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REVIEW

BIPOLAR DISORDERS WILEY

Measuring circadian function in bipolar disorders: Empirical and conceptual review of physiological, actigraphic, and self-report approaches

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Abstract

Background: Interest in biological clock pathways in bipolar disorders (BD) continues to grow, but there has yet to be an audit of circadian measurement tools for use in BD research and practice.

Procedure: The International Society for Bipolar Disorders Chronobiology Task Force conducted a critical integrative review of circadian methods that have real-world applicability. Consensus discussion led to the selection of three domains to review—melatonin assessment, actigraphy, and self-report.

Results: Measurement approaches used to quantify circadian function in BD are described in sufficient detail for researchers and clinicians to make pragmatic decisions

about their use. A novel integration of the measurement literature is offered in the form of a provisional taxonomy distinguishing between circadian *measures* (the instruments and methods used to quantify circadian function, such as dim light melatonin onset) and circadian *constructs* (the biobehavioral processes to be measured, such as circadian phase).

Conclusions: Circadian variables are an important target of measurement in clinical practice and biomarker research. To improve reproducibility and clinical application of circadian constructs, an informed systematic approach to measurement is required. We trust that this review will decrease ambiguity in the literature and support theory-based consideration of measurement options.

1 | INTRODUCTION

Evidence implicating circadian function in onset, course, and management of bipolar disorders (BD) has accumulated since circadian hypotheses were first proposed some 40 years ago (see reviews including,[1–5]). The field of research has always been strongly multi-disciplinary (eg,[6,7]), and therefore subsumes a range of approaches to measurement. The overarching aim of the present project was to provide the first empirical and conceptual review of circadian assessment methods in BD. Specifically, this paper (i) reviews major approaches to assessment of circadian parameters in sufficient detail for researchers and clinicians to make informed judgments about use and (ii) offers suggestions for advancing circadian measurement in BD, including a provisional synthesis of the relationship between constructs and measures in this area.

1.1 | The human biological clocks

Terrestrial biology has adapted to a dramatically rhythmic environment, and the term "circadian system" is used to point to key nodes and biological pathways in this adaptation. The suprachiasmatic nuclei (SCN) are the main pacemakers of biological rhythms, and they have an intrinsic endogenous period that is constantly entrained by external stimuli. The SCN act to synchronize circadian rhythms (ie, daily rhythms of 24 hours) and also regulate infradian rhythms (ie, rhythms >24 hours) such as seasonal rhythms. There is consensus on the important features of the human circadian system (see Figure 1): a quasi-ubiquitous adaption to the environment's 24-hour light-dark cycles; mediated through a loopy system of self-sustained biological clocks; synchronized daily by environmental cues ("*zeitgebers*," particularly light); generating coordinated 24-hour signals ("circadian rhythms") in processes across all levels (gene expression, core body temperature, neurocognition, mood, etc); the circadian signal interacts with a homeostatic process to determine some key parameters of sleep see, for more details, see.[8–10]

1.2 | The present review

The premise of circadian science is that scientific characterization of the human system must recognize its biological rhythmicity (eg, 24-hour, infradian, ultradian); the hope for psychiatry and psychology is that integrating this temporal complexity with existing theories of etiology will lead to improved explanations and interventions. The aim here is to advance the application of chronobiology to BD by critically reviewing existing measurement approaches and considering knowns (current applications) and unknowns (next steps) for this literature.

2 | METHODS

2.1 | Scope of the review

The International Society for Bipolar Disorders (ISBD) Chronobiology and Chronotherapy Task Force is a group of clinicians and researchers with expertise in both BD and chronobiology, charged with developing consensus statements on treatment,[5] etiology, and measurement issues (the focus here). The breadth and focus of the present review were determined in an initial series of consensus discussions. A key decision was to focus on those methods with real-world applicability in clinical practice and large-*N* research. Research into genotype/gene expression biomarkers of BD, for example, currently lacks translational potential, and was deemed outside this scope (and a better fit to the forthcoming etiology manuscript). A second decision was to exclude measures of sleep per se, and readers are directed to recent comprehensive reviews of this related literature, for example,.[11–13] Third, the group decided to exclude laboratory protocols for unmasking the endogenous circadian component of 24-hour rhythms constant routine and forced desynchrony, [14] as few studies have been conducted in BD populations using these challenging laboratory protocols, and such measures lack translational potential.

With these exclusions set, the group decided to focus on three measurement domains—melatonin measures (Section 3), actigraphy (Section 4), and self-report (Section 5). Within these domains, specific

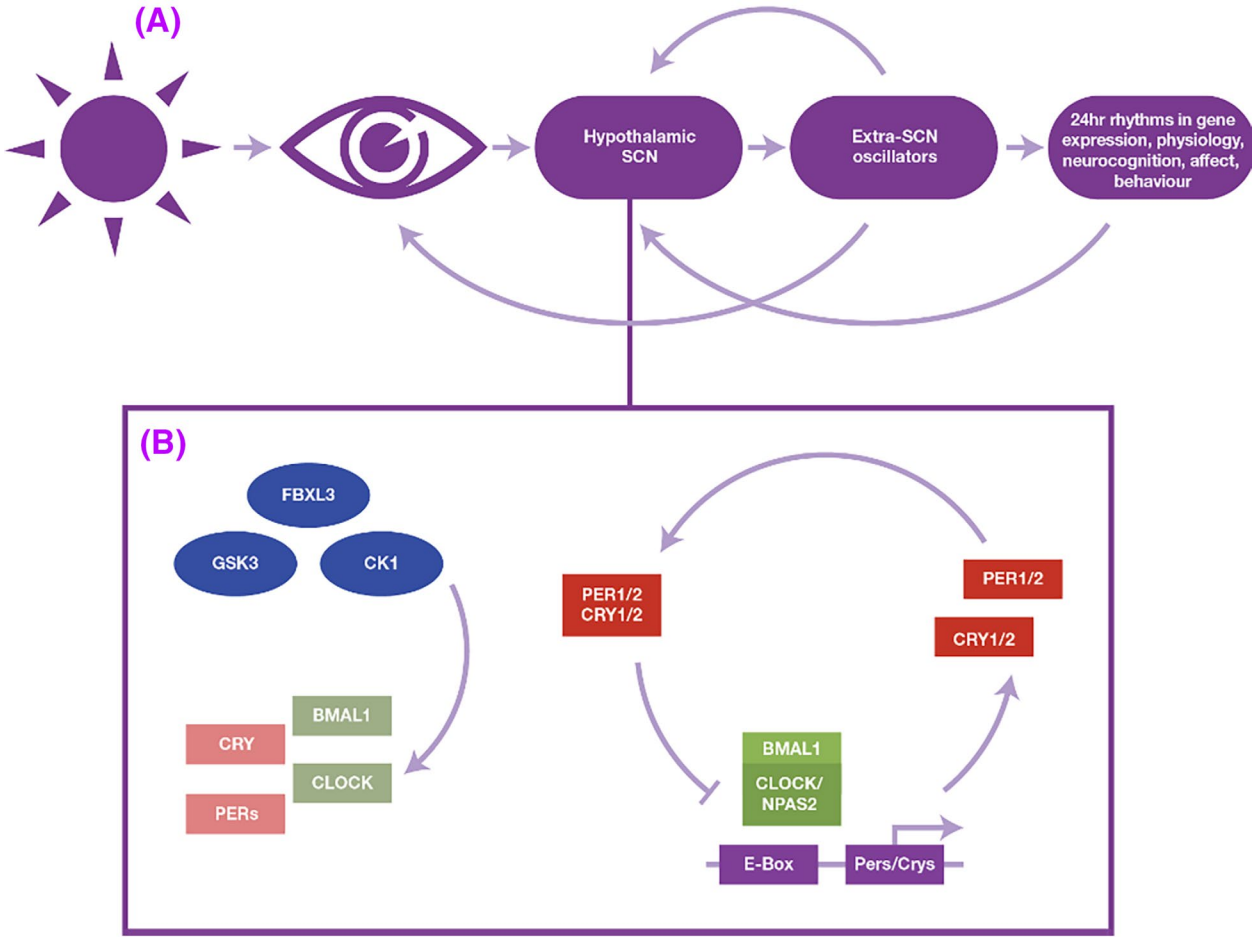

FIGURE 1 (A) Schematic representation of the human circadian system, emphasizing its open, hierarchical, and loopy nature. The light-eye pathway is emphasized for external modulation of the circadian system, but activity, eating, and temperature are also known zeitgebers in humans. (B) On the right of the figure is a simplified schematic of the core transcription-translation feedback loop in which PER/CRY complexes (transcriptional repressors, or negative elements, shown in red) inhibit BMAL1/CLOCK/NPAS2 (transcriptional activators, or positive elements, shown in green) and thus their own transcription across approximately 24 hours. On the left of the figure are modulators regulating the degradation of clock proteins. Reprinted with permission from[8]

measures for review were determined by subgroups leading each section, followed by a whole-group consensus. The primary criterion for selection of particular measures was prominence of the measures in BD research, and the aim was to review a set of measures that adequately represent existing approaches and measurement issues.

2.2 | Structure of the reviewed material

The reviews in each domain aim to provide sufficient detail for researchers and clinicians to consider using these methods as appropriate. The sections differ in the information reviewed. The melatonin section focuses on the biology of melatonin synthesis, sampling decisions, and analytic approaches; the actigraphy section focuses on analytic approaches to the high-resolution activity signal; and chronotype measures (which are the clinical phenotypic outputs of biological rhythms) are the primary focus of the self-report section. Each section concludes with consideration of existing findings when scores from these measures are correlated with BD understood categorically (manic, hypomanic, depressive episodes, etc) or dimensionally (BD risk, mania-proneness, depression-proneness, etc).

2.3 | What circadian constructs are being measured?

Core features of circadian system function (such as SCN activity and intracellular timekeeping in body cells) are difficult to observe in living humans. Instead, traditional circadian research has sought to "unmask" the endogenous circadian component of various downstream rhythms using laboratory protocols like core body temperature measurement under CR and FD conditions. More recent commentary has emphasized the limited ecological validity of such protocols—removing circadian biology from the environment to which it is adapted to entrain has self-evident limitations.[15] Consistent with the aim here of attending to real-world measurement of circadian

function, all of the reviewed measures are applied under normal entrained (nychthemeral) conditions, and therefore limited from a strict circadian viewpoint by varying degrees of masking. Some of the methods and measures account for masking factors (eg, controlling for light exposure in dim light melatonin onset [DLMO], social responsibilities and sleep debt in Munich Chronotype Questionnaire [MCTQ] calculation of mid-sleep); other variables like social rhythm stability quantified on the social rhythm metric are not considered measures of circadian output, but rather the lifestyle-mediated exposure to *zeitgebers*.

The issue of endogeneity and masking aside, the reader will note a theme around distinguishing between circadian constructs and measures. The issue arises at many points in Sections 3-5 and is directly confronted in a provisional mapping of constructs and measures in the final integrative Discussion (Section 6).

3 | MELATONIN MEASURES

3.1 | Melatonin as circadian marker

The SCN has neural projections to several other CNS-nuclei and exerts its control of peripheral tissues by direct and indirect neural efferents and hormones, an important one being melatonin. Melatonin is synthesized and released from the pineal gland which is under direct SCN control via a complex neural loop involving the superior cervical ganglion.[16] Melatonin is considered the most robust indicator of SCN timing although other less reliable indirect measures (eg, cortisol, core body temperature, peripheral intracellular clock gene mRNA) of central timing exist.[17]

Melatonin synthesis occurs primarily during the nighttime and is generally undetectable during the day. Nocturnal levels are thus 10 times higher than those in the daytime, bearing in mind that the inter-individual variability of melatonin synthesis is substantial.[18] Peak levels usually occur after midnight during the first half of the sleep period. This hormone has many physiological functions, the main function being to synchronize an individual's biological rhythms in response to photoperiods, that is, day/night cycles.[18] A normative phase delay in melatonin synthesis occurs during adolescence with a gradual phase advance in adulthood, and the amplitude of melatonin concentrations gradually declines from adulthood into old age.[9] Despite being a direct marker of SCN phase, melatonin synthesis is sensitive to and can be diminished by light exposure. The maximum sensitivity of melatonin suppression is in the short wavelength ("blue") end of the visible spectrum ($\lambda \sim 480$ nm) [19,20] and principally detected by intrinsically photosensitive retinal ganglion cells (ipRGC), with electrochemical signals transmitted to the SCN via the retinohypothalamic tract.[21]

3.2 | Melatonin sampling

Endogenous melatonin production in humans can be estimated by measuring the concentration of the hormone or its metabolites in three main biological fluids: plasma, urine, and saliva. Each of these methods has advantages and disadvantages, as summarized below, see also.[22,23]

Melatonin assessment in plasma is via blood samples from an intravenous catheter at regular intervals (eg, every 20-30 minutes up to hourly). The cannula is normally applied at least 2 hours before starting sampling, allowing blood collection throughout the night, minimizing sleep disruption, and ideally from a collection room outside the patient's room. Uninterrupted 24-hour sampling through plasma significantly increases the resolution of melatonin, especially in low melatonin secretors. Researchers can exploit blood sampling at multiple time points to obtain a complete 24-hour melatonin profile, permitting an accurate estimation of circadian phase, duration, and amplitude. However, the placement of an intravenous catheter is an invasive procedure, which requires trained health personnel and may become problematic in overweight or elderly individuals. Therefore, plasma melatonin assessment is only performed in equipped laboratory settings and cannot be easily implemented in field studies or in clinical settings.

Melatonin production can also be estimated by measuring its primary urinary metabolite, 6-sulfatoxymelatonin (aMT6s), which normally shows concentration levels delayed by 1-2 hours relative to melatonin levels.[24] Urine samples are collected at regular intervals (every 2-4 hours during the day and 8 hours overnight) for a 24- to 48-h period or longer. The time points of sampling and the total volume of all urine passed during the time intervals must be recorded, to allow the calculation of excretion rate (ng/h) and total amount of aMT6s in each sample. Urine sampling is a feasible, albeit more limited, method to assess circadian phase and peak values in clinical and field studies, since the collection can be mostly carried out in the home environment, without interrupting sleep. However, sampling frequency is necessarily limited by the ability to urinate and by compliance with collection so that the time points of measurement may be fewer than for blood or saliva sampling and the phase assessment therefore less precise.

Saliva sampling is a practical, noninvasive, and home-based method for measuring melatonin, and is commonly used in both clinical and research settings. Saliva samples are usually harvested directly or by using cotton swabs holding up to 3.0 mL of saliva. Subjects are instructed to chew the swab for 1-2 min or until it is saturated. It is possible to store the samples at 2-8°C for up to 1 week, or to freeze them at −20°C for up to 1 year. The tubes can also be transported with cold packs, but repeated freeze-thaw cycles should best be avoided. Saliva samples should be centrifuged prior to assay, to extract clear supernatant from the swabs, or to remove particulate matter. The techniques currently in use for routine melatonin measurement are competitive quantitative radioimmunoassay (RIA) or enzyme-linked immunoassay (ELISA).[24,25]

Repeated collection of saliva samples at several time points, for example, every 30-60 minutes for 24 hours, is recommended to obtain an accurate daily profile of melatonin production. However, even analyzing a few saliva samples collected in the evening hours may represent a reliable method to estimate the dim light melatonin

onset (DLMO), that is, the time at which melatonin levels begin to rise above baseline. DLMO is a reliable marker of circadian phase, representing the onset of melatonin synthesis and secretion, which normally occurs about 2-3 hours prior to habitual sleep in entrained individuals. Collection should ideally start at least 1-2 hours prior to and throughout the expected DLMO (see analysis).

Despite its feasibility, saliva sampling has a number of disadvantages:

- Melatonin levels in saliva are lower than in plasma (approximately 30%), and may be undetectable in low secretors
- A volume of at least 0.2-0.4 mL per tube (depending on the assay) or a minimum of 0.5-1 mL for duplicates is required for most assays
- Individuals must be awake to collect samples and therefore undergo sleep disruption if frequent salivary samples are collected overnight, for example, to determine amplitude and peak levels of the melatonin rhythm, which normally occur between 02:00 and 04:00 hours
- During the collection period, subjects must remain under dim light condition (preferably <10 Lux at eye level in the direction of gaze) and controlled posture
- Individuals must follow specific instructions to avoid contamination of samples with food particles, food dye, or blood. They should not drink liquids containing artificial colorants, caffeine, or alcohol during the collection period. Also, on the day of collection, they are not permitted to consume substances that interfere with melatonin measurement: bananas (high in tryptophan), chocolate (contains caffeine), or medication containing ibuprofen (interferes with melatonin metabolism).

3.3 | Analytic approaches

When the circadian rhythms of an individual are perfectly synchronized (entrained) to the 24-h light-dark cycle, melatonin levels typically rise in the evening (20:00-23:00 hours), reach a maximum (acrophase) between 02:00 and 04:00 hours, and return to baseline during the morning hours (08:00-10:00 hours). By contrast, people with circadian rhythm sleep-wake disorders exhibit a mismatch between external, environmental time and the internal, biological time (circadian misalignment).

Several methods are used to determine circadian phase from the nocturnal (or 24 hours) melatonin profile, including absolute thresholds, relative thresholds (percentage of maximum or 24-hour mean), and curve-fitting techniques.[22] Relative thresholds can be calculated as a percentage (20%, 25%, or 50%) of maximum levels on the rising or declining phase, the midpoint between the rising and declining phases, or a point (such as the acrophase/peak) determined from a cosine curve that has been fit to the raw melatonin data. They can facilitate comparisons between individuals and groups by normalizing differences in amplitude but require an overnight or 24-hour melatonin sampling. Similarly, many curve-fitting functions (including the simple, 2-harmonic, and baseline-adjusted cosine curves) can only be computed when a complete melatonin profile over a 24-h day is available.

If melatonin samples have been collected only at restricted multiple time points rather than during a 24-hour period, the markers of circadian phase that can be calculated are as follows: DLMO, acrophase (peak time of secretion), dim light melatonin offset (DLMOff), and pineal gland synthesis offset (SynOff).[26] Although there is no standard definition of this measure, the currently used parameters to determine DLMO (or DLMOff) from a partial melatonin profile are as follows: absolute threshold in the range of 2-10 pg/mL; threshold calculated at 2 SD above the average baseline (ie, 3 or more pre-rise) samples; visual estimate of the point of change from baseline to rising (or declining) levels. The timing and amplitude of intra-individual melatonin profiles are, in general, very stable. By contrast, the large inter-individual differences in the amount of melatonin synthesized, as well as the sensitivity of the assay used, must be carefully considered when defining normal ranges for melatonin levels, or choosing a specific threshold.[27,28]

3.4 | Melatonin variables as correlates of BD

While melatonin-focused measures correlate with various features of BD, specific findings are mixed. For example, Lam et al [29] and Kennedy et al [30] studied BD subjects in various mood states (depressed, manic, and euthymic) and reported reduced nighttime serum melatonin concentrations compared to healthy control subjects. The study by Kennedy et al found no significant differences depending on mood state and no significant differences in urinary aMT6s levels between BD and healthy control participants, whereas Slyepchenko et al[31] found lower levels of urinary aMT6s levels in BD participants. Nurnberger et al[32] found euthymic patients with BD type I disorder to have lower serum melatonin during dark conditions including a later peak compared to healthy control subjects. Two studies, however, failed to find any differences in nighttime serum melatonin concentrations between euthymic BD patients and controls.[33,34] Novakova et al[35] also found no differences in salivary melatonin concentrations between symptomatic BD patients and controls.

Several studies have compared melatonin kinetics among BD and unipolar depression patients. While the previously mentioned studies by Lam et al and Nurnberger et al found no differences in nighttime serum melatonin concentrations between patients with BD and unipolar depression, Robillard et al[36] found adolescents and young adults with BD to have significantly lower nighttime serum melatonin synthesis compared to those with unipolar depression. A further study comparing morning (08:00-10:00 hours) melatonin concentrations in serum and cerebrospinal fluid between symptomatic patients with BD, unipolar depression, and asymptomatic healthy controls[37] found reduced concentrations of CSF melatonin and elevated serum melatonin in BD compared to unipolar depression and

controls. Increased melatonin suppression due to the administration of white light at nighttime, the so-called "supersensitivity," has been proposed as an endophenotype in BD.[38] Higher melatonin suppression in patients with BDI disorder has been found in four studies [32,33,39,40] but not in three others.[29,34,41]

While the use of a 24-h catheter permits the most reliable measurement of 24-h melatonin production, its invasiveness makes it less practical in large-scale clinical research. The measurement of salivary melatonin (eg, to assess DLMO) or its urinary metabolite, aMT6s, may give valuable insights regarding potential abnormalities in the levels and/or timing of melatonin but their accuracy may be affected by the large inter-individual variance in melatonin production and the sensitivity of the laboratory assays. In summary, abnormalities in melatonin concentrations, synthesis pathways, and light-induced suppression have been described in BD. Whereas results are heterogeneous and thus did not lead to identification of a specific biomarker of BD, the measurement of 24-h melatonin rhythm offers a reliable objective measure of circadian rhythmicity that may help at a clinical level to better diagnose a circadian rhythm disorder or at a research level to better unravel the pathophysiology of BD and characterize more homogeneous subgroups of BD with share chronobiological alterations.

4 | ACTIGRAPHY

Actigraphy is used extensively in sleep research to objectively measure sleep timing under naturalistic conditions,[42] and has more recently been extended to attend to the full 24-hour cycle of activity, and hence potentially circadian activity variables. Actigraphs are wearable activity sensors measuring frequency, acceleration, and direction of movement via piezoelectric omnidirectional or tri-axial accelerometer.[43] Actigraphs are typically worn on the wrist of the user's non-dominant hand to minimize movement-related artefacts. A low-pass bandwidth filter in the 2-10 Hz range is used to filter out unwanted signal noise due to ambient vibration and other artefacts outside the normal range of movement in humans; a correction is also applied to account for the static acceleration force of gravity.[44,45]

A sampling rate of 30 Hz is recommended for reliable recording of activity.[46] In practice, current technologies create a trade-off between resolution of data and battery charge such that higher resolution results in shorter available recording time. An epoch length of either 30 seconds or 1 minute has been traditionally recommended for most clinical applications. However, recent analytical efforts leverage sub-second-level data to identify sleep periods,[47] detect walking,[48] and calculate gait parameters[49] with a minimum recording period of 72 consecutive hours.[42] Longer recording periods may be necessary to capture rest-activity rhythms across both weekdays and weekends, and reduce overall measurement error in estimates of the long-term exposure obtained with short-term actigraphy.[50] In fact, there is growing evidence that weekday-weekend patterns may differ substantially in people with BD.[51]

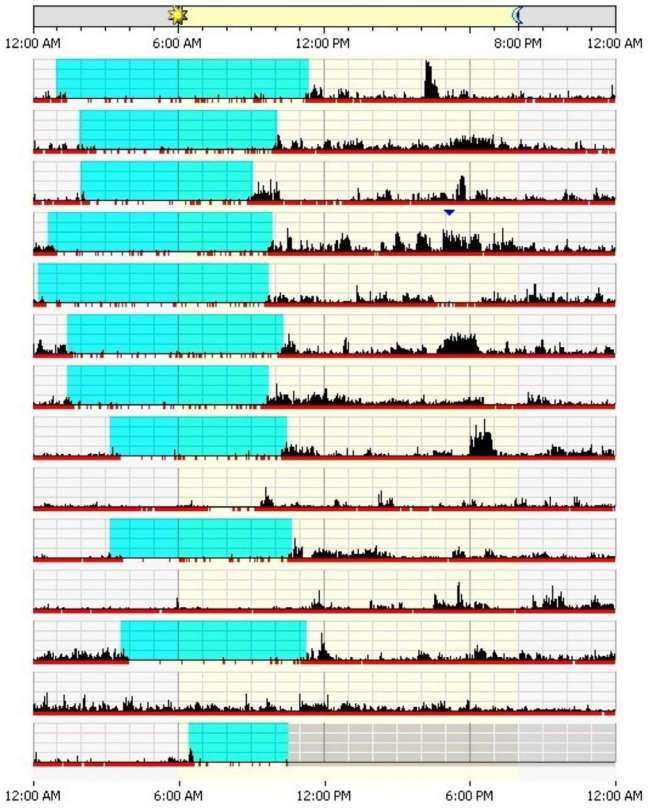

FIGURE 2 Actogram (X-axis = 24 hours, Y-axis = day 1 through day 14, blue = calculated sleep phase) of 14 days rest/activity for a research participant diagnosed with BD I whose actigraph was removed upon being involuntarily admitted to hospital for mania. Note progressive abnormalities in rest/activity over 8 days preceding intake. Reprinted with permission from ref. [53]

Instructions and guidelines for the use of actigraphy as an index of sleep have been provided by a consensus panel commissioned by the Society of Behavioral Sleep Medicine (SBSM) primarily to assist clinicians and researchers.[42] In addition to standard procedures, they recommend that actigraphy should be accompanied by daily diary measures that include subject report of the following minimal set of items:

- Time the individual got into bed
- Time the individual attempted to fall asleep at night
- Time the individual woke up for the last time in the morning
- Time the individual got out of bed to start the day in the morning (no longer trying to sleep)
- Times of any daytime naps
- Times that the actigraph was removed from or replaced on the wrist
- Any unusual circumstances that might have affected sleep/wake patterns (eg, illness, travel across time zones, novel sleeping environment, sitting still for prolonged periods of time such as during a movie)

These measures can be collected electronically, particularly through Ecological Momentary Sampling that has been used to

integrate findings from actigraphy with measures of subjective mood and other emotional states, contextual factors, and stressors in people with BD.[52]

4.1 | Common approaches to analyzing actigraphy data

The simplest approach to interpreting actigraphy data is visual inspection of the raw data, most commonly in the form of an actogram.[53] As shown in Figure 2, objective measurement of locomotor activity can provide a compelling objective characterization of illness state in BD.[54] Actigraphy data could be interpreted using different scoring methods relying on the sleep diary, the event-marker (bedtime and wake-up), the software-provided automatic algorithm, the automatic algorithm supplemented by the event-marker, and the visual inspection only.[55] Processing and derivation of these measures for the GeneActiv device that was used in the UK Biobank have been automated in an open-source package, GGIR, developed by Vincent Van Hees and colleagues in the UK.[56]

Cosinor rhythmometry, the fitting of one or more cosine curves to data using least-squares regression,[57] has proven useful in characterizing the features of biological processes that exhibit an endogenous circadian component. Such models parameterize circadian rhythms in terms of mesor, amplitude, phase, and period. Unfortunately, cosinor models are a poor fit to actigraphy data, which exhibit nonsinusoidal characteristics across 24 hours. For example, Bullock (2011) found that cosinor model-fitting using the least squares method accounted for, on average, only 15.07% of the variance in rest-activity patterns across 461 days of actigraphy data. Second- and higher-order harmonics increase explained variance, but only minimally and at significant cost to degrees of freedom.[58]

Van Someren et al[59,60] developed a nonparametric technique specifically designed for the analysis of actigraphy data. Measured characteristics of the data include the 10 most active hours (M10), and the 5 least active hours (L5) of the 24-hour period, presumed to represent subjective wake and sleep time, respectively. M10 and L5 onsets can be measured and offer two phase markers of circadian activity rhythms. A measure of amplitude is computed from these two features of the raw activity pattern (M10 and L5). Raw activity amplitude is presumed to represent the robustness of the 24-hour activity rhythm: Higher values indicate greater consolidation of rest versus activity periods, and can be interpreted as representing the robustness of the rhythm.[61] Amplitude is often presented relative to an estimate of total activity (Relative Amplitude, RA) because higher mean levels of activity affect interpretation of the amplitude value.

Van Someren and colleagues defined two further nonparametric rhythm variables.[59] Interdaily stability (IS) aims to measure strength of coupling between the rest-activity rhythm and the presumed 24-hour exogenous zeitgeber pattern of light and dark: IS is calculated as the ratio between the variance of the average 24-hour activity pattern around the mean and the variance of the overall activity pattern across multiple days. A lower IS ratio is proposed to indicate reduced stability in the activity rhythm. Intradaily variability (IV) aims to measure rhythm fragmentation, reflecting the frequency of transitions between rest and activity in a given 24-hour period: IV is calculated as the ratio of the mean squares of the difference between consecutive hours and the mean squares around the 24-hour mean. A higher IV ratio is interpreted as greater rhythm fragmentation and reduced stability of the activity rhythm.

Importantly, Van Someren and colleagues acknowledge that their nonparametric variables (RA, IV, and IS) have unknown relationships to endogenous circadian function, and although these actigraphic variables are often described in the literature as measuring something about circadian function, for example,,[62] they are more conservatively understood as parameters of the 24-hour activity rhythm (Van Someren, personal communication, September 2018).

Common actigraphy variables are thus measures of (i) traditional circadian rhythm parameters, such as period, amplitude, and phase; (ii) sleep timing, such as sleep duration, sleep latency, wake after sleep onset (WASO), time in bed, sleep efficiency, and fragmentation index (a measure of sleep continuity); (iii) activities such as amount of activity during sleep or a 24-hour period; and (iv) "variability" or stability of the activity rhythm, such as IS and IV.

4.2 | Emerging approaches to analysis of actigraphy data

Actigraphic technology generates high-resolution data streams, supporting analyses using sophisticated mathematical models, see.[63,64] Such approaches neither make restrictive assumptions of cosinor models nor reduce data to daily summaries like the Van Someren variables. Recently, for example, novel "functional" data analysis approaches have been developed that are fully data-driven and do not make any parametric assumptions about the functional form of diurnal patterns.[65] Here, "functional" is a term reflecting the idea that epoch-by-epoch actigraphy counts can be thought of as "curves" representing individuals' rest/activity pattern over 24-hour periods.

Functional principal component analysis (FPCA) is a functional data analysis technique that represents subject-specific diurnal pattern via functional "principal components," a new set of representative orthonormal functions, and calculates subject-specific functional PC scores. These subject-specific functional PC scores have been used as scalar covariates to predict mortality[66] and characterize depression within BD.[67] Day-to-day variability in subject-level diurnal patterns can be analyzed by multilevel functional principal component analysis (MFPCA)[68,69] that accounts for the repeated nature of actigraphy measures and decomposes actigraphy profiles into dominant patterns that, in addition to distinguishing participants from each other, distinguish different days within

each participant's dataset. Function-on-scalar regression (FOSR)[70] is a class of regression models with functional responses (such as diurnal patterns measured by actigraphy) and scalar covariates (such as age, gender, cognitive status, etc). Generalized Function-on-Scalar Regression[71] combines both MFPCA and FOSR to model the so-called generalized functional observations such as dichotomized diurnal patterns, represented by a sequence of active/sedentary states.[72]

More complex mathematical methods have also been applied to actigraphy data, with nonlinear dynamic indices shown to correlate with vulnerability to BD, presence of BD, and mania.[73–76] Faedda and colleagues[77] found that an algorithm including most of the analyses above discriminated between pediatric BD, ADHD, and controls.

4.3 | Actigraph-derived variables as correlates of BD

As discussed in Section 4.2, studies of actigraph-measured activity in BD have used a heterogeneous array of variables. Lower 24-hour activity compared to healthy populations has been found in people with BD[51,54,78] as has a less robust,[79,80] more unstable[81] and phase advanced 24-hour activity rhythm.[82] Differences across phases of the illness in people with BD are also apparent. More disorganized and complex patterns of activity, particularly in the morning, appear to be characteristic of the manic phase while greater minute-to-minute variability is more characteristic of the depressive phase.[83]

De Crescenzo et al [78] reviewed six studies comparing activity levels in people with a primary diagnosis of BD with healthy controls. All studies reported significantly lower mean daily activity in people with BD. Scott, Murray et al,[54] employing different inclusion criteria, reviewed 17 studies and arrived at a similar conclusion. Van Someren's RA has been shown to be associated with vulnerability to BD[84] and lifetime BD.[62] Surprisingly, one study failed to find an association between mean activity levels and illness phase in people with BD[85] and Scott et al[54] did not find evidence of increased mean activity in mania. This counterintuitive finding is a useful reminder of the complexity of the "activity" construct: Mean activity does not capture abnormal bursts of activity, or abnormal timing of activity across 24 hours.[84] Furthermore, as noted by Scott et al,[54] intra-individual data showed that activity was higher for individuals when manic than when they were depressed.

These same factors may also differentiate the rest-activity patterns of people with BD from those with other psychiatric disorders and healthy controls.[86] Later, more irregular rest-activity patterns were associated with the presence of manic-hypomanic symptoms in a retrospective investigation of people with major depressive disorder.[87]

However, when used alone (ie, without also incorporating into the analyses the sleep and the variability of sleep parameters from actigraphy), the circadian parameters (IS, IV, M10 onset, and RA) moderately discriminate patients with BD from controls (70% of individuals being correctly classified).[13]

Variability measures (which can be represented by the standard deviations [SD] in the mean scores for a particular actigraphic measure recorded for several days or weeks) may also be sensitive markers for distinguishing BD sleep patterns from those of controls.[13,88–92] It may also be useful for exploring similarities and differences in youth with emerging bipolar and unipolar disorders.[93,94]

In summary, the variety of analytic approaches to actigraphy has been a barrier to its application in research and clinical practice. There are also several challenges in the interpretation of actigraphy data in clinical samples such as medication use, clinical state, source of the sample (eg, inpatient, outpatient, non-patients), inclusion of controls, and consideration of covariates of actigraphy such as BMI, season, and day of week.[51,52,89] Likewise, differences in the procedures, processing, and analytic approaches to actigraphy have been a barrier to interpretation of findings from actigraphy in BD. There are now some ongoing efforts to standardize the methods for administration and analysis of actigraphy data in samples of people with mood disorders that will facilitate interpretation and generalizability of the findings NIMH Motor Activity Research Consortium for Health (mMARCH network, NIMH ZIA MH002954-04). Started with a core group of six sites, this network is expanding to include numerous international sites with interest in using actigraphy in BD.

5 | SELF-REPORT METHODS

In contrast to melatonin and actigraphic approaches, in which real-time data are used to infer circadian variables, self-report questionnaires rely on autobiographical memory to characterize inter-individual differences in engagement with the 24-hour day. A large number of questionnaires have been used in BD populations. The focus here is primarily on the multiple tools measuring chronotype (also called morningness-eveningness, circadian typology, diurnal preference,[95]), but more distinctive self-report measures are also noted.

5.1 | Chronotype and its measurement

Chronotype refers to a particular type of individual difference in circadian function, namely, the relative preference for (and for some theorists the actual occurrence of) activity earlier or later in the day.[96] The construct is measured dimensionally but also commonly categorized using cut-points to define "morning," "evening," and "intermediate" types.[95] Existing measurement instruments correlate highly, and as a set, (i) internal reliability is at least adequate, (ii) test-retest reliability has been demonstrated across extended periods, and (iii) convergent and/or construct validity has been demonstrated in moderate-large correlations with self-report, behavioral/sleep-wake, and physiological measures relating to time of day of activities including gold-standard measures of circadian phase.[95,97] Questions remain about the optimal factor structure of these instruments (eg,

is Morningness best seen as a discrete factor?), and about cut points for categorical approaches to measurement.[98]

Chronotype has trait-like, developmental, and state-like components. Individual differences in chronotype are relatively stable across time (all else being equal), and have a genetic basis.[99] But it also shows significant developmental patterns, with earlier preference during childhood, shifting later in adolescence with normalizing of this phase delay being called a marker of the end of adolescence,[100] then returning to an earlier preference in mid-life.[101] Chronotype also has state-like characteristics (indeed, Roenneberg's MCTQ is distinguished by its specific focus on current phase, see below), being modified by interactions with *zeitgebers* interactions with zeitgebers, etc, [96] and influenced by the build-up of sleep pressure sleep homeostasis,.[102,103] Importantly, chronotype relates not just to circadian phase but also period, with evening types having longer periods.[104–106] Indeed, constant routine studies have demonstrated that morning types awaken earlier in their circadian cycle than evening types, and this difference is moderated by age.[107]

5.1.1 | Morningness-Eveningness Questionnaire (MEQ)

The Morningness-Eveningness Questionnaire (MEQ)[108] is the most commonly used measure of diurnal preference (chronotype), and the scale against which more recent instruments are benchmarked. The MEQ generates a dimensional total score (with higher scores reflecting greater Morningness), but the score is often used to create five categories ranging from Definite Morning type to Definite Evening type.[108] Based on multiple correspondence analysis and on hierarchical clustering analysis to construct principal components, three categories been proposed: evening types scoring under 53 and morning types above 64.[97]

5.1.2 | Composite scale of morningness

The Composite Scale of Morningness (CSM)[109] was developed from three existing chronotype questionnaires, including the MEQ, with the aim of being a more pure measure of Morningness per se. The CSM mainly assesses preferred times of day (from morning to evening) for undertaking various activities, and is considered a marker of circadian phase or phase preference (morning, intermediate or evening type). Total score on the CSM has been shown to correlate 0.95 with MEQ, and categorization into evening morning and intermediate types is similarly high, see.[98]

Total score on the CSM ranges from 13 to 55 and can be used as a continuous variable with lower scores indicating proneness toward evening type. Cutoffs for the CSM can also be used for the classification of individuals as morning, intermediate, or evening type. Factor analyses have suggested that three factors can be identified: morning activities, morning affect, and eveningness. The CSM was further validated in a smaller independent sample of undergraduate students and confirmed its acceptable internal consistency (Cronbach's alpha = 0.83). Indeed, the CSM had been previously associated with melatonin serum level in healthy volunteers, evening type subjects having significantly higher levels at 09:00 hours than morning type subjects.[110]

5.1.3 | Munich chronotype questionnaire

The Munich Chronotype Questionnaire (MCTQ) was developed to assess timing of the sleep phase within the 24-hr day as a marker of phase of entrainment: The instrument's developers highlight that its target construct is *state circadian phase*, and argue that this should not be conflated with the more trait-like construct of diurnal preference (as captured on the MEQ, see Table 1).

A distinguishing feature of the MCTQ is its attention to the interaction between circadian and sleep processes in the determination of daily timing of activities. Variables derived from the MCTQ include mid-sleep on free days (MSF), and on workdays (MSW) and social jetlag (SJL—the difference between MSF and MSW). Chronotype is calculated based on MSF, assuming that sleep timing on free days is more strongly influenced by the circadian clock.[58]

By focusing on sleep timing unconstrained by socially imposed wake times ("free days"), MSF aims to tap behaviors more strongly influenced by the circadian clock. Since sleep duration on free days is also influenced by the sleep debt accumulated over the work week, sleep-corrected mid-sleep on free days (MSFsc) adjusts MSF by subtracting the sleep-debt accumulated over the workweek (calculated as the sleep duration on free days and its weekly average).[58] Very high correlations between MSF and MEQ scores (−0.74) decrease somewhat when MSF is sleep-corrected (−0.66).[101]

When comparing sleep times assessed by the MCTQ with sleep logs in a preliminary validation (N = 30), the two instruments correlated highly ($P < .0001$).[111] In a large sample (N > 55,000) collected via a public website, MSF demonstrated interactions with age and sex, specifically, women reached their maximum of lateness at a younger age than men (19.5 y.o. v 21 y.o, respectively). In terms of external validation, MSFsc has been found to have a strong correlation with DLMO, the gold standard phase marker ($r = 0.68$, $P < .001$).[112] In a sample of 117 Brazilian African descendants, data derived from the MCTQ and actigraphy were highly correlated: MSF and mid-sleep calculated from actimetry ($r = 0.66$, $P < .0001$), sleep duration on free days (MCTQ) and average sleep duration (actimetry) ($r = 0.45$, $P < .0001$), and outdoor light exposure (MCTQ) with the proportion of day exposed to more than 1000 lux ($PDELI_{1000}$, rho = 0.31, $P < .01$, N = 99).[113]

5.2 | Other self-report approaches

It is informative to also identify self-report measures purportedly tapping constructs beyond chronotype (some of which also measure

TABLE 1 Measures of chronotype commonly applied in bipolar disorder samples

Scale and primary publication	Defining features	Surface structure and scoring	Psychometric properties	Relevant validating data
Morningness-Eveningness Questionnaire (MEQ)	Original and most widely used measure of morningness-eveningness	19-item questionnaire measuring preferred patterns of sleep/wake and self-reported periods of peak activity and effectiveness. Item response formats on the MEQ range from Likert-type scales to graphical representations of clock-time in which respondents indicate their preference for certain hours of the day for sleeping, working, and general activity.	Ca = 0.77-0.86 (Di Milia et al, 2013); TR = 0.84-0.95 (Di Milia et al, 2013)	Expected differences between morning and evening chronotypes found in daily timing of body temperature, cortisol secretion, melatonin production, sleep habits, peak performance, and alertness (Di Milia et al, 2013)
Composite Scale of Morningness (CSM)	Derived in part from MEQ.	13-item questionnaire that examines preferences associated with morning or evening activities. For example, when considering questions about preferred sleeping and waking times, respondents choose their preferred option from a list of various hours of the day. Other items explore the time of performance peak, how easy it is to get up early, or how alert or tired individuals feel in the morning. Items are scored on a 4- or 5-point Likert scale.	Ca> 0.8 (Di Milia et al, 2013); TR> 0.88 (Di Milia et al)	Expected differences between morning and evening chronotypes found in daily timing of body temperature, self-reported sleep behavior, and peak alertness (Di Milia et al, 2013). Convergent validity shown in strong associations with MEQ.
Munich Chronotype Questionnaire (MCTQ)	Unlike MEQ and CSM (with which it correlates highly), MCTQ was designed to assess circadian phase by investigating mid-sleep time on free days (adjusting for social commitments and accumulated sleep debt)	The MCTQ comprises questions about daily life (sleep-wake behavior, use of alarm clock, and outdoor light exposure) assessed separately for workdays and free days (eg, "When do you go to bed?" "How long do you need to fall asleep?" "When do you wake up?").	The MCTQ is not a scale for psychometric purposes, as sleep midpoint is assessed in a single item.	Self-reported sleep midpoint on the MCTQ is strongly associated with sleep-diary collected estimates of sleep midpoint. Somewhat weaker associations with other chronotype measures, potentially representing its closer measurement of circadian phase rather than diurnal preference.

Abbreviations: Ca, Cronbach's alpha; EFA, number of factors arising in exploratory factor analysis, and match between latent and surface structure; TR, test-retest reliability.

chronotype). An outlier is the Social Rhythm Metric,[114] which aims to capture not general tendencies of the individual but diary-assessed regularity of timing of daily events.

5.2.1 | Circadian type inventory (CTI)

The Circadian Type Inventory (CTI) is an 11-item questionnaire designed to measure suitability for shift work, based on individual differences in self-reported flexibility of sleeping habits (eg, napping or sleeping in when desired), and ability to overcome drowsiness (eg, coping with missing a night's sleep): the former dimension is called flexible/rigid, the latter languid/vigorous.[115]

Principal components analysis confirmed a two-factor structure (FR scale and LV scale) explaining 52% of the variance in the control group and 47% in the bipolar group. Cronbach's alpha was 0.75 for FR and 0.73 for LV. The test-retest reliability was 0.74 for FR and 0.86 for LV (3 weeks) and 0.62 for FR and 0.72 for LV (6 months). As compared with controls, patients with BD were more languid ($P < .00001$), but they did not differ from controls with regard to flexibility/rigidity. In a second study from the same team, but using an independent sample, 100 patients with BD and 72 control subjects completed the CTI. Patients with BD exhibited a more languid and less flexible circadian type (CTI-LV $P < .0001$; CTI-FR, $P = .04$).[116]

5.2.2 | Biological rhythms interview of assessment in neuropsychiatry (BRIAN)

The Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN) was originally developed and its psychometrics investigated in a sample of 81 euthymic BD subjects and 79 matched controls, showing a Cronbach's alpha of 0.93 and an ICC test-retest of 0.98.[117] Scores on the BRIAN discriminate all mood states in individuals with MDD and BD [118,119] and are independently associated with psychosocial functioning and quality of life.[119–121] In addition, total BRIAN scores correlated with minutes of wake after sleep onset, total activity count during sleep, and urinary aMT6s, results that further corroborate to the face validity of this self-reported questionnaire. A recent study tested BRIAN total score against objective variables related to sleep and activity patterns.[122] Findings were mixed, with the sleep domain not being associated with any objective measures of sleep. However, total score was found to correlate positively with two indicators of poor sleep (wake after sleep onset and total activity count during sleep), and negatively with the first morning urinary aMT6s excretion (an index of nocturnal melatonin production).

5.2.3 | Mood rhythm instrument (MRhI)

The Mood Rhythm Instrument (MRhI) is a 15-item self-report questionnaire that assesses the presence of daily patterns and the peak timing of mood-related physiological/behavioral variables. Items were not selected on the basis of evidence of a circadian component to their variation, but rather on their being symptoms of depression, or having been noted by the authors to vary daily in clinical populations. The psychometric properties of the MRhI have been measured in community samples of three different countries, with an acceptable internal consistency reported (Cronbach's alpha = 0.70-0.75).[123–125] To examine a potential memory bias when reporting presence and timing of mood-related symptoms, the MRhI was tested against a prospective daily investigation of mood-related symptoms, when study participants were asked to prospectively fill out a daily version of the MRhI (MRhI-d) for 15 days (Pilz et al, 2018a). Results showed fair to excellent agreement rates between the MRhI and the MRhI-d ($r = 0.59$-0.97) and, except the item "irritability," no recency bias was observed with any of the other MRhI items (Pilz et al, 2018a). Interestingly, the total number of MRhI items with a perceived daily pattern has been shown to be positively correlated with depressive symptom scores ($r = 0.44$; $P < .05$) and negatively correlated with psychological well-being ($r = -0.55$; $P < .01$). While the MRhI is currently being tested in individuals with BD and MDD (Hidalgo and Frey, personal communication), its usefulness in clinical samples remains to be determined.

5.2.4 | Social rhythm metric

The Social Rhythm Metric (SRM) is a daily diary measure derived from a circadian hypothesis of BD the social zeitgeber hypothesis,[126,127] and an associated behavioral treatment.[128,129] Participants record the times of day at which signal events occur, which are then scored to quantify the extent to which these times vary across days of a 7-day reporting period. The instrument is composed of 17 items (15 required and 2 optional) assessing the degree of social interactions and the frequency and timing of daily activities (eg, first contact with other people, start of work, school, volunteer, or family care, dinner, etc). The SRM is a core tool within interpersonal and social rhythm therapy, used to identify behaviors, the timing of which could benefit (under the social zeitgeber hypothesis) from regularizing across days.

The instrument provides two main indices, the daily regularity (HIT, number of activities that are happening three or more times during the week within a variability range of 45 minutes) and the quantity of activities (the activity level index [ALI] represents the volume of activities performed per week).[7,130] The HIT scores vary from 0 to 7 (0: least regular; 7: most regular). The ALI scores a maximum of 119 (17 activities × 7 days).[131]

Due to the burden of completing the 17-items questionnaire during an extended period, reduced versions have been proposed, namely SRM-5, M-SRM, BSRS (Brief Social Rhythm Scale)[132–135] and, more recently, smartphone versions have been developed.[136,137] Adherence and missing data remain an issue for the SRM (Swartz, personal communication, October 2019).

5.3 | Self-report variables as correlates of BD

Self-reported chronotype has a reliable relationship with the BD diagnosis: When euthymic, people with BD tend to be evening types and exhibit delayed physiological measures of circadian phase.[138,139] The CSM is one of the most used morningness scales in samples of patients with BD, and the scale has demonstrated adequate internal reliability,[109] and adequate stability across 2 years.[140] A previous systematic review identified 15 studies using the CSM, most of which found BD to be associated with eveningness.[138] Boudebesse et al studied the external validity of the CSM against data generated by 21 days of actigraphy recording in a sample of 36 patients with BD. Phase preference assessed by the CSM strongly correlated with actigraphic phase markers (M10 onset rho = −0.69 and L5 onset rho = −0.63). Another study suggested that subjectively—(CSM) and objectively—measured (25-50 days of continuous actigraph data) chronotype correlated significantly with one another in a sample of 61 patients with BD.[141]

The Social Rhythm Metric aspires to measure a variable that should be understood as both an input and an output of circadian function, namely, patterns of behavior across the day, viewed through the lens of the stability of these patterns across days. Results from a large-scale study (N = 8095) using an abbreviated version of the SRM in United States, Russia, and Germany samples confirmed earlier findings of lower regularity in clinical samples (BD in particular) when compared to healthy controls.[135]

In sum, self-report instruments have been developed to measure a wide range of chronobiological constructs. One of these constructs—chronotype—has been relatively well studied, shown moderate associations with an objective chronobiological variable (viz., circadian phase), and shown reliable associations with BD. Chronotype is a multi-faceted construct, with some theorists emphasizing its state measurement, and highlighting its association with the biological construct circadian phase (Roenneberg's MCTQ), others highlighting its more stable trait like features (eg, MEQ), but nonetheless still seeking external validation in correlations with circadian phase.

6 | DISCUSSION

The overarching aim of this review was to encourage use of, and advance the measurement of circadian function in BD. An empirical review of assessment methods was organized by levels: biology (melatonin measures), objective behavior (actigraphy), and subjective behavior (chronotype and other self-report measures). The objectives of this integrative Discussion are to summarize what is known about BD in relation to these domains of measurement, and to propose tentative next steps in understanding circadian measurement in BD. Conclusions are also presented in light of the project's limitations.

6.1 | What do we know about circadian measurement in bipolar disorder?

Assessment in BD can perform several different functions.[142] A range of evidence suggests that circadian pathways are involved in BD onset and course (as noted above), but there is currently no circadian measure whose association with BD (or any of its categorical or dimensional facets) is either strong or specific enough to inform *diagnostic* specificity. Rather, the aim of circadian assessment in BD is to measure circadian parameters that are relevant to the risk/predisposition to, or mood state of the disorder.

6.1.1 | Measurement of circadian function in the clinical setting

Chronotype is a well-understood, easily measured, individual difference variable that has shown reliable associations with BD. The associations however are not specific to BD—eveningness has relationships (most likely bidirectional) with a range of psychopathology.[143] Morningness-eveningness (MEQ) should nonetheless be considered a core part of a clinical assessment in BD, for a number of reasons. First, chronotype can explain sleep problems trying to sleep at the wrong circadian time, see.[144] Second, knowledge of circadian phase may be useful to optimize timing of bright light as an adjunct in treatment of bipolar depressions see[5]; moderate-large correlations between self-reported chronotype and physiological measures of phase means that self-reported chronotype can perform this function.[145] Finally, the measurement of chronotype has psychoeducational benefits: instruments like the MEQ are face-valid descriptors of daily rhythms in behavior, and provide a tool for introducing patients to the circadian system and its relevance in BD.

A wide range of actigraph-derived measures correlate with the presence of BD, in both its state and trait form. However, there is no evidence as yet that the positive predictive value of actigraph-derived data is sufficient to use as an early warning of relapse, and protocols for the long-term use of actigraphy data in routine clinical use are yet to be validated. Reviewing a patient's actogram (eg, Figure 1), provides a detailed visualization of their activity patterns, and could be useful in dialogue with the patient to provide insight into unproductive activity or sleep-related behavior, particularly when insight may be impaired.[146] Unlike chronotype, however, actigraphy is not common in clinical practice, except when a circadian rhythm sleep disorder is suspected, and may be considered stigmatizing by some patients.[147,148]

6.1.2 | Measurement of circadian function in research

The present review was focused on less intrusive measurement approaches that have potential for use in clinical practice or large-N

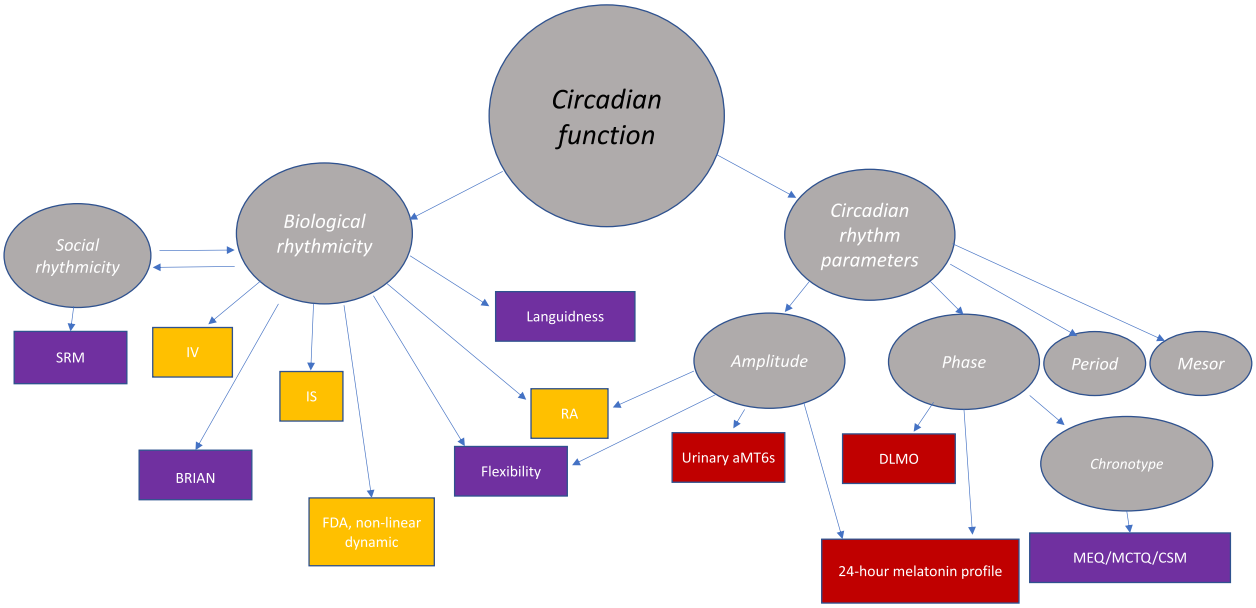

FIGURE 3 Provisional framework linking constructs (grey ovals) to measures (rectangles) in the chronobiology of bipolar disorder. Purple, yellow, and red indicate self-report, actigraphy, and physiological measures, respectively. The parameters Period and Mesor are noted because they are important in circadian biology; they are not widely used in BD research. SRM, Social Rhythm Metric; IV, Intradaily Variability, IS, Interdaily Stability; BRIAN, Biological Rhythms Interview of Assessment in Neuropsychiatry; FDA, functional data analysis; RA, Relative Amplitude; aMT6s, Urinary 6-Sulfatoxymelatonin; DLMO, Dim Light Melatonin Onset; MEQ, Morningness-eveningness Questionnaire; MCTQ, Munich Chronotype Questionnaire; CSM, Composite Scale of Morningness

trials. The review therefore covers only one part of a spectrum of ongoing (human and pre-clinical) circadian biomarker research in BD, for example.[149,150] If the present review has any implications for biomarker research, it is in highlighting the possibility of systematic measurement across multiple domains (biological, behavioral, and psychological). The understanding of circadian pathways in BD may improve by attending to measurement at these macro- and micro-levels.[144] Behavioral and self-report measures add crucial environmental and psychological context to measures closer to the biological core of the circadian system (eg, melatonin measures and intracellular pathways), and remind us of bidirectional relationships between behavior in the environment and the endogenous circadian system (Figure 1).

Future research should systematically compare all three domains of measurement, attending specifically to the constructs that are being measured within each domain. Some constructs overlap (phase is measurable through melatonin, actigraphy, and self-report); amplitude through melatonin and actigraphy (see below, and Figure 3). It is difficult to know how to validate some of the less specific "circadian constructs"—obviously it is circular to seek validation through their association with BD or other mood problems.

Circadian function should also be measured in research into other neurobiological investigations of the BD phenotype. A number of recent reports, for example, have noted that time of day differences (likely mediated in part by circadian function) impact measurement of neural reward activation, for example.[151,152]

6.2 | Next steps

To support more specific and systematic investigation of circadian measures in BD, it is useful to distinguish between circadian constructs and measures. The measures reviewed by domain above can be organized into a provisional taxonomy as shown in Figure 3. The figure borrows from structural equation modeling the technique of ovals representing constructs, and rectangles representing measured variables. To orient the reader, the upper-level construct in Figure 3 is "circadian function," which is parsed into two intermediate constructs (biological rhythmicity to the left of the figure and circadian rhythm parameters to the right).

Three key assertions about circadian measurement in BD are contained in Figure 3. First, on the far right of the figure, we note that the circadian rhythm parameter of *phase* has been measured in multiple ways (DLMO, 24-hour melatonin profile, and [via the related construct of chronotype] self-report instruments like the MCTQ). The figure suggests that a systematic approach to the measurement of circadian constructs in BD would prioritize comparisons between these measures. Phase-oriented hypotheses will also account for phase relationships: Circadian misalignment, which can be operationalized as an abnormal phase relationship between rhythms, for example,[153–156] is a primary explanatory concept in mood disorders.

The circadian rhythm parameter of *amplitude* has also been measured in various ways (24-hour melatonin profile, urinary aMT6s, actigraphy-measurement of Relative Amplitude), and systematic comparison across these measures is warranted as this construct is

explored in BD. Amplitude is something of a bridging construct in Figure 3 because it refers to both a specific parameter of a circadian rhythm, and is also used to operationalize a more general feature of rhythmicity: Reduced amplitude of downstream 24-hour rhythms reflects a weakened circadian signal, potentially etiological in BD and other pathologies see.[62,73,84,157–160] Figure 3 shows the amplitude construct is also measured in the self-report CTI variable of flexibility (flexible/rigid, see above): theoretical rationale for this CTI variable is that lower amplitude circadian rhythms are more responsive to current environmental circumstances, and thus desirable in shift workers.[115]

Finally, the left side of Figure 3 illustrates that a number of measures do not have a basis in traditional circadian parameters of phase, amplitude, period, or mesor. Rather, they can be characterized as measuring the broad, fuzzy construct of "biological rhythmicity." Biological rhythmicity is sometimes used to refer to any feature of circadian function, but is typically given a positive connotation, and thus linked to circadian robustness or strength. Like its antonyms "dysregulation" and "disruption," robustness is a complex concept from a living systems viewpoint, and could be operationalized in many ways including (as mentioned above) the amplitude of output rhythms, for example.[158,161–163] In Figure 3, the two CTI self-report variables (Languidness and Flexibility), the BRIAN score, and four actigraphy measures are presented as orphan measures—to the extent that they tap a construct more specific than "biological rhythmicity," a construct that is exclusive to the BRIAN measure and one that has not been tested or explored beyond the measure itself.

Standardization of methods is a critical step toward validation/replication of research findings, and for an evidence-based assessment practice in clinical settings. The aim of this manuscript was to encourage this standardization by offering a provisional organization of existing objective and subjective/self-report measures of circadian function in relation to common concepts in the literature.

6.3 | Limitations

The present review had several limitations. First, as noted above, we chose to exclude methods related to sleep assessment, genetic assessment, biological assessments (such as core body temperature and cortisol secretion), and laboratory protocols for unmasking the circadian component of 24-hour rhythms. While this decision improved the review's cohesiveness, and was rational given our elevation of feasibility and intrusiveness, some of the conclusions drawn about a taxonomy of measures (Figure 3) will be incomplete. Second, a formal review process (eg, Delphi, systematic literature review) was not used for the selection of domains and measures to include. Consequently, the review cannot claim to be comprehensive. Finally, no attempt was made to rate the quality of the reviewed empirical studies: While this would be a major flaw in a review of the relationship between BD and circadian function (the focus of the forthcoming third manuscript in this series from the ISBD chronobiology task force), it is simply a limitation of the present review of instruments and their application in BD.

6.4 | Conclusions

The present project had auditing and agenda-setting aims. Expert reviews of existing measures led to specific recommendations for clinical and research settings. To move the field forward, a provisional taxonomy is proposed which distinguishes between constructs and measures, highlights ambiguities, and underscores a complex systems approach to circadian function.

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