

Does circadian dysrhythmia drive the switch into high- or low-activation states in bipolar I disorder?

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Abstract

Objectives: Emerging evidence suggests a role of circadian dysrhythmia in the switch between “activation” states (i.e., objective motor activity and subjective energy) in bipolar I disorder.

Methods: We examined the evidence with respect to four relevant questions: (1) Are natural or environmental exposures that can disrupt circadian rhythms also related to the switch into high-/low-activation states? (2) Are circadian dysrhythmias (e.g., altered rest/activity rhythms) associated with the switch into activation states in bipolar disorder? (3) Do interventions that affect the circadian system also affect activation states? (4) Are associations between circadian dysrhythmias and activation states influenced by other “third” factors?

Results: Factors that naturally or experimentally alter circadian rhythms (e.g., light exposure) have been shown to relate to activation states; however future studies need to measure circadian rhythms contemporaneously with these natural/experimental factors. Actigraphic measures of circadian dysrhythmias are associated prospectively with the switch into high- or low-activation states, and more studies are needed to establish the most relevant prognostic actigraphy metrics in bipolar disorder. Interventions that can affect the circadian system (e.g., light therapy, lithium) can also reduce the switch into high-/low-activation states. Whether circadian rhythms mediate these clinical effects is an unknown but valuable question. The influence of age, sex, and other confounders on these associations needs to be better characterised.

Conclusion: Based on the reviewed evidence, our view is that circadian dysrhythmia is a plausible driver of transitions into high- and low-activation states and deserves prioritisation in research in bipolar disorders.

KEYWORDS

bipolar disorders, circadian rhythms, mood disorders

1 | INTRODUCTION

One of the most important processes for discovery and genuine therapeutic advances in clinical medicine is the iterative cycle

between observed clinical phenotypes and delineation of putative pathophysiological mechanisms. In clinical psychiatry, only rarely has this iterative process led to genuine breakthroughs. Limited examples do exist for various kinds of mood disorders, including:

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(1) delineation of “vascular depression” among older adults with a first onset of depression in later life after specific cerebrovascular lesions¹; (2) onset of depressive disorders after specific infections² or the introduction of immune-active therapies³; and (3) recognition of “atypical” mood disorders in young adults with antineuronal antibodies.⁴ The latter discovery has led to the use of immune therapies targeted to underlying pathophysiology.⁵ One pathophysiological mechanism that may be relevant to major mood disorders, and particularly bipolar I disorder (BD-I), is disturbance in the 24-h circadian system.^{6–8}

In recent years, the field of “Circadian Medicine” has made major contributions to our scientific understanding and treatment of many illnesses, including dementia, cancer, and cardiovascular disease,⁹ with the *Nobel Prize in Physiology or Medicine* awarded for the delineation of the molecular mechanisms controlling the 24-h circadian clock. While the relevance of perturbed circadian rhythms (or “dysrhythmias”) to mood disorders has been long recognised,¹⁰ more recent neurobiological, interventional, and longitudinal studies justify a more considered re-evaluation of the potentially *causative* nature of these associations, specifically regarding whether circadian dysrhythmias *drive* the switch into “activation” states in BD-I. By “activation” states, we refer to the linked phenomena of objective motor activity and subjective energy, and critically, to intraindividual change in these phenomena.¹¹

Conceptually, we first deconstruct the category of BD-I into two broad constituent states and a transition process: (1) a “high motor activation” (manic) phase; (2) a “low motor activation” (depressed) phase; and (3) a tendency to switch between these abnormal “activation” states. In this framework, the primary focus is on activation, while subjective mood is considered separately.¹¹ This phenomenological deconstruction is supported by factor analytic,¹¹ family,^{12–14} and clinical studies, which indicate that activation and mood may vary independently. Such decoupling of activation and mood is exemplified in mixed states (e.g., high activation and low mood in “dysphoric mania”; high activation and low mood in “agitated depression”); although these are not the focus here.¹⁵ Our focus on activation as a core feature of BD-I is consistent with DSM-5’s recognition of changes in activity and energy (alongside mood) as a criterion A symptom, and recent publications about the potential primacy of activation in BD, which have highlighted the need for investigation of the physiological substrates of the transition between activation states, to which circadian rhythms may be relevant.^{11,16–20}

“Circadian dysrhythmias” (variously defined) are commonly reported in individuals with BD-I and are associated with a range of core clinical features.²¹ We use *circadian dysrhythmia* as an umbrella construct that represents a “change in one or more aspects of a circadian cycle’s morphology”.²² We recognise that multiple phenotypes could be relevant to activation states in BD (e.g., phase delay, phase advance, high fragmentation, blunted amplitude, internal desynchrony, arrhythmia), and we note that most studies in this area have examined actigraphy-based estimates of phase, amplitude, and fragmentation. In this article, we consider whether circadian dysrhythmias may be a causative *driver* of the switch into high and

low motor activation states in BD-I, rather than mere correlates or epiphenomena.

We undertook a selective/narrative review of the evidence of the association between circadian dysrhythmias and changes in activation states in BD-I. We summarise the evidence in tables that examine four key questions, and finally discuss the available evidence together. Our target questions were as follows:

1. Are natural or experimental exposures that are associated with circadian dysrhythmia also associated with the switch into high- or low-activation states? (Table 1)
2. Are circadian dysrhythmias associated with the switch into high- or low-activation states? (Table 2)
3. Do interventions that affect the circadian system also affect high- or low-activation states? (Table 3)
4. Are associations between circadian dysrhythmias and high- or low-activation states confounded by “third” factors? (Table 4)

Our selection of evidence for this review was based in part on our clinical experience and associated priors (e.g., potential links between infection, circadian disturbance, and BD), literature searches using key terms (e.g., “circadian rhythms”, “actigraphy”, “motor activity”, “bipolar”, “mania”, “depression”, “clinical trial”), and searches through our personal files. We aimed to primarily include studies that explicitly report on motor activation; however, we also include studies that examined biological circadian rhythms (e.g., melatonin), and studies of patients that may not have been included based on motor activation. We note that the scope of this review is focused, and we point interested readers to a recent comprehensive review⁸ of additional areas that fell outside our scope (e.g., preclinical cellular and animal models, molecular genetic studies, studies not focused on motor activation).

2 | DISCUSSION

In this narrative review, we have outlined evidence relevant to our hypothesis that circadian dysrhythmias have the capacity to drive switches into high- or low-activation states in BD-I. While we postulate that circadian dysrhythmias *can* causally increase the likelihood of these transitions, it is highly likely that this risk is conditional on other risk factors, such as genetic risk for BD or biological and environmental factors (e.g., sensitivity to light, local variation in light or other seasonally patterned factors). In other words, circadian dysrhythmias may be a *component cause* of variation in the course of activation states in BD-I.²³ It is also important to note that while we focused our efforts on bipolar disorders (and BD-I specifically), there is evidence that circadian dysrhythmias may play a role in the course of other mental disorders (e.g., psychotic disorders, depressive disorders),^{24,25} and there are important limitations which should be addressed in future research. Most studies reviewed used correlational designs and lacked circadian recordings alongside the proposed triggers (Table 1) and in treatment studies (Table 3). Very few studies used direct measures of circadian timing, and conclusions

TABLE 1 Associations between transitions into high- or low-activation states and natural or experimental exposures capable of disrupting the circadian system.

Switch into high activation ("Mania")	Switch into low activation ("Depression")	Comments and potential confounds
Experimental conditions <ol style="list-style-type: none"> 1. <i>Time zone travel</i> <ul style="list-style-type: none"> • Some evidence of increased risk of mania/hypomania after eastward travel⁵⁹ 2. <i>Experimental misalignment and/or sleep loss</i> <ul style="list-style-type: none"> • In patients with BD-I or BD-II, one night of sleep deprivation was associated with a switch from depression into mania ($n = 4$) or hypo/mania ($n = 3$)⁶⁰ 	Experimental conditions <ol style="list-style-type: none"> 1. <i>Time zone travel</i> <ul style="list-style-type: none"> • Some evidence of increased risk of depression after westward travel⁵⁹ 2. <i>Experimental misalignment and/or sleep loss</i> <ul style="list-style-type: none"> • Among healthy controls, simulated shift work led to depressive symptoms⁶¹ • Among healthy controls, experimental sleep deprivation led to depressed mood^{62–64} 	<ul style="list-style-type: none"> • Few published studies of time zone travel; re retrospective, correlational designs • Small sample size makes conclusions regarding sleep deprivation in BD difficult⁶⁰ • Lack of objective measurement of circadian dysrhythmias
Environmental changes <ol style="list-style-type: none"> 1. <i>Seasonality</i> <ul style="list-style-type: none"> • Spring–Summer associated with increased risk of switch to mania/hypomania^{65,66} 2. <i>Light exposure</i> <ul style="list-style-type: none"> • Daytime light exposure metrics not associated with switch into manic/hypomanic/mixed episodes⁶⁷ • Variations in seasonal solar insolation associated with earlier age of onset of BD-I, with a smaller effect for initial episode of mania compared to initial episode of depression³⁵ 	Environmental changes <ol style="list-style-type: none"> 1. <i>Seasonality</i> <ul style="list-style-type: none"> • Early winter associated with increased risk of switch to depression⁶⁵ 2. <i>Light exposure</i> <ul style="list-style-type: none"> • Daytime light exposure metrics (e.g. longer time above 1000 lux, higher average illuminance) associated with decreased risk of transition into depression⁶⁷ • Variations in seasonal solar insolation associated with earlier age of onset of BD-I, with a larger effect for initial episode of depression compared to initial episode of mania³⁵ 	<ul style="list-style-type: none"> • Some studies do not observe a seasonal pattern in BD • Other meteorological factors (e.g., ambient temperature) may partly explain the link between seasonality and activation states • Lack of objective measurement of circadian changes alongside changes in seasons, photoperiod, and or light exposure
Substance use <ul style="list-style-type: none"> • Stimulants associated with precipitation of mania/hypomania⁶⁸ • Evidence of cannabis use preceding mania/hypomania^{69,70} • Illicit drugs (broadly defined) reported as a trigger of mania/hypomania⁷¹ • Corticosteroid medications (e.g., prednisone) are reported in case studies as a trigger of mania/hypomania^{38,72} 	Substance use <ul style="list-style-type: none"> • Evidence of alcohol use preceding depression⁶⁹; however, not in all studies⁷⁰ 	<ul style="list-style-type: none"> • Links between substance use and activation states may be due to non-circadian effects (e.g., effects on dopamine/glutamate) • Lack of objective measurement of circadian dysrhythmias
Childbirth <ul style="list-style-type: none"> • Puerperal psychosis follows 20%–30% of births among women with a history of BD⁷³ • Women reporting sleep loss triggering episodes of mania more likely to have experienced an episode of puerperal psychosis⁷⁴ 	Childbirth <ul style="list-style-type: none"> • Increased risk of depression during post-partum period among women with BD-I/BD-II⁷⁵ 	<ul style="list-style-type: none"> • Links between childbirth and activation states may be due to non-circadian effects (e.g., endocrine changes, sleep loss without circadian changes) • Several studies hampered by cross-sectional designs⁷⁴ • Lack of objective measurement of circadian dysrhythmias
Infection <ul style="list-style-type: none"> • Individuals hospitalised with acute mania have increased history of prescriptions for antimicrobial infections⁷⁶ 	Infection <ul style="list-style-type: none"> • Higher risk of depression after infection (e.g., Epstein–Barr, Coxiella burnetii, Ross River virus, West Nile virus, Hepatitis C)^{2,77–79} • Also mixed findings (e.g., influenza, coronaviruses)⁸⁰ 	<ul style="list-style-type: none"> • Links between infection and activation states may be due to non-circadian effects (e.g., immune activation)⁷⁶ • Lack of objective measurement of circadian dysrhythmias

about central timing based on real-world actigraphy data are hampered by their limited concordance with central measures (e.g., dim-light melatonin onset) and controlled settings (e.g., constant routine), and the susceptibility of actigraphy to various masking effects (e.g., voluntary behaviour, social activity, work schedules). Finally, we

acknowledge that our review covers a focused area (human studies relevant to motor activation in BD-I) in the wider context of chronobiology and mental disorders, for which there are reviews^{8,26} on preclinical models,^{27–29} neurobiology,^{7,30} phenomenology,³¹ measurement,^{17,31} pharmacology,²⁸ modelling,³² and genetics.^{33,34}

TABLE 2 Associations between estimated circadian dysrhythmias and the course of low- and high-activation states.

Switch into high activation ("Mania")	Switch into low activation ("Depression")	Comments and potential confounds
Rest-activity rhythms <ul style="list-style-type: none"> Intra-daily variability of rest/activity rhythm associated with relapse (manic, hypomanic, or mixed episode)⁵² Null finding of a within-person association between rest/activity rhythm and days spent in a manic/hypomanic episode⁵³ 	Rest-activity rhythms <ul style="list-style-type: none"> Rest/activity rhythms associated with relapse of depressive episode⁵² Within-person association between rest/activity rhythm and days spent in a depressive episode⁵³ 	<ul style="list-style-type: none"> Actigraphy is not a direct measure of internal circadian timing and is subject to masking effects (e.g., social activity, work schedules, volitional behaviour) Few studies have examined prospective associations of actigraphy-estimated circadian dysrhythmias and switches into mania and/or depression
Physiological rhythms <ul style="list-style-type: none"> Melatonin rhythm did not differ between patients in mania, depression, or euthymia⁸¹ No change in melatonin or cortisol rhythm across manic, depressed, or euthymic phases (in a single patient)⁸² 	Physiological rhythms <ul style="list-style-type: none"> Melatonin rhythm did not differ between patients in mania, depression, or euthymia⁸¹ No change in melatonin or cortisol rhythm across manic, depressed, or euthymic phases (in a single patient)⁸² 	<ul style="list-style-type: none"> Conclusions are hampered by small sample size (patients; $n = 9$)⁸¹ and single patient case studies⁸²
Social rhythms <ul style="list-style-type: none"> Social rhythm irregularity associated with transition to mania/hypomania among a bipolar spectrum sample⁸³ Social rhythm disturbance associated with transition into a manic episode^{84,85} 	Social rhythms <ul style="list-style-type: none"> Social rhythm irregularity associated with transition to depression among a bipolar spectrum sample⁸³ Lack of association between social rhythm disturbance and transition into a depressive episode^{84,85} 	<ul style="list-style-type: none"> Social rhythms are not a direct measure of internal circadian timing Conclusions hampered by small sample sizes in some studies⁸⁴ No study has examined whether circadian dysrhythmia mediates the association between social rhythm disruption and relapse/switch

TABLE 3 Associations between interventions that act on the circadian system and high- and low-activation states in BD-I.

Switch into high activation ("Mania")	Switch into low activation ("Depression")	Comments and potential confounds
Lithium <ul style="list-style-type: none"> Highly effective for reducing acute mania⁸⁶⁻⁸⁸ Highly effective for reducing relapse of mania⁸⁸⁻⁹⁰ 	Lithium <ul style="list-style-type: none"> Some benefit for reducing acute depression⁸⁸ Some benefit for reducing relapse of depression⁸⁸ 	<ul style="list-style-type: none"> Lithium's <i>primary</i> prophylactic effects may be non-circadian⁹¹ Only preliminary evidence that lithium has circadian effects in humans⁹² No human study has examined whether changes in circadian dysrhythmia mediate lithium's effects
Melatonergic agents <ul style="list-style-type: none"> Unclear effects for reducing acute mania Agents such as ramelteon may not be effective for reducing relapse of mania⁴⁷ 	Melatonergic agents <ul style="list-style-type: none"> Agomelatine has some benefit for reducing acute depression,^{41,42} but also negative findings⁴⁶ Agomelatine has some benefit for reducing relapse of depression⁴³ Ramelteon may not be effective for reducing relapse of depression⁴⁷ 	<ul style="list-style-type: none"> Only preliminary evidence that agomelatine has circadian effects⁴⁹ Agomelatine was adjunctive, with patients co-medicated (e.g., lithium, valpromide)^{41,46} Several studies limited by small sample⁴² or open label designs⁴¹ Some studies used a combined relapse measure for mania or depression^{43,47}
Bright light therapy <ul style="list-style-type: none"> Unclear effects for reducing acute mania or relapse of mania 	Bright light therapy <ul style="list-style-type: none"> Some benefit for reducing acute depression in some studies,^{44,45} but not others⁴⁸ May not be effective for reducing relapse of depression^{44,45} 	<ul style="list-style-type: none"> Effects of bright light therapy on acute depression could be non-circadian (e.g., direct effects on mood circuits)²⁹
Dark therapy <ul style="list-style-type: none"> Associated with reducing acute mania in some studies,⁹³⁻⁹⁵ but not others⁹⁶ Unclear effects for relapse of mania 	Dark therapy <ul style="list-style-type: none"> Does not appear to be associated with reduction in depression^{26,96} 	<ul style="list-style-type: none"> Conclusions hampered by small sample sizes⁹³
Sleep deprivation (or wake therapy) <ul style="list-style-type: none"> Not recommended for acute mania²⁶ Unclear effects for relapse of mania 	Sleep deprivation (or wake therapy) <ul style="list-style-type: none"> Some benefit for reducing acute depression²⁶ 	<ul style="list-style-type: none"> Effects of sleep deprivation may be non-circadian (e.g., synaptic plasticity)

TABLE 4 Are associations between circadian dysrhythmia and high- and low-activation states explained by a third common factor?

High activation ("Mania")	Low activation ("Depression")	Comments and potential confounds
Age and sex <ul style="list-style-type: none"> Several studies show associations between BD-I and circadian dysrhythmia independent of age and sex¹⁸ One study shows an association between transition into mania and objective circadian dysrhythmia, adjusted for age/sex⁵² 	Age and sex <ul style="list-style-type: none"> Several studies show associations between BD-I and circadian dysrhythmia independent of age and sex¹⁸ One study shows an association between transition into depression and objective circadian dysrhythmia, adjusted for age/sex⁵² 	<ul style="list-style-type: none"> More studies needed that account for age and sex
Neurodevelopmental impairment <ul style="list-style-type: none"> Unclear (limited evidence) 	Neurodevelopmental impairment <ul style="list-style-type: none"> Circadian rhythm sleep/wake disturbance (e.g., delayed sleep phase) are observed in samples excluding participants with low IQ or history of head injury⁹⁷ 	<ul style="list-style-type: none"> This evidence comes from a study of a mixed diagnostic sample⁹⁷ Few studies appear to examine these types of impairments
Genetic factors <ul style="list-style-type: none"> Mixed evidence regarding associations of circadian genes and BD (broadly defined)^{33,98} Some evidence for genetic associations among BD-I pedigrees and circadian dysrhythmia (blunted rest/activity rhythm)⁹⁹ No association between polygenic risk score (PRS) for low amplitude of rest/activity rhythm and BD, but a significant association with mood instability⁵⁸ 	Genetic factors <ul style="list-style-type: none"> Mixed evidence regarding associations of circadian genes and BD (broadly defined)^{33,98} Some evidence for an association among a seasonal pattern of depressive episodes and circadian genes¹⁰⁰ 	<ul style="list-style-type: none"> Lack of evidence regarding associations of manic and depressed states and circadian dysrhythmias, accounting for genetic factors

In the context of these limitations, we conclude there is: (1) reasonable support for the notion that natural or experimental events, circumstances, or factors that can perturb circadian rhythms can also precipitate switches into activation states; (2) reasonable support for the notion that interventions that can act directly on the circadian system can also affect activation states (with much more work needed to test whether circadian changes mediate these clinical effects); (3) limited (but emerging) support for the notion that objective or estimated circadian dysrhythmias are associated with transitions into activation states; and (4) limited evidence for the notion that associations between circadian dysrhythmias and activation states are not confounded by third factors including, but not limited to, age or development stage, sex, genetics, or neurodevelopmental injury or impairment. We will now discuss these findings with respect to their potential meaning, other limitations, and areas for further study.

To begin with, a range of studies of quite different natural or experimental factors that have all been shown to be associated with circadian dysrhythmia demonstrate a pattern of precipitation of the switch to high- and low-activation states, with some factors possibly associated also with first onset of these states (e.g., high variation in solar insolation.³⁵) Some of these factors—like seasonal changes in solar insolation, experimental sleep deprivation, and childbirth—appear to have quite reliable effects, while others, like substance use and infection, that have low absolute risk of transition to high- or low-activation states, have nonetheless been shown to be related to circadian dysrhythmia.³⁶ Of these, those that have fundamental biological links to the circadian system and also clinical or epidemiological links to activation states, such as variation in photoperiod or solar insolation across the seasons (and potentially *rate of change* in these light-related measures³⁷), are the most convincing. A key limitation

of our grouping these different exposures together is that each of these factors are highly likely to have *non-circadian* effects that may be more directly linked to depressive and manic states—for example, amphetamine-type stimulants affecting dopaminergic function, direct effects of light exposure on brain mood circuits, major endocrine changes accompanying childbirth, among others.^{29,38} By linking them together in a conceptual framework of circadian dysrhythmia, we hope to generate interest in these testable hypotheses in studies of circadian rhythms and activation states in BD. Another limitation with respect to our research question, and the main barrier to evaluating a causative effect of circadian dysrhythmia on transitions into activation states following these events, is the lack of objective circadian measures contemporaneous with these exposures. To provide a clearer answer to this question, future studies could use ambulatory measures (e.g., actigraphy) or controlled laboratory measures (e.g., dim-light melatonin onset) to estimate changes in circadian rhythms during the transition through certain exposures (e.g., comparing patients living in regions with high versus low seasonal variation in solar insolation) to test whether circadian dysrhythmias mediate transitions into mania/depression. Altogether, the natural and experimental exposures reviewed provide some suggestion that the onset of circadian dysrhythmia may precede the transition into high (mania) and low (depression) activation states and should provoke study of these exposures using prospective, hypothesis-testing designs.

The next most convincing factor is that interventions that target the circadian system (e.g., bright light therapy, dark therapy, melatonergic agents, lithium) can lead to resolution of mania or depression. While lithium has strong evidence for amelioration of mania, and reduction in relapse, its exact effects on circadian systems remain to be fully characterised. However, there is substantial

evidence of the circadian effects of lithium across a range of human and animal studies (e.g., cultured cells, healthy humans, animal models, patient-derived fibroblasts).^{27,39,40} For depression, there is also evidence that melatonergic agents (e.g., agomelatine) and bright light therapy may have significant benefits^{41–45}; however, this evidence is quite mixed,^{44–48} suggesting further investigation of treatment response (e.g., response/non-response subgroups) may be needed. Progress here now depends on better clinical trial designs that stratify mood disorders cohorts according to their circadian characteristics or include circadian-based measures (e.g., actigraphy, melatonin rhythms) within repeated assessment schedules. Such approaches would then permit direct testing of the potential mediating effects of circadian rhythms on changes in activation states. Some studies of agomelatine⁴⁹ and ketamine⁵⁰ have adopted these approaches, as have other ongoing clinical trials (e.g., brexpiprazole).⁵¹

The sparse evidence-base for examining our two remaining questions (Tables 2 and 4) means that only limited conclusions are possible. With regards to the postulate that ongoing circadian dysfunction is associated with ongoing illness, only a small number of studies have examined prospective associations between circadian markers and mania/depression. One study reported that circadian rest/activity markers were associated with relapse of manic and/or depressive episodes,⁵² and another reported an association between rest/activity rhythms and days in a depressive episode.⁵³ While one study reported a longitudinal association between change in dim-light onset melatonin rhythms and depressive symptoms,⁴⁹ the overall literature regarding relationships between biological rhythms and manic and depressive states is mixed. Finally, the influence of possible “third factors” on the observed associations between circadian perturbations and mania and depression remains an unexplored area. Few studies have examined the impacts of factors such as age, neurodevelopmental stage, and biological sex on these associations. Several recent studies have reported overlap between genetic variants associated with BD and sleep and circadian phenotypes.^{54–57} For example, a study using a polygenic risk score (PRS) for actigraphy-based relative amplitude found no association with BD, but a significant association with mood instability.⁵⁸ A genome-wide association study (GWAS) of >40,000 cases with BD reported positive genetic correlations between BD and sleep phenotypes (insomnia, daytime sleepiness, sleep duration, daytime napping, “getting up in morning”) but not chronotype.⁵⁶ Moreover, there were bidirectional (putatively causal) associations between BD and longer sleep duration, and a unidirectional (putatively causal) association between BD and a lower likelihood of being a morning person.⁵⁶ However, some GWASs have reported mixed findings, with significant genetic correlations between BD and some sleep or circadian phenotypes (e.g., sleep duration) but not others (e.g., insomnia, chronotype).⁵⁵ A case-control study observed differential associations among BD subtypes and polygenic liability to sleep duration and insomnia, but not for chronotype.⁵⁷ While mounting evidence shows shared genetic risk for BD and sleep phenotypes, we note that the role of genetic and biological factors (e.g., neurodevelopment) linking circadian phenotypes and BD is less clear, and should be explored further in genetic, twin, family, and

prospective studies, particularly those following individuals through developmental phases of peak risk of BD.

Considering the evidence reviewed, our view is that circadian dysrhythmia is a plausible driver of transition into both high- and low-activation states in BD-I. While we have mostly focused here on the associations between circadian dysrhythmias and illness course in established BD-I, there is great interest in whether these disturbances may also play a role in the aetiology of mania and depression, an under-researched question. Our hypothesis that circadian dysrhythmias can drive the transition into high- and low-activation states in BD-I, if true, has implications for indicated prevention, early intervention, and personalised treatment choices, and we believe it requires prioritisation in clinical research. We believe that the best tests of causative effects of circadian dysrhythmia on activation states in BD-I will come from genetically-informative twin and family studies, observational studies, and causal-interventionist clinical trials.

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CONFLICT OF INTEREST STATEMENT

IBH is the Co-Director, Health and Policy at the Brain and Mind Centre (BMC) University of Sydney, Australia. The BMC operates an early-intervention youth services at Camperdown under contract to headspace. Professor Hickie has previously led community-based and pharmaceutical industry-supported (Wyeth, Eli Lilly, Servier, Pfizer, AstraZeneca) projects focused on the identification and better management of anxiety and depression. He is the Chief Scientific Advisor to, and a 3.2% equity shareholder in, InnoWell Pty Ltd. InnoWell was formed by the University of Sydney (45% equity) and PwC (Australia; 45% equity) to deliver the \$30M Australian Government-funded Project Synergy (2017–20) and to lead transformation of mental health services internationally through the use of innovative technologies. EMS is the Medical Director, Young Adult Mental Health Unit, St Vincent's Hospital Darlinghurst, Discipline Leader of Adult Mental Health, School of Medicine, University of Notre Dame, Research Affiliate, The University of Sydney and Consultant Psychiatrist. She has received honoraria for educational seminars related to the clinical management of depressive disorders supported by Servier and Eli-Lilly pharmaceuticals. She has participated in a national advisory board for the antidepressant compound Pristiq, manufactured by Pfizer. She was the National Coordinator of an antidepressant trial sponsored by Servier. The other authors declare no competing interests.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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