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Treating Circadian Rhythm Disruption in Bipolar Disorder

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Abstract

Purpose of Review—Disruptions in circadian rhythms are believed to underlie the illness course of bipolar disorder (BD). This review evaluates recent studies on the treatment of circadian dysfunction in BD.

Recent Findings—Targeted social rhythm therapy may be useful for bipolar depression though some studies suggest that a non-targeted psychosocial or pharmacological intervention may be just as efficacious. Lithium holds potential for addressing circadian dysfunction in BD. Blue-blocking therapy may be useful for mania and midday bright light therapy may relieve depression.

Conclusions—Psychosocial, pharmacological, and light-based approaches are promising avenues for treating circadian dysfunction in BD.

Keywords

Bipolar disorder; Circadian rhythms; Social rhythm therapy; Light therapy

Introduction

Converging evidence across several studies posit that circadian rhythm disruption serves a key role in the etiology and course of bipolar disorder (BD) [1–3]. Broadly, the human circadian system is comprised of a set of 24-h internal clocks that maintain normal metabolic and endocrine processes (e.g., sleep/wake schedules, body temperature, hormone release) [4, 5]. Circadian rhythms are largely sustained through the activity of a primary, “master clock” within the suprachiasmatic nucleus of the anterior hypothalamus and the supplemental activity of other peripheral clocks across varied body tissues [6, 7]. The circadian system does not rely upon the activity of these clocks alone; effective operation of the system involves synchronization of the internal clocks with stimuli (referred to as “zeitgebers”) in the surrounding environment [6, 8]. Failed coordination of these internal

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and external processes contributes to circadian rhythm disruption, which can in turn lead to bipolar illness.

Research has found several markers of malfunctioning circadian rhythms in the presentation of BD [8, 9, 10••]. In bipolar patients, irregular circadian rhythms are thought to contribute to episodes of mania and depression. One leading explanation for these episodes surrounds the hormone melatonin, which helps sustain the sleep/wake cycle by supplying information about light in the environment. Melatonin is released from the pineal gland, which is coordinated by the suprachiasmatic nucleus and thus surmised to have a prominent role in circadian system regulation [10••, 11]. Data suggest abnormal melatonin release patterns in patients with BD; for instance, some studies have found increased melatonin release during mania as opposed to decreased melatonin release during depression [10••]. Differential patterns of melatonin secretion in mania versus depression may be due to activity of the noradrenergic system (given the role of norepinephrine in melatonin production) [12, 13]. During manic episodes, patients may be experiencing enhanced activity of their noradrenergic system, which is consistent with research that has found elevated urinary and/or cerebrospinal fluid norepinephrine in mania [13–17]. By contrast, research has found urinary norepinephrine to be significantly lower among patients experiencing bipolar depression [15, 17]. Indeed, this latter finding is bolstered by the particular effectiveness of drugs for bipolar depression whose mechanism of action operate on the noradrenergic system (e.g., quetiapine and its metabolite norquetiapine, which binds the noradrenaline transporter and can prevent norepinephrine reuptake) [17, 18].

Some data also suggest that mood episodes in BD are triggered by the interaction of malfunctioning circadian rhythms with zeitgebers [3]. Abnormal circadian rhythms are also thought to underlie sleep difficulties in BD, which affect approximately 70% of patients and even persist during the euthymic (e.g., remitted) state [9, 19, 20]. Sleep difficulties can include increased insomnia or hypersomnia and extended sleep onset latency during depression, a decreased need for sleep, shorter circadian phase, and increased sleep onset latency during mania, and reduced sleep efficiency, elevated anxiety about sleep, and a delayed sleep-wake phase during euthymia [9, 10••, 19–21]. Further, genetic studies also reveal a link between BD and certain circadian genes such as CLOCK, TIMELESS, ARNTL2, GSK3-β, PER3, DBP, and NR1D1 ROR [3, 22••]. Lastly, studies evaluating bipolar chronotypes (e.g., preference for wakefulness in the morning versus the evening) reveal a common pattern of eveningness preference in BD. Studies have found the eveningness chronotype to be associated with mood disorders and linked to markers of a delayed circadian phase (e.g., delayed melatonin onset) relative to a morning chronotype [10••, 22••, 23, 24]. However, other studies have suggested that circadian phases may be dependent on mood state; some research suggests a circadian phase advance in mania as opposed to a circadian phase delay in bipolar depression [25, 26]. Recent reviews have extensively explored the evidence base on circadian rhythm disruption in BD (please refer to [10••, 22••]).

For a clinician, in light of the significant and detrimental effects of circadian dysregulation on the course of BD, what can be done to reduce the impact of this dysregulation and enhance treatment outcomes? The remainder of this manuscript will explore and analyze the

recent evidence-based data on interventions for circadian rhythm dysfunction in BD. Ultimately, we hope this manuscript provides clinicians with useful information that can help guide treatment selection.

Interventions for Circadian Rhythm Disruption

Psychosocial Interventions

The social rhythm theory developed by Ehlers and colleagues posits that depression stems from life stressors that adversely affect an individual's interactions with "social zeitgebers" (e.g., social activities, relationships, and responsibilities) and in turn destabilizes circadian rhythms [27, 28]. Thus, social rhythm therapies aim to stabilize a patient's daily activities (e.g., meal schedule, sleep/wake patterns, activity times), which could have positive carryover effects to their circadian system [29]. Interpersonal and social rhythm therapy (IPSRT) is a notable social rhythm therapy initially developed for the treatment of major depression before being modified for BD by Frank and colleagues [30, 31]. Through IPSRT, the patient learns skills focused not only on enhancing the regularity of daily routines but also on improving the patient's social relationships, helping the patient cope with grief, providing the patient with skills to help them address conflicts, and maximizing the patient's role in their social environment [29, 31]. Frank and colleagues note that IPSRT was created to address three primary "pathways" for bipolar relapse: medication noncompliance, social rhythm dysfunction, and stressful experiences. As such, session content is structured with these risk factors in mind; patients are provided with tools to help them maximize their adherence to psychotropic medications and are given space to discuss the effect their bipolar illness has had on their lives [32]. Two initial studies for patients with bipolar I disorder collectively found that IPRST was effective in increasing the regularity and stabilization of social rhythms and daily routines, enhancing role functioning in the workspace, and decreasing the likelihood of another mood episode among patients in a symptomatic illness stage. The first study evaluated IPSRT relative to standard pharmacotherapy care (e.g., symptom monitoring), and the second compared various protocols of IPSRT (e.g., delivered during acute or maintenance treatment stages) [33–35]. IPSRT was also evaluated as a part of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), a large-scale study program aimed at discovering the most effective treatments for BD [36]. In STEP-BD, IPSRT was evaluated alongside other empirically-validated intensive psychotherapies for BD (cognitive-behavioral therapy, family-focused therapy). After the nine-month study period, all three intensive psychotherapies were found equally effective in promoting recovery rates [37]. This seminal study provided critical, early evidence that IPSRT could be as helpful for a given bipolar patient as other, historically-administered treatments for BD.

Recent avenues of IPSRT research have focused on evaluating the intervention's feasibility in a group format, determining its potential for treating patients with bipolar II disorder, and exploring its effectiveness for young persons. Based on the promising findings from an earlier study revealing the effectiveness of 12–16, 90-min sessions of outpatient group IPSRT in reducing depressive symptomatology [38], Hoberg and colleagues adapted IPSRT into a two-week open group program for patients with bipolar depression ($n = 9$) who were

receiving adjunctive pharmacotherapy. The treatment program involved 2, 60-min individual therapy sessions followed by 6, 60-min group therapy sessions over a two-week period. Individual sessions were focused on assessing the patient's illness background and helping the patient identify interpersonal domains to be targeted in treatment [39]. The patient was also introduced to the Social Rhythm Metric (SRM), a diary that assesses variability in daily activities such as waking time, bed time, and work/school/house chores start time [29, 39, 40]. Group sessions focused on discussing interpersonal problem areas such as grief for "losing" the healthy self and disagreements with others (both of which could lead to additional mood episodes), promoting the importance of medication adherence, discussing role transitions that can affect the patient's normal routine, supplying information on managing the bipolar illness, and providing tools for relapse prevention. Study results revealed significant improvements in depression and disability at twelve weeks, though improvements in overall illness severity and mania were not significant [39]. Another pilot study evaluated an open-ended, weekly group IPSRT program for patients with BD ($n = 17$) [41]. Sessions were 1.5 h in length, and patients could participate in the program for a period of 4 weeks to 4 months. Initial group sessions involved psychoeducation on social rhythms and use of the daily SRM. In subsequent sessions, patients discussed the SRM they had completed in the prior week with an in-depth discussion of specific events or behaviors that adversely affected their social rhythms. Pre-post treatment findings revealed significantly reduced depressive symptoms. Overall, these recent studies suggest the feasibility of IPSRT in a group format, as well as its effectiveness in reducing depressive symptomatology. Enthusiasm is tempered somewhat by the small sample sizes, lack of a control group in both studies, and varied length of treatment participation (e.g., 4 weeks to 4 months). Larger, randomized studies of group IPSRT with consistent treatment lengths are necessary to more clearly elucidate the intervention's benefit.

Initially, IPSRT was specifically evaluated for patients with bipolar I disorder [33, 34] though follow-up trials also explored the application of the intervention in patients with bipolar II disorder. The first open trial in bipolar II disorder explored 12, 45-min sessions of individual IPSRT in unmedicated patients with bipolar depression ($n = 17$) and revealed moderately positive results. Specifically, over half of the patients showed a treatment response (e.g., reduction in depression symptoms without converting to manic symptoms) by 20 weeks and nearly a third attained complete remission [42]. The second study was a randomized study in unmedicated patients with bipolar II depression ($n = 25$) that compared twelve weeks of 45-min IPSRT sessions with flexibly dosed quetiapine (25–300 mg). Outcomes were equivalent in both groups, with all patients showing significant decreases in depression and mania [43]. Recently, a larger follow-up trial randomly assigned unmedicated patients with bipolar II depression ($n = 92$) to weekly IPSRT plus quetiapine or IPSRT plus placebo [44••]. All patients received up to 20 weekly, 45-min sessions of individual IPSRT. Initial medication dosages were 50mg daily and gradually increased to a maximum dose of 300mg daily. Results revealed that patients receiving the combined IPSRT plus quetiapine treatment had significantly faster improvements in depression and mania scores, though all patients exhibited improvements in depressive symptoms. Of note, the side effect burden over time was significantly higher in the IPSRT plus quetiapine group with patients reporting more oversedation and dry mouth, as well as showing a greater body

mass index increase [44••]. Upcoming studies should evaluate whether the negative side effect burden stemming from the quetiapine adversely affects engagement with the combined treatment over time.

Data suggest that more than half of bipolar patients developed their first symptoms prior to reaching adulthood [37]. Thus, targeted psychosocial interventions for young persons with BD hold particular clinical importance. An initial study of IPSRT in adolescents (IPSRT-A) (n = 13) revealed the feasibility and acceptability of the treatment, as well as its effectiveness in reducing symptoms of depression and mania [45]. Two recent follow-up studies evaluated IPSRT-A for adolescents at risk of developing BD (e.g., due to a family history of the illness) [46, 47]. The first open study involved 12 sessions of IPSRT over a 6-month period. Session content focused on providing psychoeducation about the risk for developing BD, increasing the regularity of social rhythms (e.g., establishing set times for sleeping/waking and other activities), addressing interpersonal difficulties (e.g., conflicts with other family members that could trigger mood episodes), and discussing the patient's feelings about being "at-risk." Post-treatment findings revealed that patients attended approximately half of all treatment sessions, with missed sessions largely attributed to the parent's bipolar illness. Patients also showed more functional circadian rhythm patterns, such as more regular waking times [46]. The authors followed up this promising study with a randomized, controlled trial that evaluated 8 sessions of IPSRT adjunctive to "data-informed referral" or data-informed referral alone (n = 42) [38]. Data-informed referral involved providing patients with referrals for treatment in the community specifically tailored to the patient's diagnostic presentation. Post-treatment findings revealed that patients in the combined treatment group only attended half of the sessions. There were no emergent mood symptoms over follow-up though three patients (one in the IPSRT plus referral group, two in the referral group alone) had sub-threshold (hypo)manic symptoms [38]. As an initial step, future studies of IPSRT-A for adolescents at-risk for BD should focus on overcoming barriers to treatment attendance.

Another recent study of IPSRT in young people (e.g., aged 15–36) already diagnosed with BD randomly assigned patients (n = 100) to receive IPSRT or specialist supportive care (SSC) over a period of 26–78 weeks [48]. SSC was a control treatment that combined elements from supportive psychotherapy and psychoeducation; notably, it did not specifically focus on issues pertaining to social rhythms (e.g., sleep patterns, interpersonal difficulties). There were no significant differences between the groups at post-treatment, with patients in both groups demonstrating improvements in depressive symptoms, manic symptoms, and overall functioning [48]. These findings were maintained at three-year follow-up; specifically, patients in both groups showed sustained decreases in depression and mania though there were still no between-group differences [49]. Overall, this study is most useful in showing the value of an intensive psychotherapy in young patients with BD rather than supporting any particular benefit of a circadian-focused intervention.

Other Recent Social Rhythm-Focused Interventions

Within the past few years, other interventions have incorporated elements that target social rhythm disruption in BD. The Facilitated Integrated Mood Management (FIMM) program is

a five-session intervention that integrates several traditional practices of BD-targeted psychotherapies (e.g., psychoeducation, identification of mood relapse warning signs) in the context of a single treatment program [50]. One element of this program is focused on the stabilization of sleep/wake and daily activity times, thus holding particular application for improving social rhythm dysfunction in BD. During sessions, therapists encourage social rhythm regularity by providing guidance on how patients can maintain regular eating and sleep/wake times, suggesting that patients receive help from a family member in adhering to a regular sleep schedule, educating patients on the importance of abstaining from caffeine towards the end of the day, and promoting the potential benefits of regular meditation, among other topics [50]. A pilot study of this intervention found that it was effective in promoting mood stability and that patients increased their knowledge of mood management strategies from pre- to post-treatment [50]. A recent randomized study assigned patients (n = 121) to receive the 5-session Facilitated Integrated Mood Management intervention or a self-delivered format of the intervention (Manualized Integrated Mood Management) over a 12-week period [51]. Patients randomly assigned to the self-administered program received the Facilitated Integrated Mood Management Intervention manual though did not have any interaction with study therapists. Self-reported depression and mania symptoms did not differ between the groups through the 12-month follow-up period though patients in the Facilitated intervention reported a greater understanding of the bipolar illness at 3-month follow-up, which was associated with more weeks well at 12-month follow-up [51]. Though it is not possible to comment on the independent contribution of the social rhythm-focused elements of the intervention(s), these studies suggest that a mood management program combining elements from varied bipolar psychosocial interventions (including treatment targets focusing on social rhythm regularity) may be effective for patients with BD and also provide some initial evidence that self-administered programs may not be able to replace clinician-guided interventions. This last point is particularly important given the modern rise of mobile interventions that rely on independent self-administration, many of which lack empirical support and evaluation [52].

The prevalence of sleep disturbances among patients with BD has motivated the study of interventions specifically aimed at improving sleep in BD. Cognitive-behavioral therapy for insomnia in BD (CBTI-BP) is an 8-session intervention for patients with BD and insomnia. This intervention includes behavioral elements such as helping patients develop “winding down” activities that can take place in low lighting settings and encourage sleep, identifying ways that patients can ensure regular sleep-wake, exercise, and meal times, and educating patients on the relevance of circadian rhythms in sleep. It also includes cognitive elements such as practicing strategies to decrease anxiety surrounding sleep and modifying any cognitive distortions surrounding sleep [53]. A pilot study randomly assigned patients with bipolar I disorder (n = 58) to receive 8 sessions of CBTI-BP or psychoeducation [53]. Unlike CBTI-BP, psychoeducation did not place a specific emphasis on sleep, instead providing information about the effect of several converging factors (e.g., health behaviors, sleep, mood) on the bipolar illness, and did not supply guidance on behavior modification. Psychoeducation sessions also focused on educating patients about the origins of BD and the importance of medication adherence, among other topics. Post-treatment outcomes revealed that patients receiving CBTI-BP had increased rates of insomnia remission. In addition,

patients receiving CBTI-BP demonstrated a lower (hypo)mania relapse rate and fewer days in a mood episode through 6-month follow-up compared to patients receiving psychoeducation [53]. Overall, CBTI-BP represents a promising avenue for a sleeptargeted intervention in BD.

Another psychosocial intervention for sleep difficulties in BD targeted patients with either insomnia or hypersomnia ($n = 8$), though these data are based on an open, pilot study. Patients received two sessions of a sleep-focused psychosocial intervention that were tailored to the patient's clinical diagnosis of insomnia or hypersomnia [54]. Insomnia session topics included education on the factors that can influence poor sleep (e.g., unhealthy diet, substance use, light, noise) and specific training on the elimination of bedroom activities that are inconsistent with sleep. Hypersomnia session topics included education on the benefits of regular sleep/wake times and the importance of scheduling consistent, daytime activities that provide incentive for getting out of bed. One particularly novel aspect of this study was its inclusion of a device worn on the chest ("M1" device) during sleep that was able to collect electrocardiogram data, which could be used to evaluate sleep quality. Results did not reveal significant improvements across all mood and sleep outcomes, though an important contribution of this study is the feasibility of both the psychosocial sleep intervention and the M1 device [54]. Given the sample size and non-randomized nature of this study, replications of this intervention may be warranted.

Lastly, one study worth noting was not specifically focused on treating circadian rhythm dysregulation but did assess biological rhythms as an outcome [55, 56] Patients were randomly assigned to receive 6, 1-h sessions of psychoeducation adjunctive to treatment-as-usual (e.g., standard pharmacotherapy for BD) or to treatment-as-usual alone [55, 56]. Psychoeducation involved informing patients about BD (e.g.., the biological elements of the disorder), helping patients identify prodromes for mood episodes, and preventing illness relapses. Posttreatment outcomes were similar [55], though the combined treatment yielded marginally better improvements in depression symptoms and increased regularity of sleep and social activity at 6-month follow-up [56]. Both interventions showed effectiveness in managing biological rhythms at 12-month follow-up [56]. These data may lend further support to the notion that a targeted social rhythm treatment is not necessarily essential for a patient to achieve circadian rhythm regularity and experience symptomatic improvement; a psychosocial or pharmacological treatment for BD may be sufficient.

Pharmacological Interventions

Some data suggest that lithium, a classic mood stabilizer historically considered a first-line treatment for acute and maintenance care in BD [57], may be able to benefit circadian rhythm dysregulation in BD [10••]. A recent systematic review collected data from 95 studies and found evidence suggesting that lithium can delay sleep-wake phase rhythms and increase the regularity of daily activities (yielding benefits to social rhythm stabilization), among other positive benefits. Lithium's mechanism of action appears to be associated with previously-established circadian genes (e.g., NR1D1, PER2, ARNTL), affecting the expression of such genes and promoting the release of melatonin [58, 59]. To date, few studies have been conducted with the specific purpose of evaluating lithium as a targeted

treatment for circadian dysfunction. One study compared chronotypes and sleep patterns in euthymic patients with BD currently receiving (n = 149) or not receiving (n = 376) lithium. Patients with bipolar I disorder (but not bipolar II disorder) who were receiving lithium appeared to have better sleep efficiency and increased sleep duration, with this effect being particularly prominent in women [60].

Recent studies have also explored melatonin agonists as pharmacological interventions for stabilizing circadian rhythm disruption in BD. Agomelatine, a melatonin receptor agonist that binds to the melatonin MT1 and MT2 receptors, has been evaluated as a treatment for circadian rhythm dysregulation among patients with mood disorders [61]. However, it has only been minimally studied as a treatment for bipolar depression [62]. An initial open study randomly assigned bipolar depressed patients (n = 21) who were already on lithium or valpromide to receive 25 mg/day of agomelatine for a period of 6 to 46 weeks. By the first week of treatment, nearly half of the study patients showed a response and intent-to-treat analyses revealed that approximately 80% of patients had improvements in their symptoms. However, 4 of the patients who had already been taking lithium experienced emergent mania or hypomania during or after the agomelatine treatment period [63]. This study was followed up by another open study evaluating 6 weeks of 25 mg/day agomelatine adjunctive to lithium or valproate; patients were given the choice to extend their treatment by 30 weeks. Intent-to-treat analyses revealed response in 64% of patients after 6 weeks and in 86% of patients by 36 weeks, with some treatment-linked drop-outs due to the development of mania, hypomania, or insomnia [64]. Most recently, a randomized, controlled study assigned depressed patients with BD who were taking lithium or valproate to 25–50 mg/day of agomelatine (n = 172) or placebo (n = 172) for 8 weeks of acute treatment and 44 weeks of continued care. There were no significant differences between the two groups at post-treatment [65].

Another avenue of melatonin agonist intervention research focused on ramelteon, a sleep-enhancing medication that also exerts its mechanism of action on the MT1 and MT2 receptors in the suprachiasmatic nucleus. Ramelteon has been evaluated in two recent clinical trials with varied results. In the first study, euthymic patients with BD and sleep difficulties (n = 83) were randomly assigned to receive 8 mg/day ramelteon or placebo adjunctive to their standard psychotropic medications for up to 24 weeks or until a mood relapse. Patients receiving ramelteon were less likely to experience a relapse and also had a longer time before relapse [66]. The second study evaluating ramelteon as a maintenance treatment in BD randomly assigned patients (n = 318) to 0.1 mg, 0.4 mg, or 0.8 mg ramelteon or placebo [67]. Results revealed no significant differences between the two treatments though, unlike the agomelatine studies, neither ramelteon study reported serious adverse events associated with the medication [66, 67]. Overall, the mixed findings stemming from studies of ramelteon and agomelatine suggest that a focus on other novel melatonin agonists may be warranted.

Light and Darkness Therapies

Based on a given bipolar patient’s current mood state, a therapeutic approach that modifies light exposure may be clinically indicated. “Virtual darkness” therapies represent one novel

path for treating circadian rhythm disruption with some studies suggesting that darkness can act as a mood stabilizer for manic patients [54]. Laboratory studies have revealed important information about neural pathways that enable light inputs. Neurons known as intrinsically photosensitive retinal ganglion cells (ipRGCs) contain a light-sensitive pigment called melanopsin, enabling them to transmit a daytime signal to the suprachiasmatic nucleus [53, 54]. As ipRGCs suppress the action of the circadian-regulating hormone melatonin, intervening on the light intake of ipRGCs may have important implications for stabilizing bipolar patients' moods and, in turn, their circadian systems. Research has found ipRGCs especially responsive to blue light (which has a wave length of 400 to 500 nm), stemming from the cells' melanopsin which has an absorption spectrum that maps onto the peak wavelength of blue light [68, 69]. In the last several years, studies have evaluated blue light-blocking treatment as a method of "virtual darkness" therapy. An initial open study in this domain evaluated amber-tinted glasses and found the treatment improved sleep in manic patients [70]. Recently, a randomized, controlled trial evaluated 7 days of orange (e.g., blue-blocking) glasses versus placebo (e.g., clear) glasses in manic patients ($n = 23$) adjunctive to treatment-as-usual. Patients wore the glasses from 6pm to 8am while motor activity was assessed with a wrist actigraph. Results indicated greater mania reductions in the blue light-blocking group relative to the placebo group, with gains evidenced as soon as three days after the start of treatment [71••].

The delayed sleep phase of bipolar depression, which marks circadian rhythm dysfunction, may be particularly responsive to bright light at midday [72••]. Research in healthy subjects has found that midday bright light can contribute to a phase advance of melatonin rhythm and increased nighttime melatonin production [73]. A pilot study of bright light therapy in women with BD compared morning versus midday light therapy. Morning light induced a mixed state in 3 out of 4 patients with midday light leading to improvements in 4 out of 5 patients. Based on these findings, 45–60 min of 7000 lux midday light was thought to be most helpful [74]. Thus, a recent follow-up trial randomly assigned patients with bipolar depression ($n = 46$) to receive 7000 lux bright white light or 50 lux dim red placebo light. Relative to patients in the placebo group, patients in the bright white light group demonstrated significantly reduced depression and increased remission rates [72••], confirming the likely benefit of a midday bright light approach in reducing depressive symptomatology.

Conclusions

This review highlights a range of psychosocial, pharmacological, and light-based interventions for circadian rhythm disruption that have been conducted in BD over the past few years. Recent lines of research focused on social rhythm therapy suggest that the treatment may have important benefits in patients with bipolar depression. Specifically, some preliminary data from open studies highlight the possible effectiveness of group IPSRT on depressive outcomes [30, 32] and a seminal study in bipolar II disorder found particular benefits of IPSRT adjunctive to medication on depression *and* mania outcomes (though the combined treatment was associated with a marked side effect burden) [44••]. However, other studies suggest that IPSRT may be no more effective in mood and social rhythm outcomes than other, non-social rhythm targeted psychosocial or pharmacological

interventions [48, 49, 56]. This latter finding could be particularly important for patients in the community who are seeking psychosocial care but do not have access to a specialized IPSRT intervention. According to recent studies, a circadian-targeted intervention may not be entirely necessary for a patient to experience improvement in their social rhythms and overall bipolar illness.

Pharmacotherapy research most consistently supports the potential role of lithium on circadian rhythm regulation [58–60]. Upcoming trials should focus on identifying new targets and pathways for drug-based interventions, particularly as many patients demonstrate lithium intolerance or non-responsiveness [75]. Finally, research on light-based therapies is still in its relative infancy yet represents an exciting avenue for scientific inquiry. Darkness therapy may be able to correct circadian dysregulation in mania whereas bright light therapy may have important circadian benefits in bipolar depression [69, 70, 71••, 72•• 74]. Overall, these recent data indicate that clinicians who are looking to relieve circadian dysregulation in their patients may find that several of these treatments (e.g., lithium, cognitive-behavioral based psychotherapies) exist within the framework of their clinical centers. However, dissemination of specialized psychotherapies (e.g., IPSRT) and cutting-edge technologies (e.g., light and darkness therapies) may be key to helping correct circadian dysregulation in as many bipolar patients as possible.

Conflict of Interest

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