.87	(-0.31, 2.13)
Week5 vs BL	-0.76	(-2.07, 0.61)	-0.03	(-1.37, 1.37)
Week6 vs BL	-1.66	(-3.18, -0.09) *	-1.29	(-2.66, 0.16)

M10 onset time was the dependent variable. Age, gender, week, and positive affect were independent variables (* represents statistically significant). Abbreviations: BL: Baseline.

Table 5. 5 Results of Mann-Whitney U tests comparing actigraphy parameters in the lithium and placebo groups at baseline

Outcome	**Lithium**			**Placebo**			**p-value**
	Median	**IQR**	**N**	**Median**	**IQR**	**N**	

Table 5. 5 Results of Mann-Whitney U tests comparing actigraphy parameters in the lithium and placebo groups at baseline

Outcome	Lithium			Placebo			p-value
M10 onset time (clock time)	12:36	(9:54, 15:12)	17	12:30	(8:48, 14:54)	14	0.47
L5 onset time (clock time)	01:42	(23:30, 03:06)	17	01:06	(23:54, 02:48)	14	0.61

Abbreviation: IQR, Interquartile range.

5.3.3 The effect of lithium on the variability of circadian rest-activity in patients with bipolar disorder

Table 5.5 presents the results of the linear mixed-effects analysis comparing the effects of lithium and placebo on the variability of circadian rest-activity patterns six weeks after randomisation. Lithium significantly reduced stdAmplitude, stdMESOR and RMS Error in different weeks for each outcome. A trend towards lower RMS Error and stdMESOR was noted in the lithium group from week two to week six. In contrast, a significant increase in stdMESOR was found in week two in both groups (β = 1.32, 95% CI: 0.08, 2.67). A significant increase in RMS Error was found in week two (β = 1.66, 95% CI: 0.31, 2.91), week three (β = 1.33, 95% CI: 0.11, 2.55) and week five (β = 1.52, 95% CI: 0.06, 2.90) regardless of allocation. Male participants had larger variability of circadian rest-activity than female participants.

Table 5. 6 Results of linear mixed-effects analysis of the variability of circadian rest-activity patterns between lithium and placebo group six weeks after randomisation

	stdAmplitude		stdMESOR		RMS Error	
	Coefficient estimates	**95% CI**	**Coefficient estimates**	**95% CI**	**Coefficient estimates**	**95% CI**
(Intercept)	3.64	(1.79, 5.42)	5.02	(3.10, 6.84)	6.06	(3.72, 8.35)
Gender (Male)	1.26	(0.38, 2.20) *	1.10	(0.22, 2.00) *	1.26	(0.06, 2.52) *
Age	-0.02	(-0.06, 0.02)	-0.05	(-0.10, -0.02) *	-0.04	(-0.10, 0.01)
Allocation (Lithium)	-0.02	(-1.32, 1.33)	0.49	(-0.90, 1.97)	0.69	(-0.94, 2.28)
Week1 vs BL	0.09	(-1.06, 1.37)	0.32	(-1.02, 1.76) *	0.45	(-0.77, 1.70)
Week2 vs BL	0.88	(-0.27, 2.14)	1.32	(0.08, 2.67)	1.66	(0.31, 2.91) *
Week3 vs BL	-0.08	(-1.20, 1.12)	1.16	(-0.11, 2.45)	1.33	(0.11, 2.55) *
Week4 vs BL	1.33	(0.09, 2.73)	0.27	(-1.18, 1.71)	0.79	(-0.64, 2.35)
Week5 vs BL	1.09	(-0.09, 2.44)	0.90	(-0.58, 2.33)	1.52	(0.06, 2.90) *
Week6 vs BL	-0.31	(-1.79, 1.22)	-0.19	(-1.75, 1.54)	-0.39	(-1.92, 1.23)
Allocation* (Week1 vs BL)	1.02	(-0.73, 2.61)	0.45	(-1.57, 2.33)	0.81	(-1.05, 2.64)
Allocation* (Week2 vs BL)	-1.30	(-2.94, 0.15)	-3.07	(-4.89, -1.42) *	-3.62	(-5.31, -1.69) *
Allocation* (Week3 vs BL)	0.07	(-1.37, 1.59)	-2.47	(-4.12, -0.69) *	-2.87	(-4.44, -1.12) *
Allocation* (Week4 vs BL)	-1.85	(-3.56, -0.30) *	-1.36	(-3.10, 0.43)	-2.16	(-4.26, -0.28) *
Allocation* (Week5 vs BL)	-0.32	(-2.00, 1.20)	-1.11	(-3.04, 0.80)	-1.47	(-3.24, 0.47)
Allocation* (Week6 vs BL)	0.06	(-1.91, 1.82)	-1.60	(-3.79, 0.54)	-1.32	(-3.47, 0.76)

stdAmplitude, stdMESOR or RMS Error was the dependent variable. Age, gender, allocation, week and allocation × week interaction were independent variables (* represents statistically significant).

Abbreviations: BL: Baseline.

5.4 Discussion

This study is the first randomised, placebo-controlled study investigating the effect of lithium on the timing and variability of circadian rest-activity patterns in patients with bipolar disorder. There was no compelling evidence in this chapter to support the hypothesis that lithium could advance the phase and decrease the variability of circadian rest-activity in

patients with bipolar disorder. While the results were not robust or consistent, lithium significantly reduced the onset time of daytime activity in week four after randomisation, significantly decreased the variability of circadian rest-activity in some of the weeks, but had little effect on the onset time of night-time activity. Consistent with other studies, positive affect was associated with the timing of circadian rest-activity. Higher positive affect was associated with a greater morningness.

5.4.1 The effect of lithium on the timing of circadian rest-activity

There is insufficient evidence to support the hypothesis that lithium might advance the phase of the circadian rest-activity in patients with bipolar disorder compared with placebo in this chapter. Despite this, lithium significantly reduced the onset time of daytime activity in week 4 compared with the placebo. In within-group analysis, lithium significantly advanced the onset time of daytime activity at weeks one to three and six. In contrast, no significant changes in the daytime activity onset time were detected in placebo group. In addition, lithium had no significant impact on both manic and depressive symptoms over six weeks after randomisation (results are presented in chapter 3); thus, changes in the timing of daytime activity may not be due to symptom alleviation. The effect of lithium on modulating circadian rhythm has been supported by cellular and animal studies [156, 189]. Although a definitive conclusion cannot be drawn based on results in this study, the phase-advancing effect on daytime activity is likely to be part of the mechanism of action of lithium and warrants further investigation.

Compared to the placebo group, lithium significantly reduced the onset time of daytime activity only at week four, and this effect did not persist throughout the rest of the study. There are several possible explanations and hypotheses for this inconsistent finding. First, there was less statistical power in week five, and particularly in week six, where some participants finished recording early in the week. Second, the therapeutic effects of daily monitoring might interfere with the detection of the phase-advancing effects of lithium. Within-group analyses revealed that lithium significantly advanced the onset time of daytime activity at weeks one to three and six. However, no significant difference between lithium and placebo groups was found on the onset time of daytime activity in these time periods. A possible explanation was that both groups showed a tendency toward early initiation of daytime activities, which may partially be explained by the therapeutic effects of daily monitoring, although not as significantly and consistently as the night-time activity phase advanced. Lastly, the heterogeneity of bipolar disorder complicated the issue further. One previous study found that less than one third of patients with bipolar disorder met criteria for delayed sleep-wake phase disorder [68]. Participants in the Oxlith study were not recruited because of concerns regarding circadian disruptions. As a result, not every participant experienced a consistently late onset of daytime activity. There was a high degree of variability in phase among and within participants. Additionally, in some patients with a morningness chronotype, lithium may reach a ceiling effect. In future research, it would be of interest to examine whether lithium acts as a phase-advancing agent in bipolar patients with delayed sleep-wake phase disorder.

On the other hand, the effect of lithium on the onset of daytime activity should be interpreted with caution. Lithium had no significant effect on the phase of circadian rest-activity and lithium was not found to have a significant effect on M10 onset time in the causal mediation

analysis. Some of these findings could be explained by limitations in statistical power: instead of using daily actigraphy data, weekly actigraphy data was analysed to determine the phase of circadian rest-activity. In comparison to the traditional approach, causal mediation analyses were more sensitive to missing data, therefore they had less statistical power to detect a difference between lithium and placebo. Within-group comparisons revealed significant reductions in M10 onset times in the lithium group, but not in the placebo group. However, it was not possible to conclude that lithium had a significantly different impact on M10 onset time than placebo. Within-group analyses adopted in this chapter are only exploratory and supplementary to the between-group analyses. Researchers have found that studies that draw conclusions solely on the basis of comparisons within randomised groups have a much higher type I error rate, especially if each arm of the randomised groups has a limited sample size, which can lead to false-positive findings [239, 240].

That both the lithium and placebo groups experienced a night-time activity phase advance suggests the possibility that the daily monitoring program itself might have had a therapeutic effect. The onset time of night-time activity advanced in weeks two, five and six regardless of allocation, and the size of the effect increased over time. The possible mechanism could be that the daily monitoring programme changed patients' behaviour pattern and advanced bedtime. One other study also demonstrated a therapeutic effect of daily monitoring; in a randomised controlled trial investigating the effect of daily smartphone-based symptom monitoring in patients with bipolar disorder, participants who had daily smartphone-based monitoring reported lower levels of perceived stress and rumination [266]. Future studies should investigate the therapeutic effect of daily monitoring on circadian rhythm and sleep patterns.

The molecular basis for the phase-modifying effect of lithium could be mediated through Rev-erbα, an orphan nuclear receptor which serves as one of the major regulators in the circadian clock determining phase-shifting properties [267]. *A*t therapeutic doses, lithium increased the degradation of Rev-erbα which activated the expression of clock genes and reset the circadian rhythm [268]. This study further suggested that the effect of lithium on Rev-erbα degradation was mediated by inhibiting glycogen synthase kinase GSK 3β [268], which stabilizes Rev-erbα; by inhibiting GSK 3β, lithium increased the degradation of Rev-erbα. The finding that lithium inhibits GSK 3β has been supported by in vitro studies [269, 270] and in vivo studies in animals [271-273]. However, the effect of lithium on the activity of GSK 3β in vivo in humans is still unclear [274] as the effect occurred in vitro at concentrations twenty times higher than the therapeutic dose of lithium. Future studies on the mechanism of action of lithium as mediated by Rev-erbα and GSK 3β should utilise patients with bipolar disorder who have significant phase changes after treating with lithium, as described in the case reported by Federoff and McCarthy [275]. Induced Polypotent Stem Cell-derived neuronal cells from these patients could be used to further investigate the molecular basis of lithium's phase-regulating effect.

5.4.2 The association between mood and the timing of circadian rest-activity

In the previous chapter, the complex nature of the interaction between affect and motor activity was investigated. This chapter reveals another association with positive affect: the timing of circadian rest-activity in patients with bipolar disorder. A higher level of positive affect was associated with early onset of daytime activity and night-time activity. Other studies have found similar associations. For example, morning-type healthy adolescents and

adults were found to have higher levels of positive affect [276, 277]. These studies examined morningness-eveningness using the Composite Scale of Morningness (CSM) or Morningness -Eveningness Questionnaire (MEQ); one critique is that these scales record the preference for when to perform various activities but this preference may not translate into when the subject actually performs the behaviours [278]. In comparison, in the present study, M10 onset time variable and L5 onset time variable measured by actigraphy offered greater measurement precision for circadian timing and its association with affect.

Higher levels of eveningness are associated with more negative affect and ruminative cognitive processes [279], emotional biases [280] and maladaptive metacognitive beliefs [281]. The association between negative affect and a higher level of eveningness may be mediated by patients with greater eveningness being exposed to excessive light at night. A recent study revealed a neural pathway (from retinal melanopsin-expressing ganglion cells to the dorsal habenular nucleus to the nucleus accumbens) mediated the light-at-night induced depressive-like behaviours in mice [282].

To determine the actual effect of lithium in bipolar disorder, future studies should chart affect and circadian rest-activity of participants simultaneously as suggested by the ACE model [44]. Affect is a particularly important mediator as it is related to both lithium treatment and the onset time of circadian rest-activity. For example, lithium reduced positive affect and positive affect was associated with earlier onset of daytime activity. Thus, a failure to adjust for a negative indirect effect could lead to an underestimation of the direct effect of lithium on circadian rest-activity in bipolar disorder [283].

5.4.3 Measuring the impact of lithium treatment on the variability of circadian rest-activity

This study is the first randomised controlled trial to reveal the effect of lithium on the variability of circadian rest-activity using an enhanced methodology that recorded changes on a weekly basis over a long period of recording time. Most of the existing literature focused on the variability of circadian rest-activity within one day. For example, one study included in systematic review (chapter 2) found that patients with bipolar disorder who took lithium were associated with lower circadian rest-activity variability measured by intra-daily variability (IV) than patients who took anticonvulsants [176]. In addition, some studies selected 64 minutes of activity without more than two consecutive minutes of zero activity for each participant in the morning and the evening. Minute-to-minute variability was calculated to distinguish between mood disorder subgroups [284, 285]. However, these studies only recorded 24-hours of motor activity for each patient. Our results highlighted the value of variability of the circadian rest-activity over a week as a potential target of lithium treatment. A continuous recording of the motor activity of patients with bipolar disorder together with advanced mathematical approaches to quantify its variability is suggested.

Two factors limited the power to detect differences in circadian rest-activity variability between lithium and placebo groups. First, at least four-day of effective activity recording data for a week were required to calculate the variability variables of that week; if there were fewer than four days of data, the data for that week could not be used. Second, the variability of the circadian rest-activity was calculated for each week. Thus, there were fewer data points compared with non-parametric analysis using daily data.

Currently, there are no standardised methods to measure the variability of circadian rest-activity. One study defined stable rest-activity based on the variability of the daily active intervals duration [259]. Some studies quantify the variability of the rest-activity based on the motor activity count [225, 284, 285]. Lastly, another study adopted Interdaily Stability (IS) to characterise the overall circadian rest-activity regularity over the total recording time. This method did not reveal changes in the circadian rest-activity variability during lithium or anticonvulsant treatment [176]. By looking at the raw data of actigraphy, more features of circadian rest-activity can be extracted, including measures of variability of a time series including Standard deviation (SD), Root Mean Squared Successive Difference (RMSSD), Teager-Kaiser energy operator (TKEO) and entropy [284, 285] .

After completing this chapter's analysis, I came across an advanced computational approach that would help to further delineate the impact of lithium on circadian rest-activity variability. Using this approach, it is possible to identify two important sources of variability: volatility and noise. Volatility, also called unexpected uncertainty, is the variability produced by hidden processes (for example, the underlying mechanism of lithium), a product of the deterministic relationship between the mechanism being learned and the observations [286]. In our study, the volatility of physical activity is the changes directly produced by lithium treatment. Noise, also called expected uncertainty or irreducible uncertainty, arises because of a probabilistic relationship between observations and some hidden processes [286]. Noise increases as the association between lithium treatment and motor activity changes become less deterministic. Models like the Bayesian observer model can estimate these two kinds of variability [287]. Using this computational approach can allow us to identify different causes of circadian rest-activity variability and better understand the mechanism of action of lithium.

5.4.4 Limitations

Careful consideration should be given to several limitations in this proof-of-concept study. First, this study had a limited sample size, which may have impacted the power to achieve statistical significance. For example, the significant phase-advancing effect on daytime activity did not last through week six. Potential reasons for this effect not being significant after week four include less statistical power in week five, and particularly in week six where some participants finished recording early in the week. These results need to be replicated in a larger sample. Second, participants did not have long term follow-up, so it was not possible to assess sustained clinical outcomes and the response to lithium. Thus, the clinical validity of phase advancing induced by lithium was not proved. Third, the heterogeneity of participants undermines the statistical power to detect the effect. This empirical study is a secondary analysis of Oxlith data. Participants were not recruited based on circadian rhythm disruption. The median and interquartile range for Oxlith participants' baseline M10 onset time and L5 onset time are larger than those reported in similar studies of patients with bipolar disorder [245, 288]. On the one hand, the delayed M10 and L5 onset times suggest that these participants may serve as suitable subjects for investigating the effects of lithium on the timing of circadian rest-activity. The large interquartile range for M10 and L5 onset times, on the other hand, suggests a more heterogeneous sample, which has been shown to reduce the power of the study to detect true effects of interventions [289]. Fourth, mediation analysis may be biased by hidden or unmeasured confounding factors between the mediator and the outcome. Oxlith is a randomised controlled trial, and participants were randomly assigned to intervention groups. Hence, it may be possible to assume that intervention-outcome and intervention-mediator effects are unconfounded. However, the mediator-outcome effect might be confounded [257]. The robustness of findings has not been

examined with respect to potential unmeasured mediator-outcome confounding factors using sensitivity analysis because the medsens() function in the mediation package was not compatible with the linear mixed-effect model [224]. Fifth, limited by this short-term study design, participants were not followed long enough to evaluate their response to lithium and differentiate between lithium responders and lithium non-responders. Lithium responders had distinctive clinical features and fewer comorbidities [258]. The heterogeneous response to lithium may undermine the power to detect differences between lithium and placebo groups. Finally, circadian timing was assessed using non-parametric variables derived from daily actigraphy data, which may not be the most widely accepted and comprehensive method to measure circadian timing.

Future studies should adopt reliable methods to measure human circadian timing. Sleep midpoint, defined as (sleep onset time - wakeup time)/2) is another reliable circadian phase marker, which can be calculated from the Munich Chronotype Questionnaire (MCTQ) and a sleep diary [57]. Dim light melatonin secretion onset time (DLMO) is the gold-standard measurement for human circadian timing [290]. However, acquiring DLMO can be costly and challenging. As an example, while saliva samples were collected from participants in Oxlith, light exposure restriction was not imposed on each participant at night. Thus, the DLMOs may not be accurate because melatonin secretion may have been suppressed by light. Ideally, if one wishes to measure DLMO in outpatient settings, light restriction, monitoring of compliance, as well as control of environmental factors is required [291]. One recent study trained machine learning models using frequently sampled data, including minute-by-minute light exposure, skin temperature and physical activity data to estimate DLMO, making the acquisition of DLMO easier [292].

5.4.5 Conclusion

A synchronised and stable circadian rhythm is associated with better clinical outcomes in patients with bipolar disorder. To our knowledge, this is the first randomised, placebo-controlled study investigating the effect of lithium on the timing and variability of circadian rest-activity in patients with bipolar disorder. This study adopted digital phenotyping technology to simultaneously record daily mood changes and circadian rest-activity. There was no compelling evidence in this chapter to support the hypothesis that lithium could advance the phase of the circadian rest-activity and decrease the variability of circadian rest-activity in patients with bipolar disorder. In spite of the results being inconsistent or not robust, lithium significantly decreased the onset time of daytime activity in week four after randomisation, significantly reduced the variability of the circadian rest-activity in some of the weeks, but had little effect on the onset time of night time activity. Advanced computational models can assist in identifying different causes of variability, such as volatility and noise, which will help us better understand the mechanism of action of lithium. The association between positive affect and the timing of circadian rest-activity highlighted the need for a multimodal acquisition of mood and activity data in future studies. Bearing in mind the limitations, this chapter provided two potential targets, timing and stability of circadian rest-activity, for future studies to investigate the response and mechanism of lithium treatment.

Chapter 6: The effect of lithium on cognitive function in patients with bipolar disorder

"All I've suffered, and all the suffering I've caused, might have arisen from the lack of a little salt in my brain."

– Robert Lowell

Excerpt From: Kay Redfield Jamison. "Robert Lowell, Setting the River on Fire".

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6.1 Introduction

It has been discussed in chapter one that cognitive impairment is a problem that frequently arises among patients with bipolar disorder, leading to a detrimental effect on the patient's psychosocial functioning. Although a gold standard treatment for bipolar disorder, lithium's effect on cognitive function in patients with bipolar disorder remains unclear.

6.1.1 The impact of lithium on cognitive function is unclear

Two recent reviews have suggested that lithium may have a minor impact on certain cognitive functions in patients with bipolar disorder; however, no consistent conclusions have

been drawn. The findings of a meta-analysis of twelve studies of lithium in both healthy individuals and individuals with mood disorders concluded that lithium had a minor negative impact on verbal learning, memory and creativity. However, no specific sub-analysis was performed for patients with bipolar disorder, and only patients in euthymic states or clinical remission were included in the study [293]. In another review [294], lithium was found not to negatively affect attention, but it negatively impacted psychomotor speed in patients with bipolar disorder. Furthermore, the authors concluded that the impact of lithium on other cognitive domains, including processing speed, intellectual abilities, memory and executive function, remained unclear [294].

In patients recovering from their first episode of mania, lithium is associated with a greater improvement in cognitive performance than quetiapine and valproate. In a manic state, patients with bipolar disorder have cognitive deficits in attention, verbal learning and memory, language, and executive function [79]. Based on a randomised controlled trial comparing the effect of lithium and quetiapine following a first manic episode, lithium was found to improve verbal fluency, whereas quetiapine did not; there was no differences in other cognitive domains [295]. Another randomised controlled trial compared healthy participants with patients with bipolar disorder receiving lithium or valproate in the 3 months following their first manic or mixed episode. Lithium-treated patients performed better on working memory tasks than those treated with valproate; however, both treated groups had greater cognitive impairments than healthy participants overall [296]. Taken together, these findings indicate that lithium treatment is associated with an improvement in cognition in patients with mania.

In patients with bipolar depression, lithium treatment has been shown to be associated with cognitive impairments in affective processing and sustained attention, when compared with unmedicated patients with bipolar depression [297]. In light of the fact that these differences can partly be attributed to the cognitive impact of bipolar depression and/or the severity of depressive symptoms per se rather than the treatment, the interpretation of cross-sectional studies is challenging.

Lithium's impact on cognition is less clear and consistent when used as a mood stabiliser in euthymic patients with bipolar disorder. In longitudinal studies, euthymic patients with bipolar disorder who took lithium had worse (but stable) cognitive performance compared with healthy participants [298-300]; no direct comparison has been made between lithium-treated patients and unmedicated patients. Two cross-sectional studies have demonstrated no difference in cognitive function between unmedicated and lithium-treated euthymic patients with bipolar disorder. However, these studies differ in their findings in other regards; one study found that neither group differed from healthy participants, whereas the other found both groups of patients with bipolar disorder displayed lower performance on verbal episodic and visual-verbal memory tasks, regardless of medication status [301, 302]. In cross-sectional studies comparing lithium-treated patients with patients treated with other mood-stabilizing medications, attention, memory and most executive function may be better preserved in lithium-treated patients [303, 304], although this has not been consistent across all studies [305].

The cognitive performance of lithium responders is better than that of lithium non-responders. The term ‘excellent lithium responders’ (ELRs) refers to a subgroup of lithium-treated patients that exhibit several positive clinical features, including stable treatment

responses and fewer comorbidities [258]. There is evidence to suggest that cognitive function was preserved better in ELRs than in non-ELRs, but was impaired when compared to healthy participants [298]. Due to the correlation between cognitive impairment and the number of affective episodes [90], this observation may be explained by the efficacy of lithium in reducing relapses among patients with bipolar disorder and cognitive impairment. Considering that no comparative data from baseline neuropsychological assessments are available at present, the possibility that ELRs may begin with better cognitive performance cannot be ruled out [306].

6.1.2 Methodological limitations in existing literature

Several methodological limitations have made it difficult to investigate the effects of lithium on cognitive function in patients with bipolar disorder. First, most studies investigating the effects of lithium on cognition are cross-sectional in design, and few have attempted to account for factors such as illness severity, past treatments, comorbidities, or subsyndromal symptoms. For example, mood instability is associated with poorer outcomes in patients with bipolar disorder [307, 308], but most studies fail to account for this factor. In addition, there are studies in which healthy participants were recruited as the only comparison group against patients with bipolar disorder treated with lithium [298, 300]. Therefore, it is unclear to what extent observed cognitive impairments commonly associated with bipolar disorder are caused by lithium treatment or the illness per se. A group of unmedicated patients with bipolar disorder is needed in order to elucidate the effects of lithium on cognitive function in bipolar disorder.

Second, the side effects of lithium are affected by its serum level. One study found that frontal lobe dysfunction was correlated with higher brain lithium levels in geriatric patients with bipolar disorder[309]. Few previous studies have monitored the serum level of lithium and accounted for its impact on cognitive function. Therefore, when assessing the effects of lithium on cognitive function, the serum level of lithium needs to be carefully monitored. Third, polypharmacy is common among most patients with bipolar disorder, which makes assessing lithium's impact on cognitive function even more difficult when combined with other neurotropic medications.

Lastly, the cognitive function of patients with bipolar disorder was infrequently assessed in previous studies. In cross-sectional studies, cognitive function was assessed only once due to the nature of the study design. None of the earlier studies assessed the cognitive function of patients with bipolar disorder daily. As a result, it was difficult to characterise the subtle changes in cognitive function and its variability. In addition, frequent cognitive assessment is necessary to detect short-term changes in cognition in patients with bipolar disorder following initiation of lithium therapy.

This chapter aimed to examine whether lithium impairs the cognitive function of patients with bipolar disorder. This chapter addressed the above limitations by adopting the following methods: (1) a randomised, double-blind, placebo-controlled trial study design was implemented; (2) one group of patients with bipolar disorder received lithium monotherapy; (3) the serum level of lithium was closely monitored to keep it within the therapeutic range; (4) the comparison group consisted of patients with bipolar disorder who received a placebo; (5) ecological momentary assessments were used to measure daily mood changes so that mood could be adjusted for in cognitive performance; and (6) daily mobile-based cognitive

tasks were used to characterise greater detail of cognitive changes in patients with bipolar disorder.

6.1.3 Mobile-based contextual cueing task

The contextual cueing task was designed to measure the implicit learning of contextual information; it is also commonly used as a tool to investigate memory and attention [310]. Contextual cueing refers to the application of repeated contextual information to aid in the localisation of the target [311]. The contextual cueing task is a visual search experiment in which participants search for a target among distractors; at the same time, some trials employ repeating configurations of distractors which aid in locating the target [310]. The contextual cueing effect refers to learning and using the implicit regularities to identify the target more efficiently; in the context of this task, this effect can be expressed as a significant reduction in search reaction time in the repeated condition compared to the novel condition [310]. In healthy participants, the reaction time for the repeated condition can be 50-100 milliseconds (ms) faster than that for the novel condition [310].

The mobile-based contextual cueing task used in the Oxlith has been modified from the original design in order to measure cognitive function over a longer period of time [311]. The configurations repeated across days rather than within a day and participants were asked to complete the contextual cueing task daily throughout the clinical trial. The utility of this mobile-based cognitive task was demonstrated in the COgnition and Mood Evolution across Time (COMET) study; the presence of the contextual cueing effect was found in healthy participants with mood instability [312]. Using the contextual cueing task, the COMET study

compared cognitive functions between healthy participants with high and low mood instability [312].

The mobile-based contextual cueing task offers several advantages for exploring the short-term effect of lithium on cognitive function in patients with bipolar disorder. First, a contextual cueing task only requires one or two minutes each day to complete [312], making it feasible for short-term, high-frequency assessments. By contrast, each of the neurocognitive tests recommended by the Lithium Battery-Research takes three to fifteen minutes to complete [313]. Second, one contextual cueing task can assess three cognitive domains that often exhibit impairments in patients with bipolar disorder, including attention, learning, and memory [6]. In other words, this task can "kill three birds with one stone". Additionally, the task is also relevant to the real-life experiences of patients with bipolar disorder. In the context of daily living, individuals pay attention to the regularities in their surroundings. They implicitly learn and integrate these regularities to enable them to identify targets more efficiently [311]. Lastly, this task has been proven to be sensitive in detecting cognitive impairment in individuals with high levels of mood instability compared to individuals with low levels of mood instability [312]. It is promising that its use can be extended to patients with bipolar disorder.

For the contextual cueing task to be used as a cognitive assessment tool for patients with bipolar disorder, its effectiveness must be demonstrated in this population. The first aim of this chapter was to examine the utility of this task in patients with bipolar disorder, specifically, to ensure patients with bipolar disorder could learn and employ the implicit contextual patterns over time to identify targets more rapidly. **The second and primary objective of this chapter was to examine whether lithium had an adverse impact on**

attention, learning and memory in patients with bipolar disorder by using both a self-report questionnaire and a mobile-based contextual cueing task.

6.2 Methodology

6.2.1 Study design

The Oxlith study design is described in full in chapter 3 (3.1.1 section)

Relevant to this chapter, participants who met the eligibility criteria entered the pre-randomisation phase, which lasted for approximately two weeks. The pre-randomisation phase enabled participants to be familiar with the daily and weekly digital symptom monitoring tools. At the screening visit, every participant completed the perceived deficits questionnaire (PDQ) and received an iPad where cognitive tasks were installed. During the six-week randomised phase, participants completed cognitive tasks daily. At the 6-week visit, each participant completed a PDQ.

6.2.2 Measurement of subjective cognitive function

The PDQ is commonly used as a measure of subjective cognitive dysfunction in patients with a neurological or psychiatric disorder [202]. The PDQ consists of 20 items, each with a score ranging from 0-4. A higher score indicates greater impairment of cognitive function. As a result, the total score can range from 0-80. Twenty items of the PDQ can be categorised as

four 5-item subscales, including attention/concentration, prospective memory, retrospective memory, and planning/organization. Each subscale has a score range of 0-20 [203]. Participants in the Oxlith study completed this questionnaire twice, once at the randomisation visit and again at the week six visit.

6.2.3 Contextual cueing task

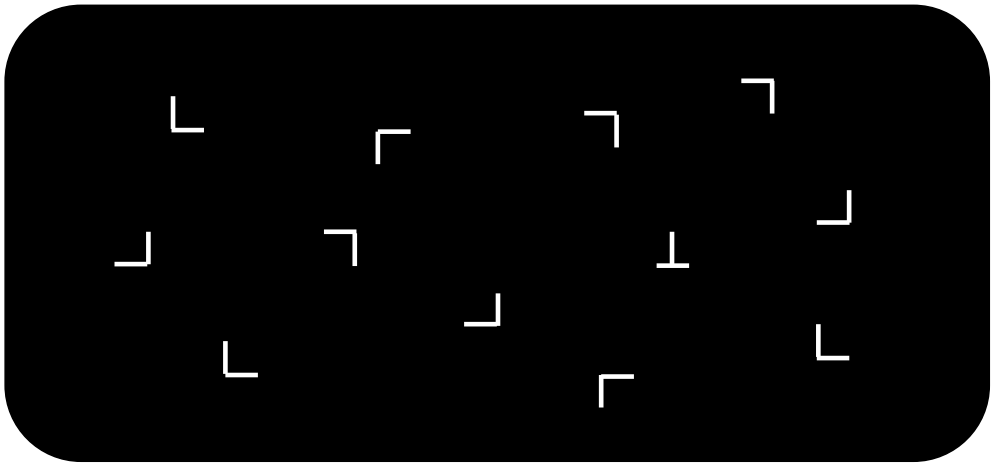
Procedures:

As part of the Oxlith trial, each participant had an iPad with the contextual cueing task installed and were instructed to complete the task daily until the end of the study. The task consisted of 60 trials per day in which the participant had to identify a target letter "T" among distractor letters "Ls". The program recorded the search reaction time for each trial. Participants were provided with two different logins, one for the pre-randomisation phase, the other for the post-randomisation phase.

Task design:

The contextual cueing task was completed on an iPad 2, which has a 9.7-inch (diagonal) screen and a resolution of 1024 x 768 pixels. An invisible eight-by-six grid divided the screen, within which targets and distractors appeared. The stimuli were white and the background was black. Every trial had one target T and twelve distractors L. The target T could be located at ten different locations, which were selected randomly from a set of possible locations (neither at the border nor at the centre). The location of Ls was not restricted. Although the orientation of the letters T and L varied according to the configuration, they were the same for subsequent repetitions [312] (see Figure 1). .

Figure 6. 1 A paradigm for contextual cueing on the iPad



Participants completed 60 trials a day during which two conditions were presented. The novel condition was a set of configurations generated for every day of the trial and were not repeated. The repeated conditions were the following configurations repeated at a different frequency:

(1) Twice-daily repetition: ten different configurations in total, repeated twice a day.

(2) Daily repetition: ten different configurations in total, repeated daily.

(3) Alternative day repetition: twenty different configurations in total, ten for odd days and ten for even days, repeated every two days.

(4) Within-day repetition: one configuration per day, ten repetitions within a day but never repeated on another day.

Each day, the order in which configurations are shown was randomly selected, but a within-day repetition trial did not immediately follow a within-day repetition trial. To prevent participants from noticing the pattern, a twice-daily repetition trial did not appear soon after another twice-daily repetition trial.

6.2.3 Data processing and statistical analysis

Contextual cueing data cleaning and processing

To ensure the quality of the data, data with reaction times more than 10000 ms were removed as any reaction time exceeding 10000 ms was considered abnormal. Next, the accuracy, defined as the percentage of trials in which the participant correctly identified the target, for each condition was calculated. A Fisher's exact test was conducted to compare the accuracy of contextual cueing tasks between lithium and placebo groups for both the repeated and novel conditions. Further analysis of the data was limited to those trials in which the participant selected the correct answer, defined as those who were able to locate the correct target. The mean and the standard deviation of reaction times for each condition were calculated. For each condition, only reaction times within three standard deviations of the mean in each dataset were utilized in the analysis in order to ensure that outliers did not skew the mean value of the reaction time [310].

Examining the contextual cueing effect across days

To examine whether a contextual cueing effect could be observed over time in patients with bipolar disorder, linear-mixed effects models were used to compare performance between the

novel and the repeated conditions. The reaction time was used to determine the cognitive performance. In the linear mixed-effects models, reaction time was dependent variable; gender, age, trial type, days (days is a continuous variable that reflects the length of time after randomisation), trial type × days interaction were independent variables. Participants were included as a random effect. Bootstrapping procedures were conducted to circumvent distribution assumptions of the linear mixed-effect model and to produce estimates of the model parameters. The lme4 package did not provide p-values; however, 95% confidence intervals were calculated using bootstrapping. If the 95% confidence interval did not contain zero, the results were considered to be statistically significant.

Utilising the standard contextual cueing protocol, only data from the novel condition and one of the repeated conditions were compared [310]. Among all the repeated conditions, twice-daily repetition and daily repetition conditions were used to compare with the novel condition. Alternative day repetition was not utilised because this condition did not work in the pilot experiments and within-day repetition was not utilised because it was designed for contextual cueing within a single day as opposed to contextual cueing across days.

In the COMET study, the contextual cueing effect detected in healthy individuals with mood instability took more than two weeks to develop [312]. Thus, six-week post-randomisation data from patients with bipolar disorder who received the placebo were used to examine the contextual cueing effect in bipolar disorder (in patients with bipolar disorder receiving lithium, cognitive function may have been perturbed by the pharmacological treatment).

Correlation analysis

Pearson correlation was used to examine the association between cognitive performance measured by the contextual cueing task and subjective cognitive function measured by PDQ. At baseline, the correlation between cognitive performance under the novel condition and subjective cognitive function measured by PDQ was examined. In addition, the correlations between changes in subjective cognitive function after six weeks measured by PDQ and changes in cognitive performance under the novel or the repeated condition were also examined.

During the baseline period or week six, cognitive performance was evaluated based on the average reaction time under each condition. A minimum of four-day effective cognitive performance data was required for each week. Changes in cognitive performance were calculated by comparing the average reaction time in week six to baseline. Data from each variable were tested for normality using the Shapiro-Wilk test. All data were analysed with R (R Core Team, Vienna). If $p < 0.05$, the differences were considered to be statistically significant.

Spearman correlation was used to examine the association between cognitive function and circadian rhythm measured by relative amplitude. The median of relative amplitude at baseline was not normally distributed, therefore it was decided to use the Spearman correlation, as it does not assume that the measurements are normally distributed [211]. At baseline, cognitive function was measured through total scores on the PDQ questionnaire and the average reaction time under the novel condition when using the contextual cueing task. All data were analysed with R (R Core Team, Vienna). If $p < 0.05$, the differences were considered to be statistically significant.

Comparing cognitive functions between the lithium and placebo groups

In order to detect the significant interaction between allocation and week for the total scores of the perceived deficits questionnaire and its subscale scores, two-way analysis of variance was used to compare the group means between lithium and placebo groups. All data were analysed with R (R Core Team, Vienna). If $p < 0.05$, the differences were considered to be statistically significant.

The daily contextual cueing task was adopted to compare cognitive functions between the lithium and placebo groups. The performance in the novel condition was an indicator of attentional function. The performance in the repeated condition was an indicator of attention, implicit learning, and memory function [312]. The reaction time and the standard deviation of the daily reaction time were used to determine the cognitive performance. The shorter the reaction time and the smaller the standard deviation of the daily reaction time, the better the cognitive performance.

At baseline, the cognitive functions were evaluated based on the average reaction time under each condition and the total scores of the PDQ questionnaire. The Shapiro-Wilk test was used to determine the normality of the average reaction time under each condition and the total scores of the PDQ questionnaire. The assumption of homogeneity of variance was examined using Levene's test. A two-tailed independent t-test was conducted to compare cognitive performance between the lithium and placebo groups at baseline. If $p < 0.05$, the differences were considered to be statistically significant.

After randomisation, linear mixed-effects models were used to compare cognitive functions across days between the lithium and placebo group. In the linear mixed-effects models, the reaction time or the standard deviation of the daily reaction time was dependent variable; gender, age, allocation, days, allocation × days interaction were independent variables. Participants were included as a random effect. If the 95% confidence interval did not contain zero, the results were considered statistically significant.

6.3 Results

6.3.1 Demographics

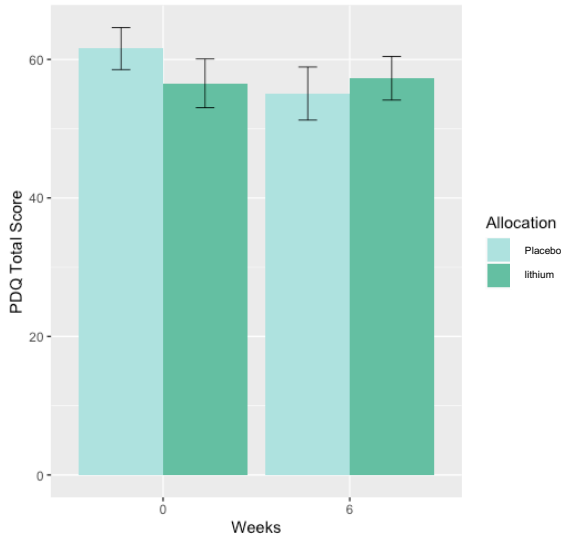
The demographic characteristics of the participants were described in Chapter 4 (section 4.3.2).

6.3.2 The effect of lithium on subjective cognitive function in patients with bipolar disorder

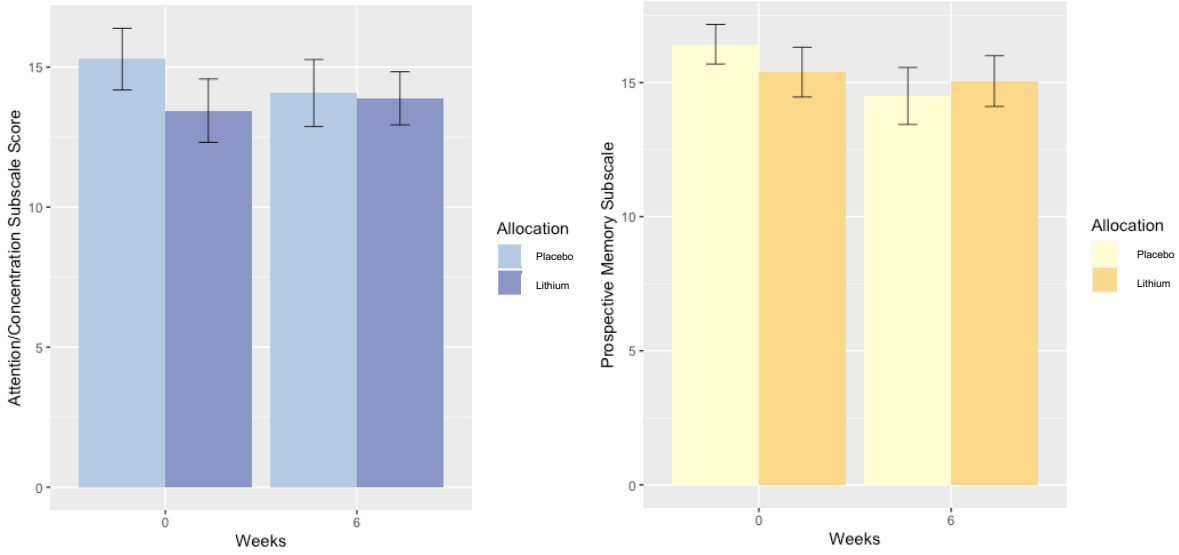
Thirty-two of thirty-five (91%) participants completed the PDQ questionnaire in both the screening visit and the week 6 visit. The total scores of the PDQ questionnaire revealed frequent cognitive dysfunction in both the lithium and placebo groups at baseline. There was no significant difference in the total scores of the PDQ questionnaire between the lithium and placebo groups ($t(30) = 1.04$, $p = 0.30$) (Table 6.1). From baseline to week six post-treatment, no significant difference was detected on the total scores of the PDQ between the lithium and placebo groups ($F_{1,60} = 1.103$, $p = 0.298$). In addition, no significant differences

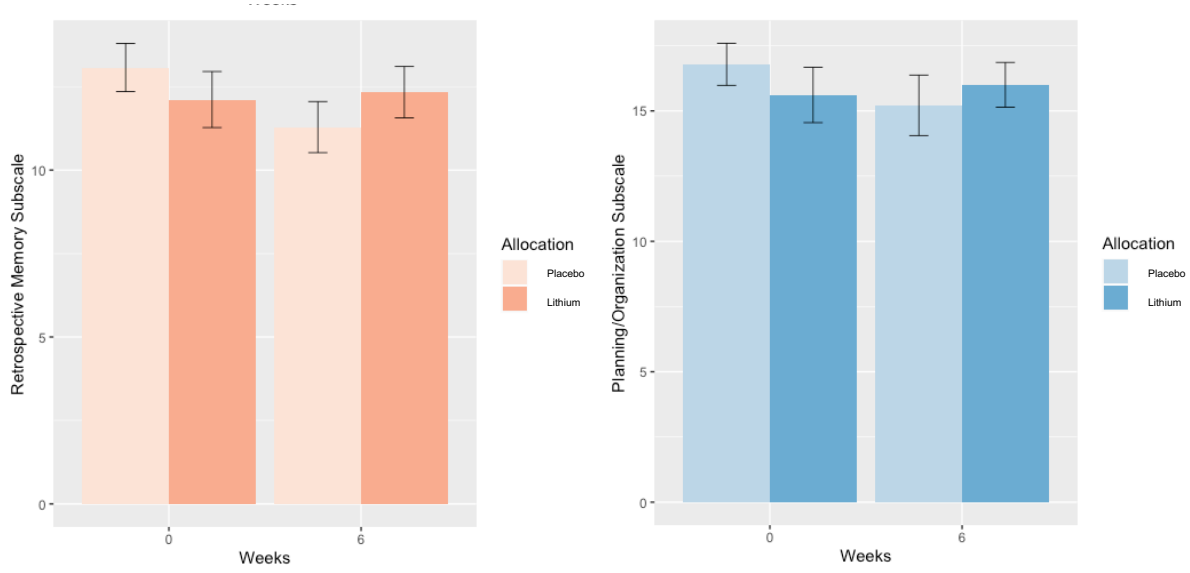
were found between the two groups in the individual cognitive domains, including attention, prospective memory, retrospective memory and planning domains (all $p > 0.05$, see Figure 6.2, Table 6.2).

Figure 6. 2 Effect of lithium on subjective cognitive function measured by perceived deficits questionnaire (PDQ)


PDQ Total Score
60
40
20
0
0
6
Weeks
Allocation
Placebo
lithium

(A)


Attention/Concentration Subscale Score
15
10
5
0
0
6
Weeks
Allocation
Placebo
Lithium
Prospective Memory Subscale
15
10
5
0
0
6
Weeks
Allocation
Placebo
Lithium



(B)

(A) Total scores of the PDQ questionnaire analysis

(B) Subscales of the PDQ analysis. Results are expressed as mean ± SEM for each group (lithium group: n= 18, placebo group: n=14), week 0 denotes the randomisation visit and week 6 represents week six visit.

Table 6.1 Results of independent samples t-tests of the total PDQ scores at baseline between the lithium and placebo groups

Outcome	Lithium		Placebo		t-statistic value	degree of freedom	p-value
	Mean (SD)	N	Mean (SD)	N			
PDQ total scores	56.6 (6.2)	18	61.6 (11.4)	14	1.04	30	0.30

Table 6. 2 Allocation × week interaction effects for subjective cognitive functions variables.

	Two-way ANOVA (Allocation × Week)		
	F	df	P Value
PDQ Total scores	1.103	(1, 60)	0.298
Attention subscale scores	0.565	(1, 60)	0.455
Prospective memory subscale scores	0.714	(1, 60)	0.402
Retrospective memory subscale scores	1.594	(1, 60)	0.212
Planning subscale scores	0.973	(1, 60)	0.328

6.3.3 Contextual cueing performance in patients with bipolar disorder

The contextual cueing effect in patients with bipolar disorder was investigated with daily contextual cueing task data (Figure 6.3). The accuracy of the contextual cueing task in both the novel and repeated conditions was greater than 99.7%. In both the pre-randomisation and post-randomisation phase, we found no significant difference between lithium and placebo group in the accuracy of the contextual cueing task (all p values > 0.05, Table 6.3).

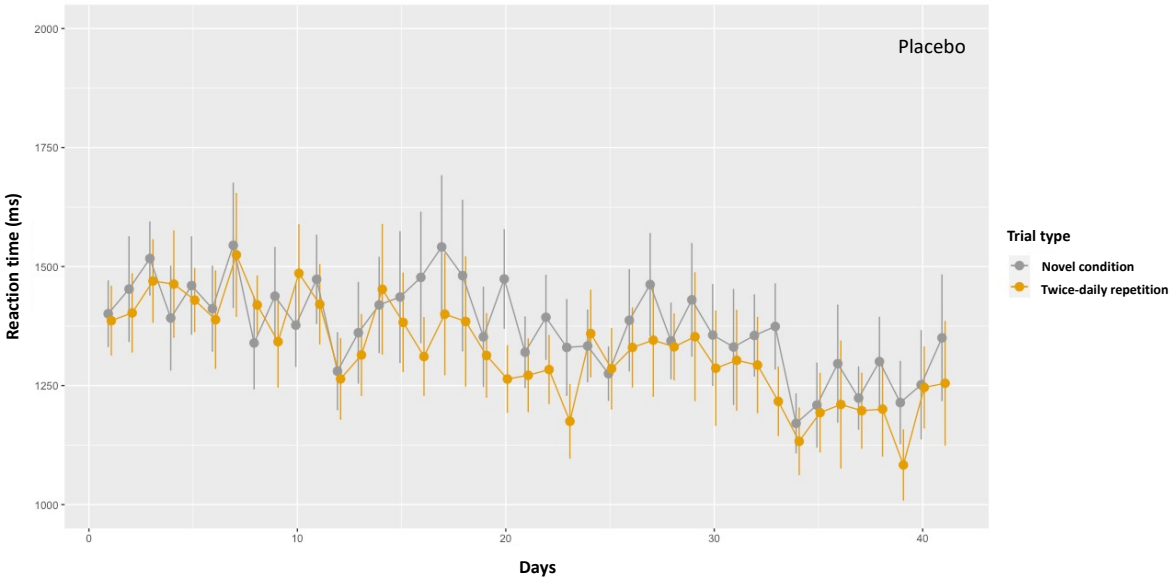
Table 3 shows the linear mixed-effects analysis comparing the reaction time of contextual cueing tasks between the novel condition and the repeated condition over six weeks. A significant reduction in reaction time in the repeated condition as compared to the novel condition was observed in twice-daily repetition (β = -1.86, 95% CI: -3.61, -0.23) but not in daily repetition (β = -1.24, 95% CI: -3.65, 1.01). Therefore, twice-daily repetition was used as the repeated condition for further comparisons of lithium and placebo effects on cognitive performance.

At baseline, the Pearson correlation analysis showed no association between cognitive performance in the novel condition and self-reported attention function (p = 0.85, Figure 6.4A). In addition, the Pearson correlation analysis demonstrated no association between changes in self-reported cognitive function and changes in cognitive performance in the novel or twice-daily repetition conditions (all p >0.05, Figure 6.4).

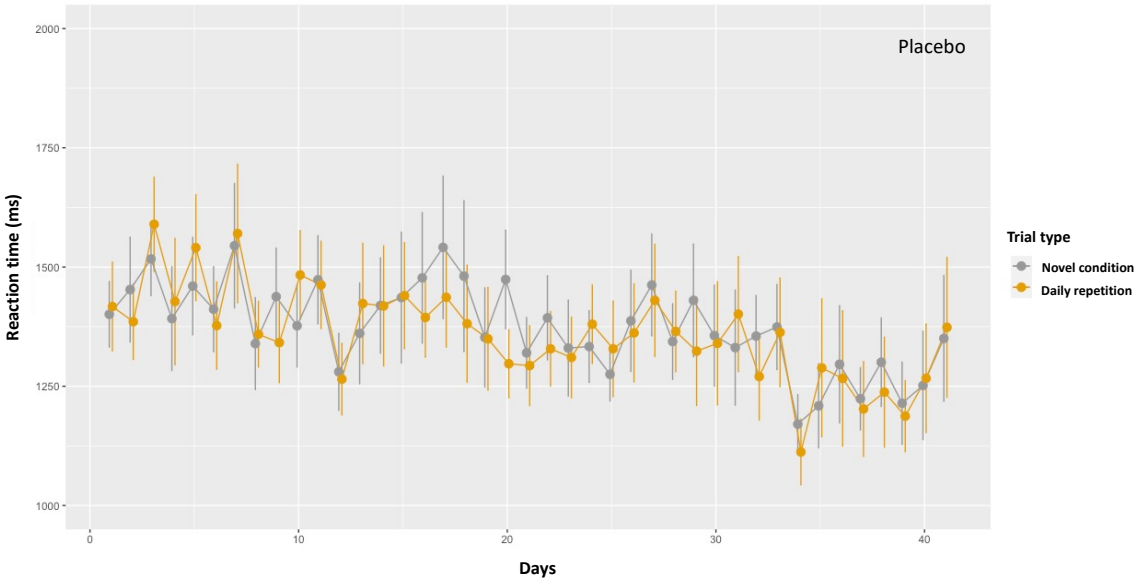
Table 6. 3 Comparisons of the accuracy of the contextual cueing task between the lithium and placebo groups for the repeated and the novel conditions during the pre-randomisation and post-randomisation phases

	Pre-randomisation phase		
	Lithium group	Placebo group	p value
Accuracy in the novel condition	0.998	0.998	0.73
Accuracy in the twice-daily repetition condition	0.998	0.999	>0.99
Accuracy in daily repetition condition	0.999	0.997	0.48
	Post-randomisation phase		
	Lithium group	Placebo group	p value
Accuracy in the novel condition	0.998	0.998	>0.99
Accuracy in the twice-daily repetition condition	0.997	0.998	0.88
Accuracy in daily repetition condition	0.997	0.998	0.51

Figure 6. 3 Contextual cueing task performance in patients with bipolar disorder treated with placebo during post-randomisation phase.



(A)



(B)

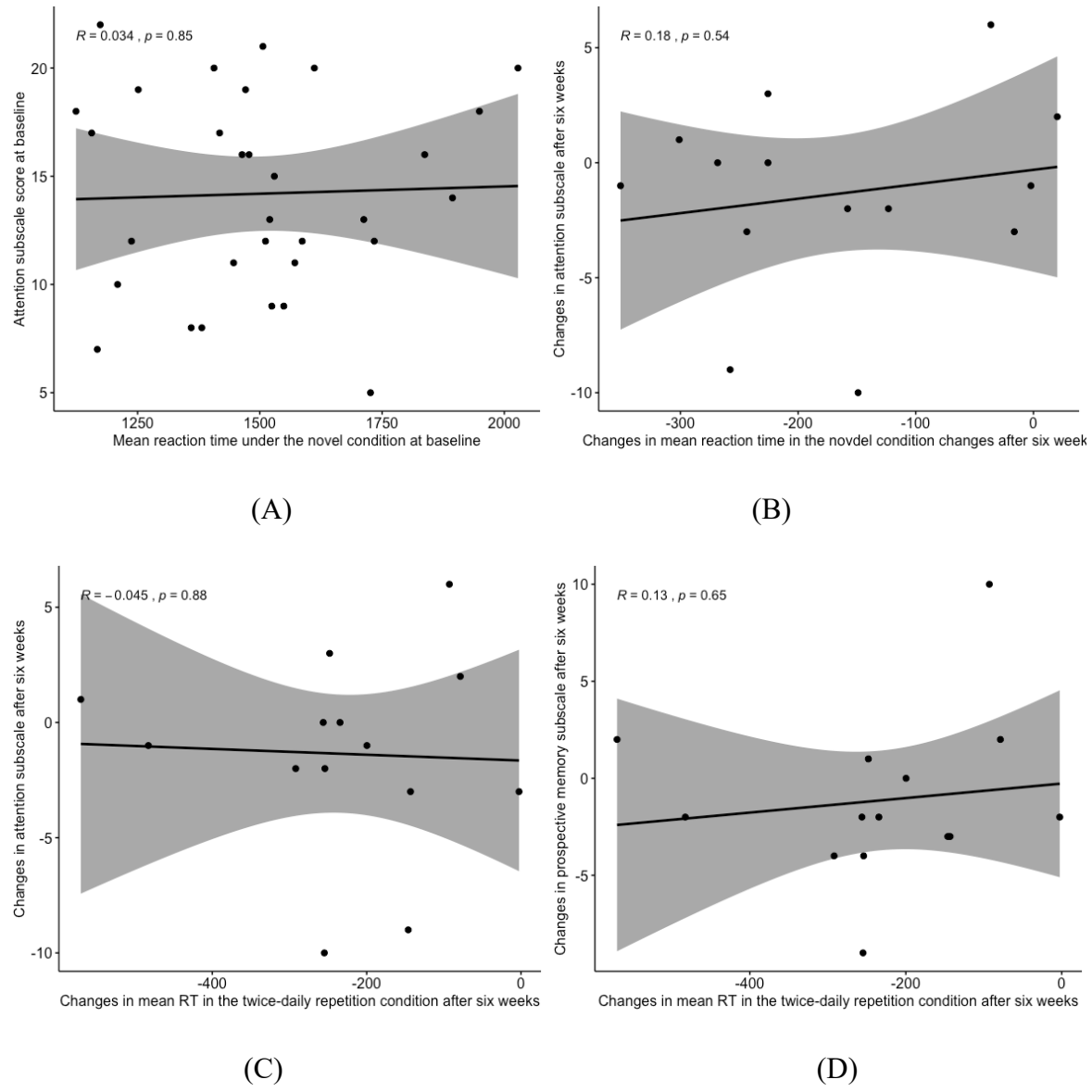
(A) The twice-daily repetition condition was compared to the novel condition. (B) The daily repetition condition was compared to the novel condition. Results are expressed as mean ± SE for each day. Day 0 represents the randomisation visit.

Table 6. 4 Results of linear mixed-effects analysis comparing the reaction time changes between the novel and the repeated conditions six weeks after randomisation

	Twice-daily repetition		Daily repetition	
Reaction time	**Coefficient estimates**	**95% CI**	**Coefficient estimates**	**95% CI**
(Intercept)	1040.35	(675, 1392)	1041.33	(697, 1407)
Gender (Male)	98.38	(-147.87, 352.82)	73.80	(-172.62, 330.54)
Age	10.53	(1.48, 19.80) *	10.80	(1.73, 19.72) *
Trial type (R)	-14.88	(-52.66, 23.20)	6.92	(-38.37, 58.98)
Days	-1.68	(-3.00, -0.34) *	-1.42	(-3.12, 0.24)
Trial type (R) × Days	-1.86	(-3.61, -0.23) *	-1.24	(-3.65, 1.01)

The repeated condition for the model on the left was twice-daily repetition. The repeated condition for the model on the right was daily repetition. Reaction time was the dependent variable. Age, gender, days and trial type × days interaction were independent variables (* represents statistically significant). Trial type R represents the repeated condition. Trial type A represents the novel condition.

Figure 6. 4 Pearson correlation between cognitive performance measured by the contextual cueing task and subjective cognitive function measured by PDQ



(A) Correlation between attention subscale score and mean reaction time in the novel condition at baseline. (B) Correlation between changes in attention subscale score and changes in mean reaction time in the novel condition after six weeks. (C) Correlation between changes in attention subscale score and changes in mean reaction time in the twice-daily repetition condition after six weeks. (D) Correlation between changes in prospective memory subscale score and changes in mean reaction time in the twice-daily repetition condition after six weeks. R represents correlation coefficient; shaded area represents 95% CI; dots show individual data points.

6.3.4 The effect of lithium on the contextual cueing performance in patients with bipolar disorder

At baseline, there was no significant difference in contextual cueing performance between the lithium and placebo groups in the novel ($t(32) = 0.72$, $p = 0.48$) or the repeated condition ($t(32) = 0.79$, $p = 0.44$). The Shapiro-Wilk test revealed that average reaction time was normally distributed for both groups. The assumption of homogeneity of variance was examined by Levene's test.

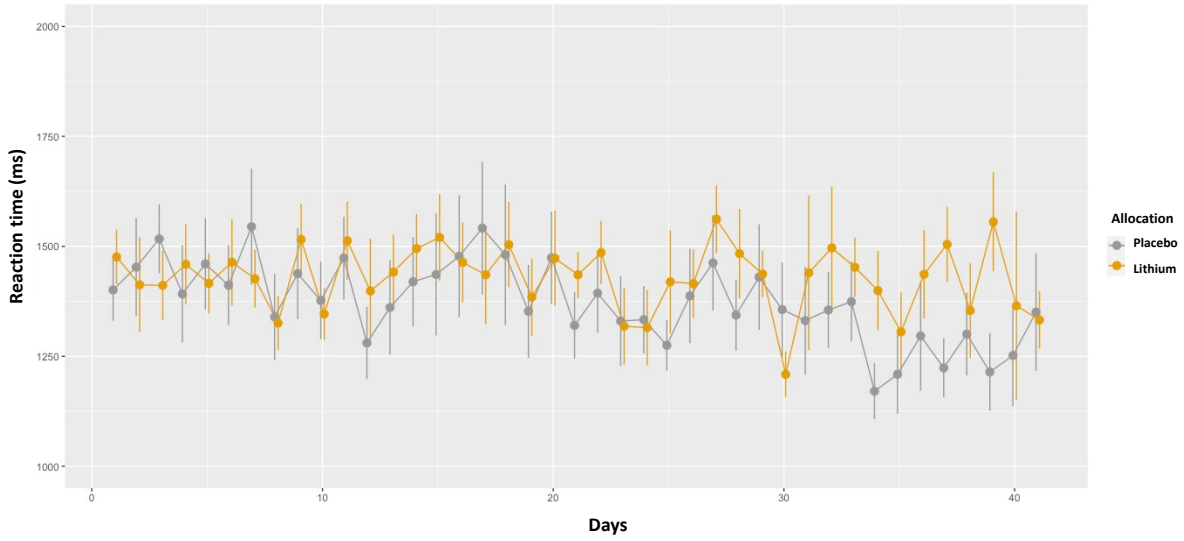
After randomisation, the effect of lithium on daily reaction time and the standard deviation of daily reaction time was examined with daily contextual cueing performance data (Figure 6.5 and Figure 6.6). In the novel condition, no significant difference were found on the lithium × days interactions on reaction time ($\beta = 0.64$, 95% CI: -1.37, 2.78) and on the standard deviation of the daily reaction time (β: -0.70, 95% CI: -2.70, 1.38); age ($\beta = 9.53$, 95% CI: 3.69, 15.49) and days (β= -1.75, 95% CI: -3.34, -0.22) were found to be significant predictors of the reaction time (Tables 6.6 and 6.7).

In the repeated condition, no significant differences were found on the lithium × days interactions on reaction time ($\beta = 0.17$, 95% CI: -1.29, 1.55) and on the standard deviation of the daily reaction time ($\beta = 0.25$, 95% CI: -1.17, 1.58); age and days were significant predictors of both the reaction time and the standard deviation of the reaction time (Tables 6.6 and 6.7).

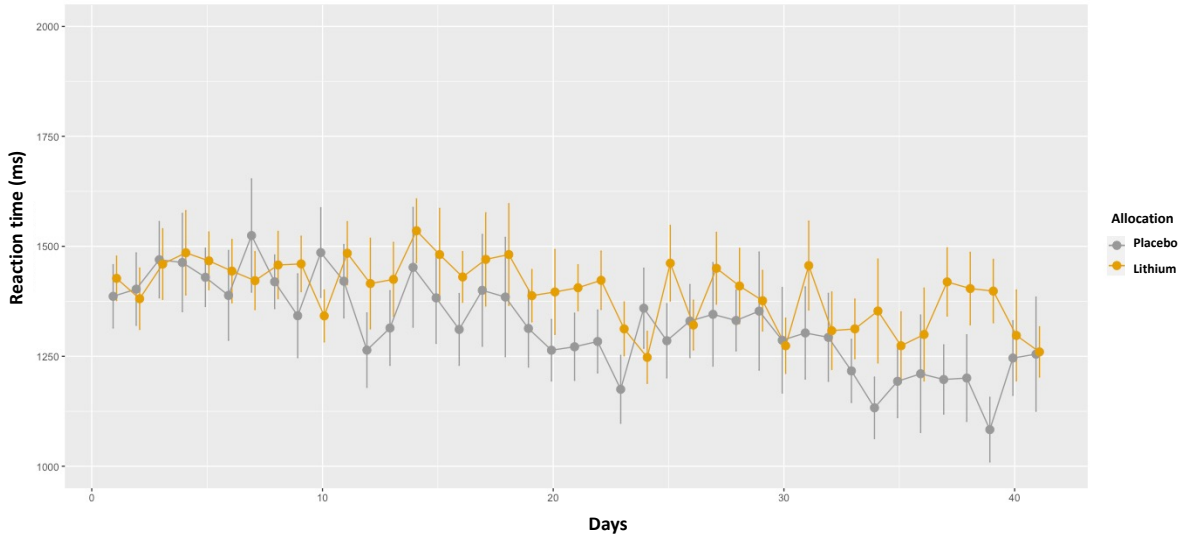
Table 6. 5 Results of independent samples t-tests between the lithium and placebo groups at baseline

	Placebo Mean (SD)	Lithium Mean (SD)	t-statistic value	degrees of freedom	P value
Novel condition	1546(267)	1487 (212)	0.72	32	0.48
Repeated condition	1469(251)	1409 (190)	0.79	32	0.44

Figure 6. 5 Effects of the lithium and placebo on the daily contextual cueing performance in patients with bipolar disorder.



(A)



(B)

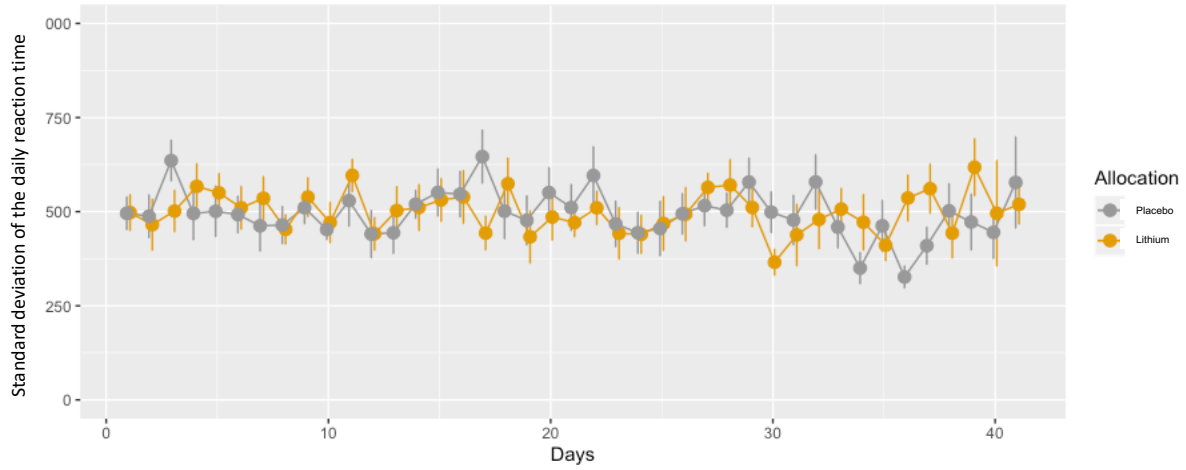
(A) under the novel condition. (B) under the repeated condition. Results are expressed as mean ± SEM for each day. Day 0 represents the randomisation visit.

Table 6. 6 Results of linear mixed-effects analysis of daily reaction time between the lithium and placebo groups six weeks after randomisation in the novel condition or in the repeated condition

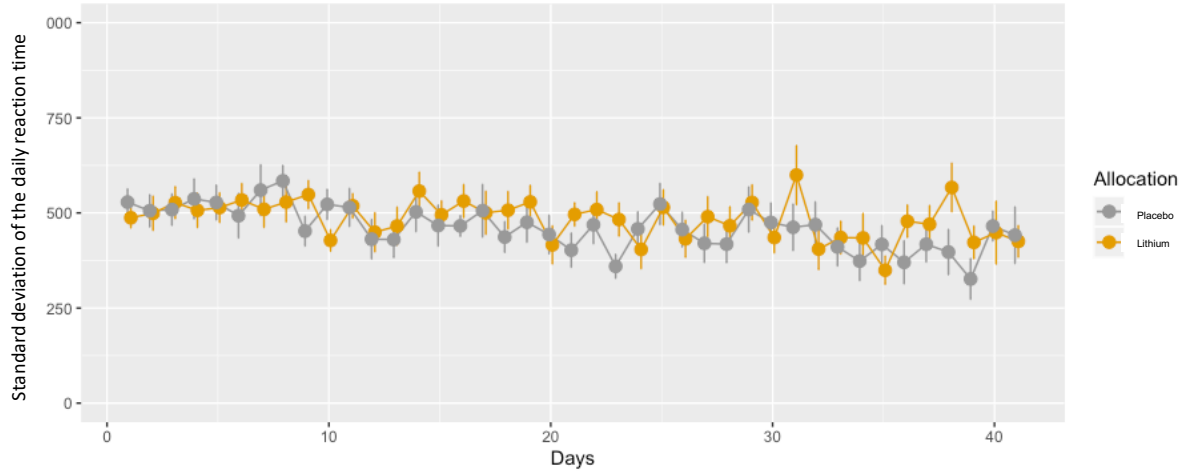
	Novel condition		Repeated condition	
Reaction time	**Coefficient estimates**	**95% CI**	**Coefficient estimates**	**95% CI**
(Intercept)	1084.53	(838, 1325)	1067.25	(792, 1300)
Gender (Male)	70.70	(-66.61, 209.25)	72.09	(-67.77, 227.04)
Age	9.53	(3.69, 15.49) *	9.62	(3.39, 16.53) *
Allocation (Lithium)	70.57	(-73.70, 227.01)	99.52	(-47.44, 250.4)
Days	-1.75	(-3.34, -0.22) *	-3.59	(-4.60, -2.57) *
Allocation (Lithium) * Days	0.64	(-1.37, 2.78)	0.17	(-1.29, 1.55)

Reaction time was the dependent variable. Age, gender, allocation, days, allocation×days interaction were independent variables (* represents statistically significant).

Figure 6. 6 Effects of the lithium and placebo on the variability of daily contextual cueing performance in patients with bipolar disorder



(A)



(B)

(A) under the novel condition. (B) under the repeated condition. Results are expressed as mean ± SEM for each day. Day 0 represents the randomisation visit

Table 6. 7 Results of linear mixed-effects analysis of the standard deviation of daily reaction times between the lithium and placebo groups six weeks after randomisation in the novel condition or in the repeated condition

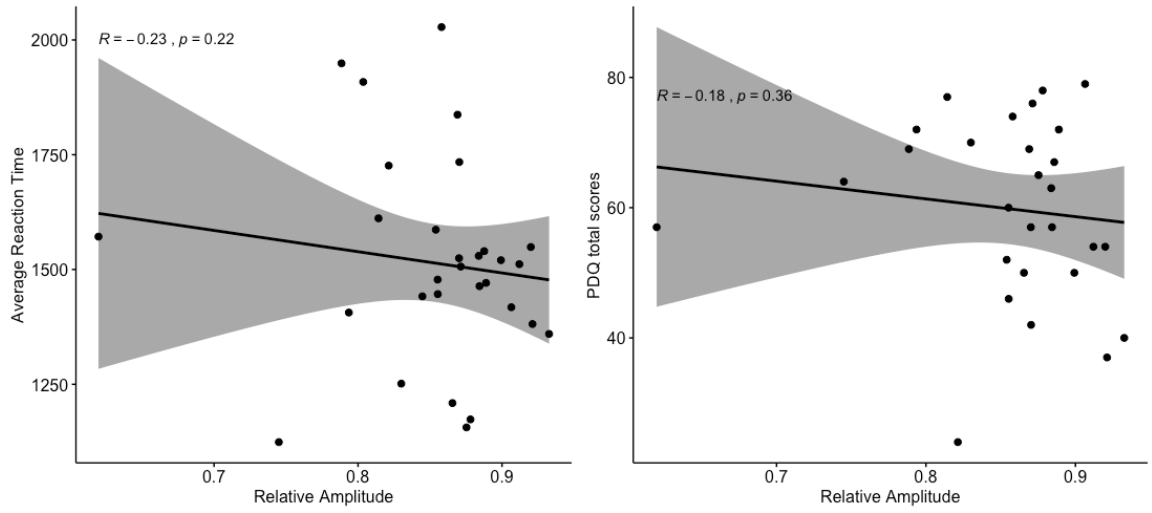
	Novel condition		Repeated condition	
Standard deviation of the daily reaction time	**Coefficient estimates**	**95% CI**	**Coefficient estimates**	**95% CI**
(Intercept)	399.77	(277.10, 523.60)	393.53	(272.80, 517.10)
Age	2.73	(-0.18, 5.80)	3.08	(0.12, 6.03) *
Gender (Male)	37.92	(-31.91, 102.66)	38.00	(-32.15, 108.53)
Allocation (Lithium)	27.33	(-49.23, 108.91)	30.06	(-48.82, 107.09)
Days	-0.11	(-1.69, 1.29)	-2.10	(-3.14, -1.07) *
Allocation (Lithium) * Days	-0.70	(-2.70, 1.38)	0.25	(-1.17, 1.58)

The standard deviation of daily reaction time was the dependent variable. Age, gender, allocation, days, and allocation × days interaction were independent variables (* represents statistically significant).

6.3.5 Relationship between cognitive function and circadian rhythm:

At baseline, the Spearman correlation analysis showed no association between cognitive performance in the novel condition and relative amplitude (p = 0.22, Figure 6.7A). In addition, the Spearman correlation analysis demonstrated no association between subjective cognitive function and relative amplitude (p=0.36, Figure 6.7B).

Figure 6. 7 Spearman correlation between cognitive performance and circadian rhythm measured by relative amplitude.



(A) (B)

(A) Correlation between relative amplitude and average reaction time in the novel condition at baseline. (B) Correlation between relative amplitude and PDQ total scores at baseline. R represents correlation coefficient; shaded area represents 95% CI; dots show individual data points.

6.4 Discussion

The present study is the first to use daily mobile-based contextual cueing tasks to investigate the effects of lithium on cognitive function in patients with bipolar disorder. The main finding of this study was that no significant differences were detected between the lithium and placebo groups on contextual cueing task performance. This result suggests that lithium may not significantly affect attention, implicit learning, and memory in patients with bipolar disorder.

6.4.1 Contextual cueing effect in bipolar disorder

While a similar approach has been utilised in a group of healthy participants with mood instability in the COMET study [312], this chapter is the first to report the contextual cueing effect across days in patients with bipolar disorder. A significant reduction in reaction time was recorded in the repeated condition compared with the novel condition of the contextual cueing task, supporting the use of the contextual cueing task as an cognitive assessment tool for implicit learning and memory function in bipolar disorder [310]. Performance in the novel condition can be used to determine attentional function over time; performance in the repeated condition can serve as an indicator of implicit learning and memory over time.

In the COMET study, the contextual cueing effect has been identified in healthy participants with mood instability under daily repetition conditions [312]. As described in this chapter,

this contextual cueing effect was not found in patients with bipolar disorder under the same condition; it could only be detected under the conditions of twice-daily repetition. There could be several reasons for the contextual cueing effect not to have been observed under daily repetition conditions. The sample size of this study is relatively small, with only sixteen bipolar patients receiving the placebo used to evaluate the contextual cueing effect in bipolar disorder. Second, the follow-up period is shorter than that of the COMET study, which monitored the cognitive function of participants for ten weeks; the contextual cueing effect may not have fully developed after six weeks of daily repetition. Lastly, patients with bipolar disorder might have some degree of implicit learning and memory deficits. In the COMET study, healthy participants with high mood instability had greater impairments in memory and learning contextual regularities as compared to healthy participants with low mood instability [312]. Thus, patients with bipolar disorder and significant mood instability who enrolled in the Oxlith study were very likely to have impairments in implicit learning and memory. In addition, a previous study found that the more frequent exposure to visual contexts was associated with stronger implicit learning and associative memory strength [314]. Based on an indirect comparison, patients with bipolar disorder, in this study, required more frequent contextual exposures to learn context-dependent regularities than healthy participants with mood instability in the COMET study, suggesting implicit learning and memory impairments in bipolar patients. Due to the absence of healthy participants in the present study, there was no direct comparison; therefore, this conclusion must be confirmed by further studies involving healthy participants as a comparison group.

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6.4.2 The effect of lithium on cognitive function in patients with bipolar disorder

Subjective and objective cognitive assessments revealed no significant differences between the lithium and placebo groups, suggesting that lithium may not significantly impair the attention, implicit learning, and memory of individuals with bipolar disorder. The daily contextual cueing task offered fine-grained data on cognitive performance and its variability over six weeks. Based on the novel trials, no significant differences in attentive performance between the two groups were observed. This result further supports previous findings that lithium had no adverse effect on attention [294]. Furthermore, repeated trials revealed no significant differences between the two groups in learning and using implicit contextual regularities for target identification, indicating that there were no significant impairments in implicit learning or memory in the lithium group. Other investigators have also reported that lithium has not affected cognitive performance. A large cohort study of eighty-eight patients with bipolar I disorder found no significant impairment in verbal learning or memory after initiation of lithium monotherapy [315]. In addition, a small cohort study demonstrated that lithium did not impair memory function in patients with bipolar disorder after six years of follow-up [316].

Neuroimaging studies in patients with bipolar disorder may provide additional evidence that lithium does not impair cognitive function; in fact, these studies suggest that lithium may have neuroprotective properties and provide neuroanatomical evidence for this finding. A large-scale MRI study found that patients with bipolar disorder had smaller hippocampal volumes as well as subfield volumes than healthy individuals; however, these differences were not evident in bipolar patients receiving lithium, but were found in bipolar patients not receiving lithium [317]. In addition, a cohort study has shown that long-term lithium treatment increases hippocampal volume. This cohort study of twelve patients with bipolar disorder receiving lithium monotherapy demonstrated increases in hippocampal volumes and

improvements in learning and memory after 4 years of lithium treatment [318]. Also, lithium treatment has been associated with increased cortical grey matter volume as well as decreased white matter damage in patients with bipolar disorder receiving lithium compared to those not receiving lithium treatment [319, 320].

Lithium has also shown beneficial effects on cognitive function in other conditions such as mild cognitive impairment and dementia. A randomized, placebo-controlled study of elderly patients with amnestic mild cognitive impairment treated with two years of lithium demonstrated prevention of cognitive decline and improvement of cognitive performance in the areas of attention and memory [321, 322]. Moreover, a meta-analysis of randomised placebo-controlled studies confirmed lithium's beneficial effects on reducing cognitive decline in individuals with mild cognitive impairment and Alzheimer's disease [323]. In contrast to patients with major depressive disorder or the general population, patients with bipolar disorder have a higher risk of developing dementia; lithium has been found to reduce this risk [324]. These findings suggest that lithium may not impair the cognitive function of patients with bipolar disorder and may even be protective in some cases.

6.4.3 Innovative ways to evaluate the cognitive effect of medication using mobile technology

This chapter presents an innovative approach to cognitive assessment through mobile devices. This mobile-based contextual cueing task was first used in the COMET study monitoring cognitive changes over a ten-week period. It was sensitive enough to detect the differences in learning and, using contextual repeated information, to facilitate target identification between healthy individuals with high and low mood instability [312]. In this

chapter, use of the task was extended to bipolar disorder and as a tool to assess the cognitive impact of pharmacological treatment.

Monitoring cognitive function in patients with bipolar disorder has been strongly recommended by the Targeting Cognition Task Force of the International Society for Bipolar Disorders. Specifically, this group recommended that clinicians monitor cognition in patients with bipolar disorder at least every five years, emphasising the importance of long-term cognitive function monitoring [325]. Most studies investigating cognition in bipolar disorder have relied on a limited number of neurocognitive tests; subtle changes in cognitive functioning have not yet been well characterised.

The task used in this chapter is advantageous because it meets the need to identify subtle changes in cognitive functioning in several ways. First, the participants completed the task daily, offering a more detailed assessment of changes in their cognitive function. In the future, the visualisation of cognitive changes early in the course of lithium treatment may be beneficial to both clinicians and patients for clinical review and early intervention. Second, this task directly pertains to the real-life experience of users. Detecting and utilising repeated information to assist with target identification is something that everyone does on a daily basis [326]. Last but not least, the task has the potential to be useful for long-term follow-up as it takes only one to two minutes to complete and game-based cognitive assessments have been shown to both entertain and engage participants [327, 328].

6.4.4 The relationship between cognitive function and circadian rhythm disruption

As discussed in chapter 1, both cognitive impairments and circadian rhythm disruption have been commonly observed in patients with bipolar disorder. Studies have shown that short-term sleep deprivation negatively impacts attention, decision-making, and memory in healthy adults [329]. Nevertheless, the association between cognitive dysfunction and circadian rhythm disruption is still not well studied in patients with bipolar disorder. This study examined this association using subjective and objective cognitive measures as well as actigraphy data. No significant association was found between cognitive function and relative amplitude, a measure of circadian disruption. In a study using data from the UK biobank, lower relative amplitude was found to be associated with slower reaction times [188]. There are two reasons why there are no significant findings on the association between cognitive function and circadian rhythm. First, this study has a much smaller sample size compared with the study using data from the UK Biobank.

Neurocognitive heterogeneity might be a second explanation for the negative results, and studies with a smaller sample size are more susceptible to this issue. The term cognitive reserve is defined as " the capacity of the brain to endure neuropathology in order to minimize clinical manifestations" [330]. It has been reported that bipolar patients with higher cognitive reserve perform better on cognitive tests [331]. Contrary to bipolar patients with low cognitive reserve, those with a high cognitive reserve might be able to endure the disruption of the circadian rhythm and report fewer cognitive complaints and perform better on cognitive tasks. Oxlith did not collect any data to determine high cognitive reserve, including IQ, educational level, and occupational achievements [331]. Therefore, when these two subgroups of patients were mixed together, especially in a small sample size study, this reduced the statistical power to detect an association between cognitive function and circadian rhythm disruption. Future studies should examine the relationship between

cognitive function and circadian rhythm disruption in subgroups of patients with bipolar disorder, such as those with low cognitive reserve.

In this thesis, the association between circadian disruption and cognition was investigated using actigraphy and mobile-based contextual cueing tasks in real time, without significant temporal separation. In future cohort studies following patients with bipolar disorder for an extended period of time, this real-time, high frequency monitoring approach provided by digital devices will provide valuable insights into the relationship between cognitive functions and circadian rhythm disruption.

6.4.5 Limitations

This study has several limitations. First, the sample size of this study was small, which may have affected the power to detect differences between the two groups. Second, the contextual cueing task assessed attentional performance, implicit learning, and memory [310]; however, no other cognitive functions, such as executive function and creativity, were assessed. It is not possible to generalise the findings to all aspects of cognition in bipolar disorder. Third, the study examined lithium's effects on cognitive function for six weeks only and its long-term effects remain uncertain. Fourth, this empirical study is a secondary analysis of Oxlith data. Participants were not recruited for the purpose of examining their cognitive function under the treatment of lithium. Participants from both groups reported frequent cognitive dysfunction at baseline, making them a suitable sample for testing the pro-cognitive effects of pharmacological treatments. To achieve the objective of this chapter, it would be more sensitive to examine whether lithium adversely affects cognitive function in a group of bipolar patients with less cognitive impairment. Finally, due to the short-term study design,

participants were not followed long enough to assess their response to lithium and differentiate between lithium responders and lithium non-responders. Since the cognitive functions of lithium responders are better preserved than those of lithium non-responders [298], the heterogeneous response to lithium may undermine the power to detect differences between lithium and placebo groups.

There are also some limitations to this innovative mobile-based cognitive assessment. First, a further determination of the reliability and validity of this novel test should compare it to a standardised neurocognitive test and replicate its use in larger groups of patients with bipolar disorder. Second, the bright blue light emitted by the light-emitting diodes in digital devices was of concern as recent studies have suggested that blue light exposure might disrupt circadian rhythm and further impair a wide range of physio-psychological processes [332]. In patients with bipolar disorder, higher levels of exposure to light in blue wavelength ranges before bedtime were associated with worse sleep quality [333]. For digital devices to be used in clinical settings and for experimental medicine studies, further studies are necessary to investigate the impact of blue light exposure and how to prevent disruption of the circadian rhythm.

6.4.5 Conclusion

This study is the first to use a mobile-based contextual cueing task in a randomised, placebo-controlled, double-blind experimental medicine study to investigate the effect of lithium on cognitive function in patients with bipolar disorder. A contextual cueing effect was reported in patients with bipolar disorder, which supported the use of the contextual cueing task for assessing the attentional performances, implicit learning and memory function in patients

with bipolar disorder. Other analysis demonstrated no significant difference between lithium and placebo on attention, implicit learning, and memory, suggesting lithium might not impair these cognitive domains in patients with bipolar disorder. While interpretation of the results was limited by a small sample size, this innovative approach to cognitive assessment presents a new methodological paradigm for assessing the impact of pharmacological treatment on cognitive function in bipolar disorder.

Chapter 7: General discussions and future directions

"How do you pollinate my blood so exactly with sanity Does my brain's infinite heart burden you Why find my grandmother too late
Why not kiss everyone who needs your fix Why leave some
to their singed waves Who do you speak to in my body that listens"
-Erlichman, Shira. Odes to Lithium (p. 56)

There were two main objectives in this thesis: the first was to examine whether lithium has direct effects on reversing circadian rhythm abnormalities commonly reported in patients with bipolar disorder, and the second was to examine whether lithium has an adverse impact on cognitive functioning in patients with bipolar disorder.

7.1 Summary of main findings

7.1.1 Few studies investigate the effect of lithium on circadian rhythm in patients with bipolar disorder (chapter 2)

In chapter 2, a systematic review was conducted to answer the question of whether lithium has an impact on circadian rhythm in patients with bipolar disorder. Both experimental and observational studies were included and the primary outcome was the measurement of circadian rhythm using validated tools with real-world applicability. This systematic review highlights the paucity of studies elucidating lithium's effect on circadian rhythm in patients with bipolar disorder. Most of the studies were observational; only two studies investigated

lithium's effect on circadian rest-activity. This field requires high-quality research studies where the primary outcome is the measurement of circadian rhythm.

7.1.2 No consistent and robust evidence supporting the rhythm-modifying effect of lithium (chapter 2, chapter 4, and chapter 5)

The meta-analysis in chapter 2 reported a potential association between lithium and greater morningness. This result is subject to two different interpretations. First, morningness chronotype could be a predictor of the clinical outcome of lithium treatment. Second, the advance in the circadian phase or the increased morningness might be a part of lithium's therapeutic effects, an aspect that was explored further in chapters four and five using data collected as part of the Oxlith study.

In chapter 4 and 5, no compelling or robust evidence supported the hypothesis that lithium might increase the levels of circadian rest-activity, advance the phase of the circadian rest-activity, and reduce the variability of the circadian rest-activity. Nevertheless, there were tentative findings that lithium reduced daytime activity, decreased the onset time of daytime activity, and reduced the variability of the circadian rest-activity. Additionally, the significant associations between mood and motor activity and the timing of circadian rest-activity found in chapter 4 and chapter 5 highlight the need for a multimodal acquisition of mood and activity data in future studies.

7.1.3 The application of a novel mobile-based cognitive assessment adds to our knowledge about the effect of lithium on cognitive function (chapter 6)

It is unclear whether lithium has an adverse impact on cognitive function in patients with bipolar disorder. In chapter six, this question was further explored using data collected as part of the Oxlith study. A novel mobile-based contextual cueing task was applied in patients with bipolar disorder to monitor attentional performance, implicit learning, and memory function after six weeks of treatment. No significant difference between lithium and placebo was found on attention, implicit learning, and memory, suggesting lithium might not impair these three cognitive domains in patients with bipolar disorder. While interpretation of the results was limited by a small sample size, this innovative method of cognitive assessment provides a finer-grained method of evaluating cognitive changes in patients with bipolar disorder under pharmacological treatments.

7.2 Challenges and limitations

Specific limitations are discussed in the pertinent chapters of this thesis; however, there are some overarching limitations to consider.

7.2.1 Differentiating Lithium Responders (Li-R) from Lithium Non-Responders (Li-NR)

The participants in Oxlith were not followed long enough to evaluate their response to lithium and distinguish between Li-R and Li-NR. The Oxlith investigated the short-term effects of lithium rather than focusing on the long-term effects of lithium as a maintenance

therapy. There have been findings that Li-R and Li-NR exhibit different circadian rhythms and cognitive function phenotypes. McCarthy and colleagues found that Li-R had different chronotype and cellular circadian rhythms patterns than Li-NR [144]. Li-R have been shown to have better cognitive functions than Li-NR [298, 306]. Thus, a heterogeneous response to lithium may limit the ability to detect differences in circadian rhythms and cognitive function between lithium and placebo groups in patients with bipolar disorder. Future studies can combine a short-term intensive measurement design with a long-term follow-up; with the advancement of telepsychiatry, long-term psychiatric evaluations are feasible.

7.2.2 Insufficient statistical power

This is the first randomised, placebo-controlled study investigating the effect of lithium on circadian rhythm in patients with bipolar disorder using actigraphy. However, data collection on circadian rhythm occurred in the context of the Oxlith study whose primary outcomes were related to mood instability, not circadian rhythm, and so the target sample size for the Oxlith was calculated based on mood symptoms variability data from the OXTEXT-6 randomised controlled trial, not on data relating to circadian rhythm[198]. Therefore, the Oxlith may not have sufficient sample size to detect the differences in circadian rhythm between groups. Further, the interquartile ranges for M10 and L5 onset times of Oxlith participants appear wider than those reported in similar studies of bipolar patients, indicating a more heterogeneous sample from a circadian measures perspective [245, 288]. In comparison with a more homogeneous sample, a heterogeneous sample has been found to reduce the statistical power to detect true effects of interventions [289].

The issue of missing data must also be addressed when considering limitations in statistical power. Two causes accounted for the majority of missing data for circadian rest-activity: a total of twelve actigraphs were discovered to have stopped unexpectedly during day eight visits and eight actigraphs were found to have technical problems during the week six visit. The actigraphy experience in this trial suggests that data quality can be improved in several ways. First, the research coordinator should receive adequate training on actigraphy and ensure accurate data collection by properly setting up the actigraph (some actigraphs stopped unexpectedly due to incorrect set up) and should monitor the quality of the collected data. Once technical problems or missing data are identified during the trial, researchers can take action. Second, fewer actigraphs should be used to cover the entire recording period; the ideal device would have better data storage capacity and a longer battery life. In addition to losing fewer data during the trial, continuous data from the same device will be available without the need for calibration.

7.2.3 Secondary analysis

Weakness in measurements

It should be noted that the empirical studies presented in chapters 4-6 are secondary analyses of Oxlith data, which presents a challenge for this thesis since Oxlith data were collected for purposes that are different from those explored in this thesis. The primary outcome of Oxlith was mood severity and stability over the 6-week randomised period. Circadian rhythm, sleep and cognitive function were secondary outcomes of the Oxlith [9].

The measurements in the Oxlith were adequate, though not optimal, for the purposes of this thesis. Circadian rhythm measurements were primarily based on actigraphy. Ideally, DLMO would have been used as a phase marker to examine the hypothesis that lithium might advance the phase of circadian rest-activity in patients with bipolar disorder. To assess the melatonin secretion profile, participants in the Oxlith were asked to collect cheek and saliva samples every four hours over two 32-hour periods, one at pre-randomisation phase and one at week 4; however, this sampling frequency was not frequent enough to obtain a reliable melatonin production profile as saliva samples should be collected every 30-60 minutes over 24 hours [57]. A few samples in the evening hours may suffice for DLMO acquisition, but participants must remain under dim lighting conditions during the entire process. Light exposure restriction was not imposed on each participant at night. Therefore, DLMO, the circadian-phase marker, may not be accurate since light may have suppressed melatonin secretion [57]. The meta-analysis in chapter 2 highlighted a possible association between lithium and greater morningness as measured by CSM and MEQ, however, chronotype was not assessed in the Oxlith using self-report methods.

One of the secondary outcomes of Oxlith was to assess the relationship between variability in daily mood measures and the performance of daily cognitive tasks related to decision making, implicit learning, and explicit learning [9]. This secondary outcome was more exploratory in nature. It was not feasible to use the neurocognitive tests recommended by Lithium Battery-Research for this purpose, since each of them would take a minimum of three to fifteen minutes to complete [313]. The cognitive tasks adopted in the Oxlith allowed for analysis of cognitive performance changes at higher temporal resolutions.

However, the objective of chapter six was more confirmatory in nature. For the purpose of determining whether lithium adversely affected cognitive function in patients with bipolar disorder, it would have been optimal to use a common set of objective neurocognitive assessments, which have demonstrated some promise and utility in patients with bipolar disorder. In addition, the results would have been more comparable to those of other studies that employed the same neurocognitive assessments. The Lithium Battery-Research, a set of standardised neurocognitive tests specific to lithium treatment, has been proposed; it offers comprehensive assessments of key cognitive domains, including executive function and working memory, verbal learning and memory, visual learning and memory, as well as psychomotor and processing speed [313]. Future research should use standardised neurocognitive assessments to verify the validity of this mobile-based cognitive task.

Limitations in study samples:

The samples in the Oxlith were suitable, but not optimal for the purposes of this thesis. Participants with both a diagnosis of bipolar disorder and a clinical complaint of significant mood instability were recruited. Two studies using UK Biobank data found that great mood instability was associated with disrupted circadian rhythms [188, 334]. A recent systematic review has shown that mood instability is closely associated with delayed sleep timing [335]. These studies suggest that bipolar patients with significant mood instability can be suitable samples to examine the effect of lithium on circadian rest-activity. However, there are following limitations in the study samples. First, given the significant association between mood and the circadian rest-activity, mood instability increased the variance in circadian measures among individuals, making it difficult to detect a consistent and robust change in those circadian measures under lithium treatment, especially in a small sample size such as

Oxlith. Second, the participants were heterogeneous with respect to circadian measures, which undermined the statistical power to detect the effect of lithium on circadian measures. The interquartile ranges for baseline M10 and L5 onset time of participants in Oxlith are larger than those reported in other similar studies of bipolar patients [245, 288], which implies a heterogeneous sample with respect to circadian timing. It was found that a heterogeneous sample reduced the statistical power to detect true effects of interventions, compared to a more homogeneous sample [289]. Third, to examine the adverse effect of lithium on cognitive function, it would be ideal to study a group of bipolar patients with less cognitive impairment. The participants in both groups reported frequent cognitive dysfunction in a wide range of domains at baseline, suggesting they may not be able to detect minor adverse effects induced by pharmacological treatment compared to patients with a more intact cognitive functioning.

7.2.4 Representativeness of study samples and generalisability of results:

This thesis examined the effect of lithium treatment on a subgroup of bipolar patients, and there are limitations to the generalisability of the results to patients with bipolar disorder in the community. First of all, the exclusion criteria of no clinically significant substance abuse and no immediate risk of suicide or self-harm restricted the participants to a less severe group. A high rate of alcohol and drug use disorders has been observed among people with bipolar disorder, particularly bipolar I disorder [336]. The rate of suicide among those with bipolar disorder is the highest of all psychiatric disorders [337]. Clinical trials investigating bipolar disorder commonly have adopted these two criteria, thereby making their results less generalisable [338]. Second, participants were not experiencing an acute mood episode requiring immediate treatment. In addition, most of the participants reported mild manic

symptoms and mild-to-moderate depressive symptoms. Lastly, significant mood instability was one of the inclusion criteria. Given the association between affect and motor activity, as well as the timing of circadian rest-activity, one can expect a greater degree of instability of circadian measures in the participants [245]. The implications of this inclusion criterion on the results were discussed in greater detail in section 7.2.3, limitations in study samples. Overall, this study recruited a subgroup of patients with non-severe bipolar disorder and had significant mood instability. The results should not be generalised to all bipolar patients.

7.2.5 Avoiding false-positive inferences:

The following factors may together increase the risk of type I error (false-positive error) and lead to inaccurate interpretation of results. First, some of the results in this thesis are not robust or consistent. In chapter 2, the association between lithium and greater morningness was not statistically significant. In the empirical studies presented in chapters 4 and 5, the effects of lithium on modifying circadian rest-activity were only found in some of the weeks after randomisation. The different approaches or variables used to investigate the same aspect of circadian rest-activity did not yield consistent results. Second, some of the statistical analyses used in this thesis may increase the risk of making false-positive conclusions. Throughout chapters 4 and 5, within-group comparisons were used as a complement to between-group comparisons and were exploratory in nature. Conclusions drawn solely from within-group comparisons will increase the rate of type I errors significantly [239, 240]. Additionally, the multiple testing problem should also be considered in this thesis. The term 'multiple testing' refers to a dataset that has undergone multiple statistical tests, which raises the risk of false-positive findings [339, 340]. Throughout this thesis, the two treatment groups have been compared multiple times on a variety of outcomes, as well as on the same outcome

at different times, increasing the likelihood of discovering a statistically significant result by chance. In this thesis, no multiple testing adjustments have been made because the empirical studies are largely exploratory in nature [339]. As with all the situations discussed above, the possibility of false-positive findings must be acknowledged. Therefore, no definitive conclusion could be drawn about the effects of lithium on circadian rest-activity in patients with bipolar disorder. Future research is required to confirm the results of this thesis.

7.3 Research and clinical implications

7.3.1 A need to address heterogeneity in bipolar disorder

The majority of the significant effects of lithium on circadian rest-activity detected in this thesis did not persist throughout the study. Besides the influence of small sample sizes and missing data, the heterogeneity of bipolar disorder further complicates the issue. Investigating bipolar disorder can be challenging due to its heterogeneity, which defined as " the degree to which a system deviates from perfect conformity" [341]. In this thesis, there are several factors contribute to the heterogeneity of participants. First, a mixture of patients with bipolar I disorder and bipolar II disorder were recruited in the Oxlith study. The genome-wide association study revealed differences in genetic architecture between bipolar I disorder and bipolar II disorder [342]. These findings may indicate different pathophysiological mechanisms associated with each subtype of bipolar disorder. Second, participants in the Oxlith study were not recruited due to concerns regarding circadian disruptions. For example, one previous study found that less than one third of euthymic bipolar patients met the diagnosis of delayed sleep-wake phase disorder [68]. Therefore, not every participant in the

current study experienced a consistently late onset of daytime activity. There was a high degree of variability in phase among participants.

Chronobiological phenotypes, which are objectively measurable, can be used to address the heterogeneity in bipolar disorder. Chronotypes is one of the well-established chronobiological phenotypes in patients with bipolar disorder that have been associated with various clinical presentations, clinical outcomes, and treatment responses [343]. In future studies, it would be of interest to examine whether lithium acts as a phase-advancing agent in bipolar patients with delayed sleep-wake phase disorder.

7.3.2 Discrepancy between subjective and objective measures

Discrepancy between subjective and objective measures were found in chapters four and six. As reported in chapter 4, no correlation between Sleep Condition Indicator total score and L5 at baseline, nor between L5 and Sleep Condition Indicator sub-item scores. A similar finding was found in one previous study that there was no significant correlation between L5 and PSQI total scores or PSQI component scores (sleep quality) in remitted patients with bipolar disorder [187]. These findings suggest that objective circadian markers like L5 may not be sufficient to assess sleep quality; a validated self-report questionnaire should be utilised.

The poor correlation between subjective cognitive measures and objective cognitive measures has been well documented [344-346]. Further evidence was provided by results of chapter six in which no correlation was found between cognitive performance as assessed by the contextual cueing task and subjective cognitive function as assessed by the perceived deficits questionnaire. In a previous study, self-report psychosocial disturbances were found

to be associated with subjective cognitive impairments, but not with objective cognitive impairments [345]. In addition, Miskowiak and colleagues found that objective cognitive assessments were warranted in patients with bipolar II disorder, residual affective symptoms, and hospitalisation, which predicted broader discrepancies between subjective and objective cognitive tests [346]. Therefore, both subjective and objective cognitive assessments are necessary in the assessment of cognition in patients with bipolar disorder.

7.3.3 The importance of chronobiological phenotypes in treating bipolar disorder

As reported in chapter 2, a potential association between lithium and greater morningness was found, suggesting that morningness chronotype might be a predictor of the clinical outcome of lithium treatment. There have been two previous studies that support this finding. McCarthy and colleagues found that Li-R had greater morningness than lithium-Li-NR [144]. Another study found that fibroblast cells extracted from Li-R tend to have a shorter circadian period compared to Li-NR [143]. Among individuals with bipolar disorder, chronotype is not only related to treatment response, but also to clinical presentation and outcome. Patients with bipolar disorder with a higher level of eveningness had an early age-at-onset, more prior mood episodes, more disordered eating behaviours, higher rates of suicide attempts, substance abuse and somatic comorbidities [180, 261]. In contrast, patients with bipolar disorder with a higher level of morningness was associated with better clinical outcomes including milder depressive and manic symptoms, a lower risk of depressive episode relapse, and fewer past suicide attempts [144, 262]. Considering the importance of chronotype as a clinically relevant phenotype, its measurement should potentially be implemented into clinical practice.

In this thesis, lithium showed effects in stabilising and advancing the circadian rest-activity. While these findings are preliminary and should be replicated in larger samples, they indicate that lithium may be useful in treating bipolar patients with significant circadian rhythm disruption. Federoff and McCarthy reported a bipolar I disorder patient with circadian rhythm disruption. An advanced phase was noted after taking low-dose lithium, changing from very low morningness to high morningness in this patient [275]. The pharmacogenomics of bipolar disorder trials evaluated patients with bipolar I disorder's response to lithium after 12 weeks of treatment and categorised them as Li-R or Li-NR. Both groups had a significant reduction in affective symptoms of depression. By contrast, only Li-R improved the circadian symptoms of depression (including sleep and activity) [347]. Taken together, these findings suggest that chronobiological phenotypes should receive more consideration in treatment of bipolar disorder.

7.4 Future directions

7.4.1 Further exploration of the role of circadian rhythm in lithium's mechanism of action

This thesis argues that circadian rhythm plays an important role in lithium's mechanisms of action. There is a need to develop more prospective, longitudinal studies focusing on circadian rhythm as the primary outcome, as well as to better characterise the circadian rhythm changes when investigating lithium's mechanism of action. A more comprehensive and systematic measurement of the circadian rhythm changes should be adopted in future studies. Actigraphy, self-report questionnaires, and melatonin analysis are useful tools recommended by the International Society for Bipolar Disorder for studying circadian

rhythms in clinical studies [57]; additionally, bipolar patient-derived fibroblasts and induced pluripotent stem cells derived neurons can also be valuable tools to investigate the cellular circadian rhythm [348].

Different measures of circadian rhythm exist, including circadian amplitude, circadian phase, and circadian variability. A 24-hour melatonin profile and the actigraphy measurement of motor activity can be used to measure circadian amplitude [57]. DLMO, actigraphy, and sleep midpoint can all be used to obtain an accurate estimate of circadian phase. Measuring chronotype is another indirect method to quantify the circadian phase [57, 63] and chronotype measurements are more affordable and more easily obtained than actigraphy and melatonin assessment. MEQ, CSM, and MCTQ are validated self-report questionnaires to measure chronotype [57, 349]. At present, there is no standard method to quantify circadian variability. Interdaily stability (IS) and Intradaily variability (IV), two variables derived from the nonparametric analysis of actigraphy data, has been commonly used to quantify the synchronisation and fragmentation of the circadian rhythm [350]. Certain measures and methods used in mood instability and heart rate variability can be applied to quantify circadian variability, such as the Teager-Kaiser energy operator (TKEO), root mean squared successive differences (RMSSD), entropy, and nonlinear time-series approaches [37, 225].

7.4.2 The measurement of bipolar phenotypes with greater resolution and accuracy using digital devices

In this thesis, two types of mobile monitoring were employed: passive assessment of circadian rest-activity using movement data collected via actigraphy, as well as active assessment of cognitive performance using data from a mobile, game-based cognitive

assessment. The present study demonstrated that digital devices can be used to monitor bipolar phenotypes and the effects of therapeutic interventions.

Future studies will generate vast amounts of high-resolution data to assess mental health conditions from more digital sources. Data generated by passive detection has been applied to mental health research; for instance, anonymised geographic location data [351], usage of cell phones (including battery, screen time and app usage) [352], and voice features during phone [353]. Additionally, data can be generated from engaging human behaviour, such as the daily self-report questionnaires and the game-based cognitive assessments used in this thesis. The use of digital devices for gaming is a popular leisure activity, and it has great potential to be repurposed as a mental health assessment that provides high-quality data [354]. Certain internet games are designed specifically to address a mental health condition. For instance, Sea Hero Quest, in which participants' navigational skills are measured [355], is designed for the assessment of dementia. Additionally, off-the-shelf games can provide a wealth of data which can be used to generate digital biomarkers on mental health conditions including cognitive performance, motor performance, social interaction, and affect [354].

In light of this real-time, high-frequency monitoring approach using digital devices, new insight into mental health research can be gained, but it is critical to consider various factors which could compromise the predictive power of digital phenotypes derived from such data. As participants are not in a controlled research environment, unrelated life events such as changes in relationships, employment, studies, and finances may have a significant negative impact on the outcome researchers are trying to measure. Another issue to consider is the ethical and legal use of digital data, including participants' privacy and right to consent [135].

7.4.3 Use early effects data to determine treatment response

While there was no robust evidence for the rhythm-modifying effect of lithium, there were some tentative evidence that lithium reduced daytime activity, decreased the onset time of daytime activity, and decreased the variability of the circadian rest-activity, suggesting that changes in circadian rhythms might be a potential indicator of lithium response. While the validity of this marker should be evaluated by comparing short-term changes in circadian rhythm caused by lithium with the long-term therapeutic efficacy of lithium, this thesis presents a novel methodological paradigm for rapid assessment of treatment response to lithium and other novel mood stabilisers. Currently, psychiatrists who treat patients with bipolar disorder must rely on a 'trial and error' approach that requires patients to take lithium for a number of months in order to determine the degree of response [2]. There is a need for reliable and reproducible biomarkers of lithium response in patients with bipolar disorder to avoid lengthy and ineffective treatment trials.

The majority of existing studies focused on using data collected at baseline (demographics, family history, clinical data, genetic data) to predict treatment response to lithium in patients with bipolar disorder. Social-demographic and clinical factors are the most common predictors of lithium treatment response; however, once results are restricted to high-quality studies, there is no reliable, validated predictor of lithium treatment response [2]. Despite the findings of genome-wide association studies and polygenic risk scores studies supporting the genetic contribution of lithium response in bipolar disorder [120-123], the clinical utility of genetic testing is limited for the following two reasons. First, due to the relatively low frequency of the response-associated genetic variants, genetic testing is not informative for most patients with bipolar disorder [121]. Second, polygenic load for psychiatric traits like

schizophrenia or depression accounted for less than 1% of the variance in lithium treatment response observed in patients with bipolar disorder [122, 123]. Therefore, additional studies are needed to improve the predictive models.

Early effect data have been used to predict lithium response through a prospective study design. Kafantaris and colleagues used early changes in white matter microstructure after lithium treatment to predict lithium response [356]. Another study extracted features of circadian timing and rhythmicity from 21 days of actigraphy data collected from patients with bipolar disorder after lithium treatment; this study was able to explain more than 20% of the variance in patient's response to lithium [357].

So far, no single type of data is sufficient to provide a reliable prediction of lithium's clinical response. Future studies can use each of these categories of information, including early changes in circadian rhythm, as components of a multimodal prediction model that incorporates both individual characteristic data and early effects data; with the aid of machine learning algorithms, which are powerful tools for identifying hidden patterns in the data, lithium response prediction modelling can be improved [358].

7.4.4 Multimodal modelling in a deep phenotyping cohort predicts treatment response

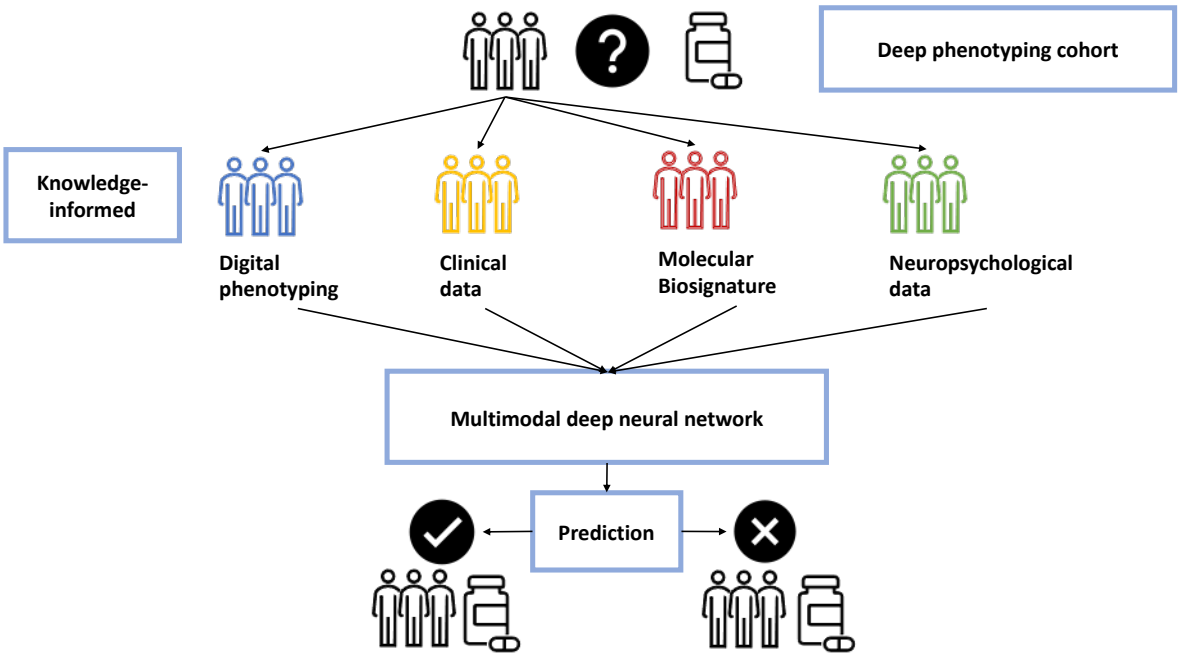
In this thesis, a deep phenotyping cohort was used to investigate the effects of lithium. Specifically, a deep phenotyping cohort is one that characterises disease manifestations or treatment effects in a more detailed, comprehensive manner [359]. Participants in this thesis underwent short-term, intensive assessments of mood, circadian rhythms, and cognitive

function. The relatively small sample size, however, limits the application of more comprehensive statistical models that are described below.

Multimodal modelling has been developed using deep learning algorithms. Each data stream feeds into a specific network; finally, the fully connected layers are applied to integrate all the data streams [358]. Deep learning, the latest development in machine learning, is capable of capturing hidden patterns, acquiring knowledge, and aiding in decision-making using complex data. As opposed to conventional machine learning algorithms, deep learning algorithms do not require as much feature engineering to improve the performance of the model [360].

Deep learning in psychiatry has been primarily used to improve diagnosis of mental health conditions. In future studies, this AI technology could prove useful for facilitating drug discovery, treatment response prediction, and relapse risk prediction [358]. Deep learning algorithms can be applied to those deep phenotyping cohorts receiving short-term lithium or other mood stabilisers. The following data can be used to predict the treatment response of bipolar patients to lithium or other mood stabilisers: digital phenotyping (including circadian rest activity), molecular biosignature (including comprehensive multi-OMICs data), neuroimaging and neuropsychological testing, and clinical information (See Figure 1). Furthermore, interpretable neural networks have been developed, which enable us to measure the contribution of each feature in the inputs to the output, as well as to identify signatures that can be used to predict the outcome of treatments [358].

Figure 7. 1 An illustration of a deep learning algorithm used for treatment response prediction.



To predict treatment response, each participant undergoes deep phenotyping. Clinical data, digital phenotyping data, molecular biosignatures and neuropsychological data are collected from each individual over a short period of treatment. Existing biomedical knowledge informs the selection of each feature. To integrate these multi-dimensional data, one can use a multimodal deep neural network approach.

7.4.5 A brief example of a future study plan

With all the future directions and implications discussed in this chapter, the following provides a specific study plan to investigate the effects of lithium (or other treatment) on circadian rhythm in bipolar disorder. The primary outcome of this study will be changes in the phase of the circadian rhythm as measured by DLMO time. This represents a step towards developing a valid experimental medicine model for bipolar disorder.

Participant：

Participants with a diagnosis of bipolar disorder and an eveningness chronotype determined by the Morningness-Eveningness Questionnaire will be recruited to reduce the heterogeneity of study samples.

Study design:

This experimental medicine study will adopt a short-term intensive measurement design with a long-term follow-up. During the intensive measurement phase, participants will be subjected to a battery of multi-modal investigations, including remote monitoring of mood and sleep quality as well as comprehensive measurements of circadian rhythms. Participants will be asked to provide skin biopsies in order to culture fibroblasts and to grow human neurons through the use of induced pluripotent stem cells (iPSCs) technology [361]. Thus, molecular biosignatures such as gene expression changes and cellular circadian rhythms can be acquired. After a long-term follow-up period, participants will be divided into two groups based upon their clinical responses to the treatment.

Measures:

Circadian rhythms and sleep parameters:

A comprehensive assessment of circadian rhythm will be conducted using salivary melatonin, actigraphy. The phase of the circadian rhythm will be determined by the DLMO time. DLMO time should preferably be acquired in a sleep unit or sleep laboratory under medical supervision. Participants should be carefully instructed if DLMO time has to be acquired at home. It is recommended that the research team provides participants with written instructions regarding sample collection procedures as well as a sleep diary to record sample collection times and bedtimes [362]. During the study, participants will wear an actigraph to monitor their level of light exposure and their circadian rest-activity patterns. The chronotype will be determined by the Morningness-Eveningness questionnaire.

It is ideal to use polysomnography to measure sleep objectively. Additionally, actigraphy may also be used to provide objective sleep parameters. The Pittsburgh Sleep Quality Index will be utilised to assess subjective sleep quality.

Molecular biosignatures:

The clock gene expression and cellular circadian rhythm of neurons from each patient with bipolar disorder will be examined. These neurons are acquired using iPSCs technology. A bioluminescent reporter, Per2-luc, will be used to measure the cellular circadian rhythm [361]. The correlation between changes in neuronal rhythms and changes in circadian rhythms as measured by melatonin and actigraphy after treatment would be of interest to examine.

7.5 Conclusions

This thesis provides new insights into the effects of lithium on circadian rhythm and cognitive function in patients with bipolar disorder using finer-grained actigraphy data and daily cognitive performance data. The systematic review suggested lithium was associated with greater morningness. No definitive conclusion could be drawn regarding the effect of lithium on circadian rest-activity. In spite of this, there was some tentative evidence that lithium reduced daytime activity, suggesting it had a stabilising effect. In addition, it reduced the onset time of daytime activity as well as the variability of circadian rest-activity. This thesis did not find significant differences between lithium and placebo on attention, implicit learning, and memory using a mobile-based contextual cueing task and a self-report questionnaire, suggesting short-term lithium treatment does not impair these cognitive domains in patients with bipolar disorder. Moreover, this thesis demonstrates the potential of real-time, high-frequency mobile assessment techniques to characterise bipolar phenotypes with greater resolution and accuracy, which may provide new insights into the pathogenesis of bipolar disorder.

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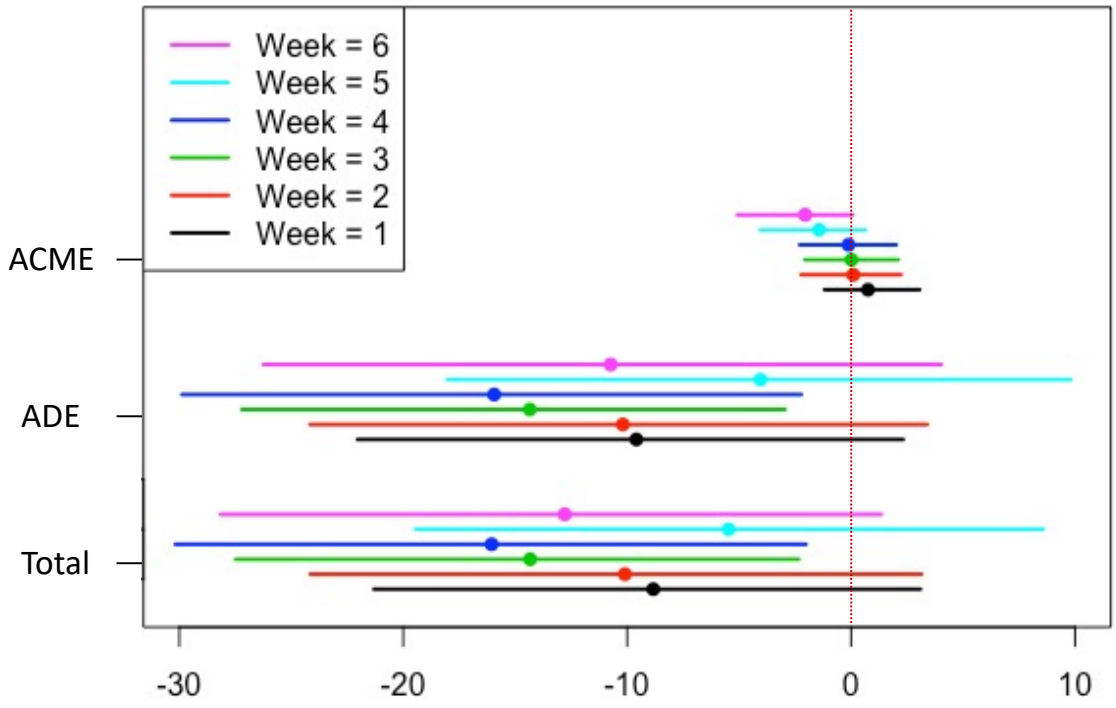
Appendix

Supplementary Table1. Sleep Condition Indicator [238]

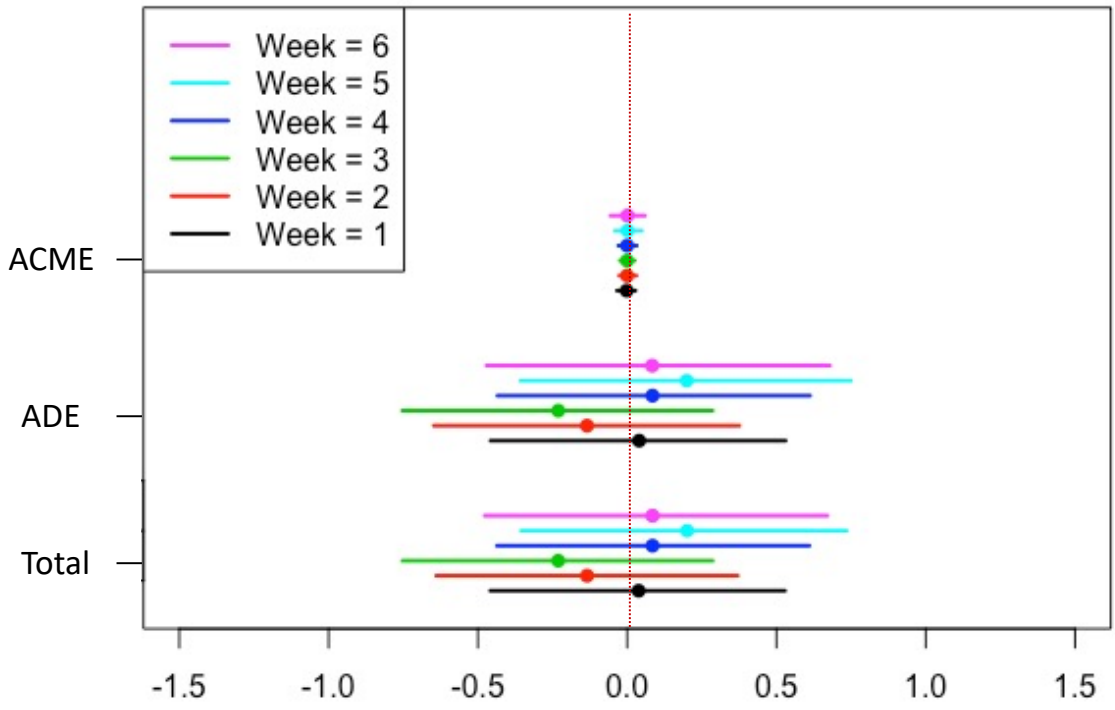
	4	3	2	1	0
Thinking about a typical night over the past month					
1. ... how long does it take you to fall asleep?	0-15 min	16-30 min	31-45 min	46-60 min	≥ 61 min
2. ...if you then wake up during the night ... how long are you awake for in total? (add all the wakenings up)	0-15 min	16-30 min	31-45 min	46-60 min	≥ 61 min
3. ... how many nights a week do you have a problem with your sleep?	0-1	2	3	4	5-7
4. ... how would you rate your sleep quality?	Very good	Good	Average	Poor	Very poor
Thinking about the past month, to what extent has poor sleep ...					
5. ... affected your mood, energy, or relationships?	Not at all	A little	Somewhat	Much	Very much
6. ... affected your concentration, productivity, or ability to stay awake	Not at all	A little	Somewhat	Much	Very much
7. ... troubled you in general	Not at all	A little	Somewhat	Much	Very much
Finally					
8. ... how long have you had a problem with your sleep?	I don't have a problem/ < 2 weeks	1-2 months	3-6 months	7-12 months	> 1 year

Supplementary Figure 1 A graphical summary of the results of a casual mediation analysis of the effect of lithium on M10 during six weeks after randomisation



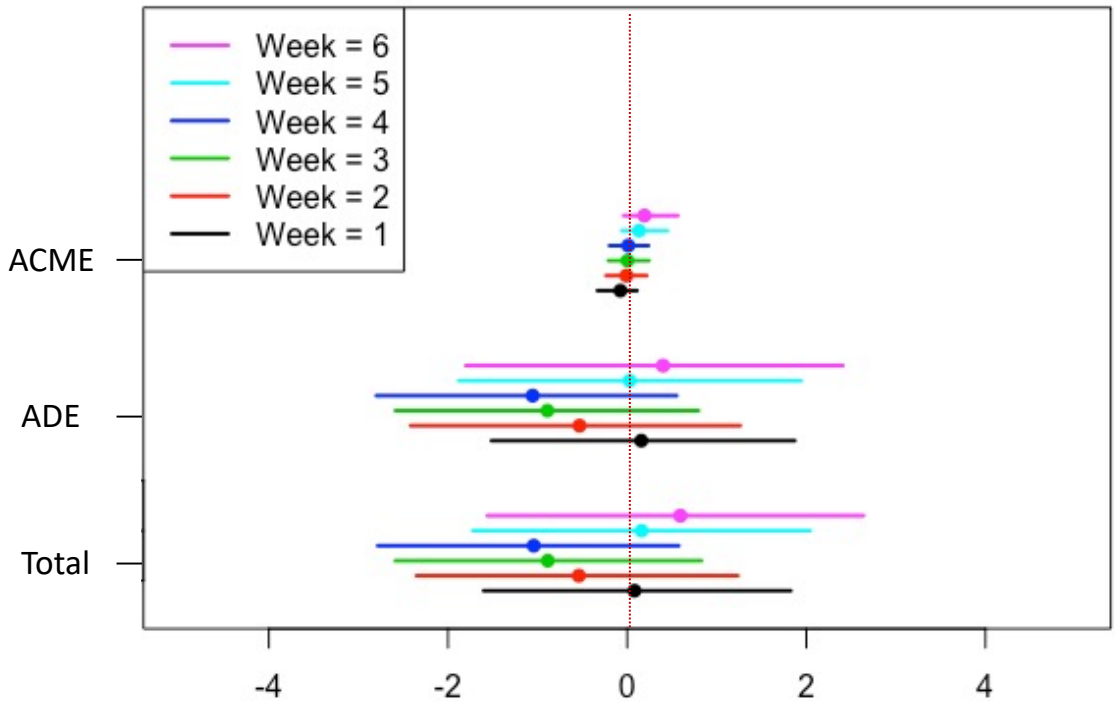
Mediation analysis with Allocation as a predictor, M10 as the outcome, positive affect as a mediator, and Week as a moderator. Total = ACME + ADE. ACME, average causal mediation effect; ADE, average direct effect; Total, total effect. The dots and bars correspond to the effect sizes and 95% confidence intervals. If the 95% confidence interval does not contain 0, the results are statistically significant.

Supplementary Figure 2 A graphical summary of the results of a casual mediation analysis of the effect of lithium on L5 during six weeks after randomisation



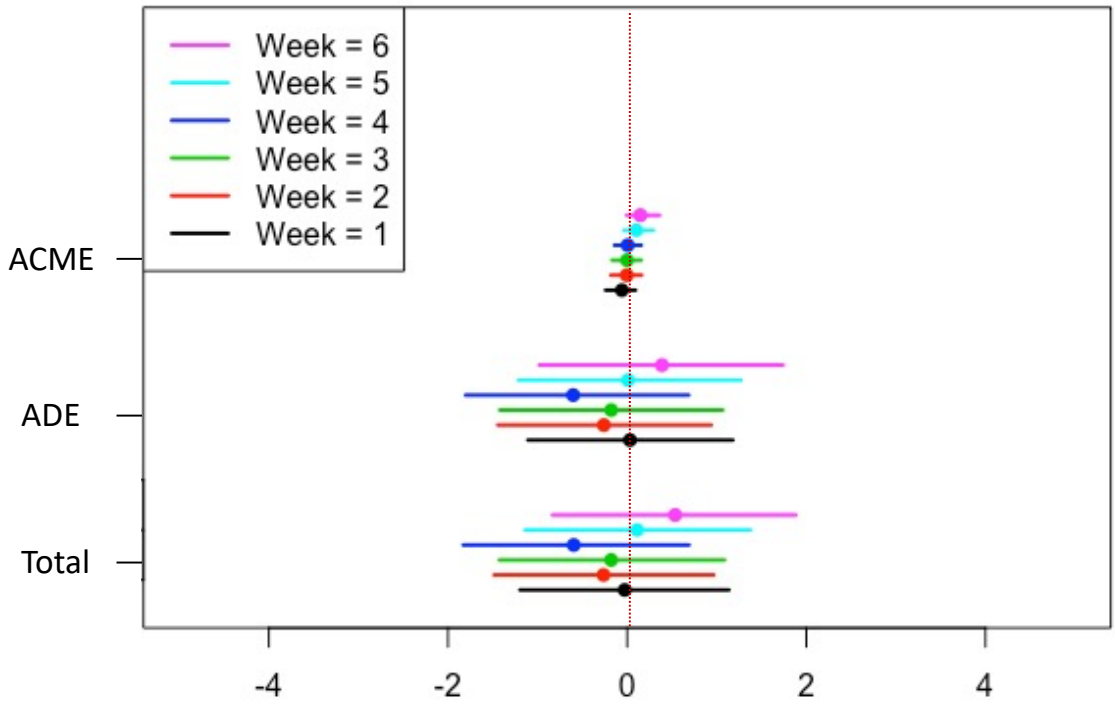
Mediation analysis with Allocation as a predictor, L5 as the outcome, positive affect as a mediator, and Week as a moderator. Total = ACME + ADE. ACME, average causal mediation effect; ADE, average direct effect; Total, total effect. The dots and bars correspond to the effect sizes and 95% confidence intervals. If the 95% confidence interval does not contain 0, the results are statistically significant.

Supplementary Figure 3 A graphical summary of the results of a casual mediation analysis of the effect of lithium on M10 onset time during six weeks after randomisation



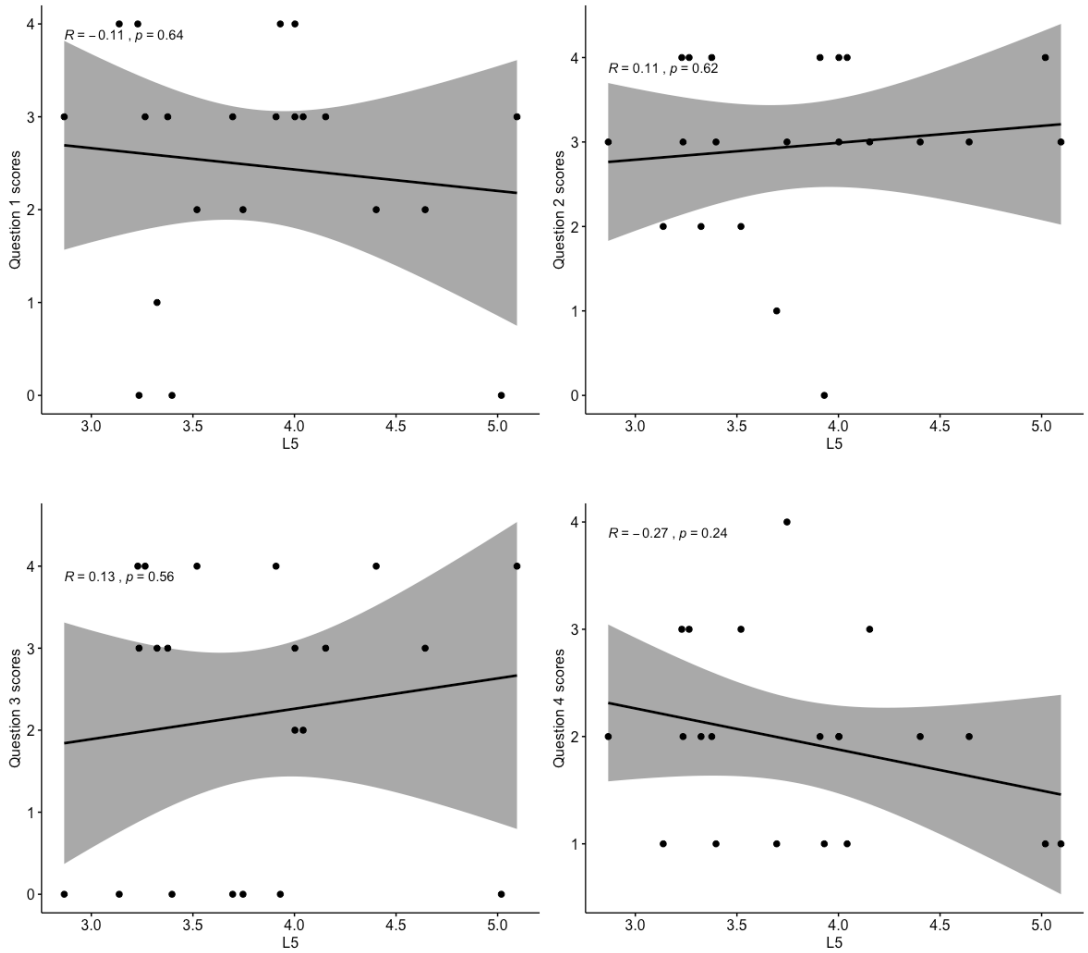
Mediation analysis with Allocation as a predictor, M10 onset time as the outcome, positive affect as a mediator, and Week as a moderator. Total = ACME + ADE. ACME, average causal mediation effect; ADE, average direct effect; Total, total effect. The dots and bars correspond to the effect sizes and 95% confidence intervals. If the 95% confidence interval does not contain 0, the results are statistically significant.

Supplementary Figure 4 A graphical summary of the results of a casual mediation analysis of the effect of lithium on L5 onset time during six weeks after randomisation



Mediation analysis with Allocation as a predictor, L5 onset time as the outcome, positive affect as a mediator, and Week as a moderator. Total = ACME + ADE. ACME, average causal mediation effect; ADE, average direct effect; Total, total effect. The dots and bars correspond to the effect sizes and 95% confidence intervals. If the 95% confidence interval does not contain 0, the results are statistically significant.

Supplementary Figure 5. Pearson correlation between L5 and SCI sub-item scores: Q1, Q2, Q3 and Q4



R represents correlation coefficient; shaded area represents 95% CI; dots shows individual data points.

Supplementary Table 2. Participants influenced by the daylight-saving time (DLS) throughout the study.

	Details of DLS time change	Number of participants affected by DLS	Details
2015	25 Oct 2:00 --> 1:00	2	OL0002 (4 days of data excluded) OL0025 (4 days of data excluded)
2016	27 Mar 1:00 --> 2:00	1	OL0094 (15 days of data excluded)
	30 Oct 2:00 -- > 1:00	1	OL0162 (1 day of data excluded)
2017	26 Mar 1:00 --> 2:00	0	NA
	29 Oct 2:00 -- > 1:00	0	NA
2018	25 Mar 1:00 --> 2:00	0	NA

Supplementary Table. 3 Results of a casual mediation analysis of the effect of lithium on M10 during six weeks after randomisation

		Effect size	95% Confidence Interval	p-value
Week 1	**ACME**	0.76	(-1.19, 3.06)	0.47
	ADE	-9.59	(-22.04, 2.33)	0.14
	Total Effect	-8.83	(-21.31, 3.10)	0.18
Week 2	**ACME**	0.10	(-2.23, 2.23)	0.94
	ADE	-10.19	(-24.16, 3.40)	0.14
	Total Effect	-10.10	(-24.16, 3.15)	0.14
Week 3	**ACME**	0.02	(-2.07, 2.12)	0.98
	ADE	-14.35	(-27.21, -2.95)	0.01 *
	Total Effect	-14.33	(-27.49, -2.33)	0.02 *
Week 4	**ACME**	-0.12	(-2.30, 2.02)	0.88
	ADE	-15.94	(-29.88, -2.23)	0.02 *
	Total Effect	-16.05	(-30.17, -2.01)	0.02 *
Week 5	**ACME**	-1.43	(-4.06, 0.65)	0.16
	ADE	-4.04	(-18.04, 9.83)	0.54
	Total Effect	-5.47	(-19.44, 8.59)	0.41
Week 6	**ACME**	-2.05	(-5.08, 0.06)	0.06
	ADE	-10.73	(-26.24, 4.03)	0.13
	Total Effect	-12.79	(-28.16, 1.34)	0.08

Mediation analysis with Allocation as a predictor, M10 as the outcome, positive affect as a mediator, and Week as a moderator. Total = ACME + ADE. ACME, average causal mediation effect; ADE, average direct effect; Total, total effect. * represents statistically significant

Supplementary Table. 4 Results of a casual mediation analysis of the effect of lithium on L5 during six weeks after randomisation

		Effect size	95% Confidence Interval	p-value
Week 1	**ACME**	-0.00	(-0.03, 0.03)	0.91
	ADE	0.04	(-0.46, 0.53)	0.88
	Total Effect	0.04	(-0.46, 0.53)	0.89
Week 2	**ACME**	0.00	(-0.02, 0.03)	0.99
	ADE	-0.13	(-0.65, 0.38)	0.60
	Total Effect	-0.13	(-0.64, 0.37)	0.60
Week 3	**ACME**	-0.00	(-0.02, 0.03)	0.95
	ADE	-0.23	(-0.75, 0.29)	0.39
	Total Effect	-0.23	(-0.75, 0.29)	0.40
Week 4	**ACME**	0.00	(-0.03, 0.03)	0.99
	ADE	0.08	(-0.43, 0.61)	0.72
	Total Effect	0.08	(-0.44, 0.61)	0.72
Week 5	**ACME**	0.00	(-0.04, 0.05)	0.99
	ADE	0.20	(-0.36, 0.75)	0.50
	Total Effect	0.20	(-0.36, 0.74)	0.51
Week 6	**ACME**	0.00	(-0.06, 0.06)	0.98
	ADE	0.08	(-0.47 0.68)	0.75
	Total Effect	0.08	(-0.48, 0.67)	0.75

Mediation analysis with Allocation as a predictor, L5 as the outcome, positive affect as a mediator, and Week as a moderator. Total = ACME + ADE. ACME, average causal mediation effect; ADE, average direct effect; Total, total effect. * represents statistically significant.

Supplementary Table. 5 Results of a casual mediation analysis of the effect of lithium on M10 onset time during six weeks after randomisation

		Effect size	95% Confidence Interval	p-value
Week 1	**ACME**	-0.08	(-0.33, 0.11)	0.44
	ADE	0.16	(-1.52, 1.87)	0.85
	Total Effect	0.08	(-1.60, 1.83)	0.91
Week 2	**ACME**	-0.01	(-0.24, 0.22)	0.94
	ADE	-0.53	(-2.42, 1.26)	0.53
	Total Effect	-0.54	(-2.35, 1.24)	0.54
Week 3	**ACME**	0.00	(-0.21, 0.24)	0.99
	ADE	-0.89	(-2.59, 0.80)	0.29
	Total Effect	-0.89	(-2.59, 0.83)	0.30
Week 4	**ACME**	0.01	(-0.20, 0.24)	0.93
	ADE	-1.06	(-2.80, 0.55)	0.23
	Total Effect	-1.04	(-2.78, 0.58)	0.25
Week 5	**ACME**	0.13	(-0.06, 0.45)	0.22
	ADE	0.03	(-1.88, 1.94)	0.99
	Total Effect	0.16	(-1.72, 2.04)	0.88
Week 6	**ACME**	0.19	(-0.04, 0.56)	0.13
	ADE	0.40	(-1.80, 2.41)	0.72
	Total Effect	0.59	(-1.56, 2.64)	0.58

Mediation analysis with Allocation as a predictor, M10 onset time as the outcome, positive affect as a mediator, and Week as a moderator. Total = ACME + ADE. ACME, average causal mediation effect; ADE, average direct effect; Total, total effect. * represents statistically significant.

Supplementary Table. 6 Results of a casual mediation analysis of the effect of lithium on L5 onset time during six weeks after randomisation

		Effect size	95% Confidence Interval	p-value
Week 1	**ACME**	-0.06	(-0.24, 0.09)	0.43
	ADE	0.03	(-1.11, 1.18)	0.96
	Total Effect	-0.03	(-1.20, 1.14)	0.96
Week 2	**ACME**	-0.00	(-0.18, 0.16)	0.96
	ADE	-0.26	(-1.44, 0.94)	0.68
	Total Effect	-0.26	(-1.49, 0.97)	0.69
Week 3	**ACME**	-0.00	(-0.17, 0.16)	0.98
	ADE	-0.18	(-1.42, 1.07)	0.76
	Total Effect	-0.18	(-1.43, 1.09)	0.78
Week 4	**ACME**	0.01	(-0.14, 0.16)	0.93
	ADE	-0.60	(-1.80, 0.69)	0.33
	Total Effect	-0.60	(-1.83, 0.69)	0.34
Week 5	**ACME**	0.10	(-0.04, 0.30)	0.15
	ADE	0.01	(-1.21, 1.27)	0.99
	Total Effect	0.11	(-1.14, 1.38)	0.86
Week 6	**ACME**	0.15	(-0.00, 0.36)	0.06
	ADE	0.39	(-0.98, 1.74)	0.56
	Total Effect	0.54	(-0.83, 1.88)	0.45

Mediation analysis with Allocation as a predictor, L5 onset time as the outcome, positive affect as a mediator, and Week as a moderator. Total = ACME + ADE. ACME, average causal mediation effect; ADE, average direct effect; Total, total effect. * represents statistically significant.