



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 and external processes contrib-

utes 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

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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 non-compliance, 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 sleep-targeted 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. Post-treatment 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.

Compliance with Ethical Standards

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References

Papers of particular interest, published recently, have been highlighted as:

•• Of major importance

1. Murray G, Harvey A. Circadian rhythms and sleep in bipolar disorder. *Bipolar Disord*. 2010;12(5):459–72.
2. Soreca I. Circadian rhythms and sleep in bipolar disorder: implications for pathophysiology and treatment. *Curr Opin Psychiatry*. 2014;27(6):467–71.
3. Gold AK, Sylvia LG. The role of sleep in bipolar disorder. *Nat Sci Sleep*. 2016;8:207–14.
4. Hastings M, O'Neill JS, Maywood ES. Circadian clocks: regulators of endocrine and metabolic rhythms. *J Endocrinol*. 2007;195(2):187–98.
5. Richardson GS. The human circadian system in normal and disordered sleep. *J Clin Psychiatry*. 2005;66:3–9 quiz 42-3.
6. Wehrens SM, Christou S, Isherwood C, Middleton B, Gibbs MA, Archer SN, et al. Meal timing regulates the human circadian system. *Curr Biol*. 2017;27(12):1768–75.e3.
7. Richards J, Gumz ML. Advances in understanding the peripheral circadian clocks. *FASEB J*. 2012;26(9):3602–13.
8. Harvey AG. Sleep and circadian rhythms in bipolar disorder: seeking synchrony, harmony, and regulation. *Am J Psychiatr*. 2008;165(7):820–9.
9. Plante DT, Winkelman JW. Sleep disturbance in bipolar disorder: therapeutic implications. *Am J Psychiatry*. 2008;165(7):830–43.
- 10.•• Takaesu Y. Circadian Rhythm in Bipolar Disorder: A review of the literature. *Psychiatry Clin Neurosci*. 2018. **This recent review discusses mechanisms underlying circadian rhythm disruption in BD, as well as interventions for treating circadian dysfunction.**
11. Brown GM. Light, melatonin and the sleep-wake cycle. *J Psychiatry Neurosci*. 1994;19(5):345–53.
12. Mitchell HA, Weinshenker D. Good night and good luck: norepinephrine in sleep pharmacology. *Biochem Pharmacol*. 2010;79(6):801–9.
13. Kennedy SH, Tighe S, McVEY G, Brown GM. Melatonin and cortisol "switches" during mania, depression, and euthymia in a drug-free bipolar patient. *J Nerv Ment Dis*. 1989;177:300–3.
14. Lewy AJ. *Biochemistry and regulation of mammalian melatonin production*: Elsevier biomedical. New York; 1983.
15. Post RM, Stoddard FJ, Gillin JC, Buchsbaum MS, Runkle DC, Black KE, et al. Alterations in motor activity, sleep, and biochemistry in a cycling manic-depressive patient. *Arch Gen Psychiatry*. 1977;34(4):470–7.
16. Juckel G, Hegerl U, Mavrogiorgou P, Gallinat J, Mager T, Tigges P, et al. Clinical and biological findings in a case with 48-hour bipolar ultrarapid cycling before and during valproate treatment. *J Clin Psychiatry*. 2000;61(8):585–93.
17. Kurita M. Noradrenaline plays a critical role in the switch to a manic episode and treatment of a depressive episode. *Neuropsychiatr Dis Treat*. 2016;12:2373–80.
18. Dell'Osso B, Palazzo MC, Oldani L, Altamura AC. The noradrenergic action in antidepressant treatments: pharmacological and clinical aspects. *CNS Neurosci Ther*. 2011;17(6):723–32.
19. Robillard R, Naismith SL, Hickie IB. Recent advances in sleep-wake cycle and biological rhythms in bipolar disorder. *Curr Psychiatry Rep*. 2013;15(10):402.
20. Harvey AG, Schmidt DA, Scarnà A, Semler CN, Goodwin GM. Sleep-related functioning in euthymic patients with bipolar disorder, patients with insomnia, and subjects without sleep problems. *Am J Psychiatr*. 2005;162(1):50–7.
21. Harvey AG, Lee J, Williams J, Hollon SD, Walker MP, Thompson MA, et al. Improving outcome of psychosocial treatments by enhancing memory and learning. *Perspect Psychol Sci*. 2014;9(2):161–79.
- 22.•• Alloy LB, Ng TH, Titone MK, Boland EM. Circadian rhythm dysregulation in bipolar spectrum disorders. *Curr Psychiatry Rep*. 2017;19(4):21. **This manuscript synthesizes the evidence base supporting circadian rhythm disruption as a relevant mechanism in BD.**
23. Adan A, Archer SN, Hidalgo MP, Di Milia L, Natale V, Randler C. Circadian typology: a comprehensive review. *Chronobiol Int*. 2012;29(9):1153–75.
24. Melo MC, Abreu RL, Neto VBL, de Bruin PF, de Bruin VM. Chronotype and circadian rhythm in bipolar disorder: a systematic review. *Sleep Med Rev*. 2017;34:46–58.
25. Moon JH, Cho CH, Son GH, Geum D, Chung S, Kim H, et al. Advanced circadian phase in mania and delayed circadian phase in mixed mania and depression returned to Normal after treatment of bipolar disorder. *EBioMedicine*. 2016;11:285–95.
26. Hickie IB, Naismith SL, Robillard R, Scott EM, Hermens DF. Manipulating the sleep-wake cycle and circadian rhythms to improve clinical management of major depression. *BMC Med*. 2013;11:79.
27. Ehlers CL, Frank E, Kupfer DJ. Social zeitgebers and biological rhythms: a unified approach to understanding the etiology of depression. *Arch Gen Psychiatry*. 1988;45(10):948–52.
28. Grandin LD, Alloy LB, Abramson LY. The social zeitgeber theory, circadian rhythms, and mood disorders: review and evaluation. *Clin Psychol Rev*. 2006;26(6):679–94.
29. Haynes PL, Gengler D, Kelly M. Social rhythm therapies for mood disorders: an update. *Curr Psychiatry Rep*. 2016;18(8):75.
30. Klerman GL, Weissman MM. Interpersonal psychotherapy of depression: a brief, focused, specific strategy. Jason Aronson, Incorporated; 1994.
31. Frank E. Interpersonal and social rhythm therapy: a means of improving depression and preventing relapse in bipolar disorder. *J Clin Psychol*. 2007;63(5):463–73.
32. Frank E, Swartz HA, Boland E. Interpersonal and social rhythm therapy: an intervention addressing rhythm dysregulation in bipolar disorder. *Dialogues Clin Neurosci*. 2007;9(3).
33. Frank E, Hlastala S, Ritenour A, Houck P, Tu XM, Monk TH, et al. Inducing lifestyle regularity in recovering bipolar disorder patients: results from the maintenance therapies in bipolar disorder protocol. *Biol Psychiatry*. 1997;41(12):1165–73.
34. Frank E, Kupfer DJ, Thase ME, Mallinger AG, Swartz HA, Fagioli AM, et al. Two-year outcomes for interpersonal and social rhythm therapy in individuals with bipolar I disorder. *Arch Gen Psychiatry*. 2005;62(9):996–1004.
35. Frank E, Soreca I, Swartz HA, Fagioli AM, Mallinger AG, Thase ME, et al. The role of interpersonal and social rhythm therapy in improving occupational functioning in patients with bipolar I disorder. *Am J Psychiatry*. 2008;165(12):1559–65.
36. Sachs GS, Thase ME, Otto MW, Bauer M, Miklowitz D, Wisniewski SR, et al. Rationale, design, and methods of the systematic treatment enhancement program for bipolar disorder (STEP-BD). *Biol Psychiatry*. 2003;53(11):1028–42.
37. Miklowitz DJ, Otto MW, Frank E, Reilly-Harrington NA, Wisniewski SR, Kogan JN, et al. Psychosocial treatments for bipolar depression: a 1-year randomized trial from the systematic treatment enhancement program. *Arch Gen Psychiatry*. 2007;64(4):419–26.
38. Swartz HA, Frank E, O'Toole K, Newman N, Kiderman H, Carlson S, et al. Implementing interpersonal and social rhythm therapy for mood disorders across a continuum of care. *Psychiatr Serv*. 2011;62(11):1377–80.
39. Hoberg AA, Ponto J, Nelson PJ, Frye MA. Group interpersonal and social rhythm therapy for bipolar depression. *Perspect Psychiatr Care*. 2013;49(4):226–34.

40. Monk TK, Flaherty JF, Frank E, Hoskinson K, Kupfer DJ. The Social Rhythm Metric: An instrument to quantify the daily rhythms of life. *J Nerv Ment Dis.* 1990.
41. Bouwkamp CG, de Kruiff ME, van Troost TM, Snippe D, Blom MJ, de Winter RF, et al. Interpersonal and social rhythm group therapy for patients with bipolar disorder. *Int J Group Psychother.* 2013;63(1):97–115.
42. Swartz HA, Frank E, Frankel DR, Novick D, Houck P. Psychotherapy as monotherapy for the treatment of bipolar II depression: a proof of concept study. *Bipolar Disord.* 2009;11(1):89–94.
43. Swartz HA, Frank E, Cheng Y. A randomized pilot study of psychotherapy and quetiapine for the acute treatment of bipolar II depression. *Bipolar Disord.* 2012;14(2):211–6.
44. Swartz HA, Rucci P, Thase ME, Wallace M, Carretta E, Celedonia KL, et al. Psychotherapy Alone and Combined With Medication as Treatments for Bipolar II Depression: A Randomized Controlled Trial. *J Clin Psychiatry.* 2018;79(2). **This RCT evaluates IPSRT adjunctive to pharmacotherapy for patients with bipolar II depression.**
45. Hlastala SA, Kotler JS, McClellan JM, McCauley EA. Interpersonal and social rhythm therapy for adolescents with bipolar disorder: treatment development and results from an open trial. *Depress Anxiety.* 2010;27(5):457–64.
46. Goldstein TR, Fersch-Podrat R, Axelson DA, Gilbert A, Hlastala SA, Birmaher B, et al. Early intervention for adolescents at high risk for the development of bipolar disorder: Pilot study of Interpersonal and Social Rhythm Therapy (IPSRT). *Psychotherapy.* 2014;51(1).
47. Goldstein TR, Merranko J, Krantz M, Garcia M, Franzen P, Levenson J, et al. Early intervention for adolescents at-risk for bipolar disorder: a pilot randomized trial of interpersonal and social rhythm therapy (IPSRT). *J Affect Disord.* 2018;235:348–56.
48. Inder ML, Crowe MT, Luty SE, Carter JD, Moor S, Frampton CM, et al. Randomized, controlled trial of interpersonal and social rhythm therapy for young people with bipolar disorder. *Bipolar Disord.* 2015;17(2):128–38.
49. Inder ML, Crowe MT, Moor S, Carter JD, Luty SE, Frampton CM, et al. Three-year follow-up after psychotherapy for young people with bipolar disorder. *Bipolar disorders.* 2017.
50. Miklowitz DJ, Price J, Holmes EA, Rendell J, Bell S, Budge K, et al. Facilitated integrated mood management for adults with bipolar disorder. *Bipolar Disord.* 2012;14(2):185–97.
51. Bilderbeck AC, Atkinson LZ, McMahon HC, Voysey M, Simon J, Price J, et al. Psychoeducation and online mood tracking for patients with bipolar disorder: a randomised controlled trial. *J Affect Disord.* 2016;205:245–51.
52. Buijink A, Visser BJ, Marshall L. Medical apps for smartphones: lack of evidence undermines quality and safety. *Evid Based Med.* 2013;18(3):90–2.
53. Harvey AG, Soehner AM, Kaplan KA, Hein K, Lee J, Kanady J, et al. Treating insomnia improves mood state, sleep, and functioning in bipolar disorder: a pilot randomized controlled trial. *J Consult Clin Psychol.* 2015;83(3):564–77.
54. Sylvia LG, Salcedo S, Bianchi MT, Urdahl A, Nierenberg AA, Deckersbach T. A novel home sleep monitoring device and brief sleep intervention for bipolar disorder: feasibility, tolerability, and preliminary effectiveness. *Cognit Ther Res.* 2014;38(1):55–61.
55. Faria AD, de Mattos Souza LD, de Azevedo CT, Pinheiro KA, Pinheiro RT, da Silva RA, et al. The influence of psychoeducation on regulating biological rhythm in a sample of patients with bipolar II disorder: a randomized clinical trial. *Psychol Res Behav Manag.* 2014;7:167–74.
56. de Azevedo CT, Mondin TC, Reyes AN, Zeni CP, de Mattos Souza LD, da Silva RA, et al. Biological rhythm and bipolar disorder: twelve-month follow-up of a randomized clinical trial. *J Nerv Ment Dis.* 2015;203(10):792–7.
57. Dinan TG. Lithium in bipolar mood disorder: evidence suggests that lithium should still be first choice for prophylactic treatment. *British Medical Journal Publishing Group;* 2002.
58. Moreira J, Geoffroy PA. Lithium and bipolar disorder: impacts from molecular to behavioural circadian rhythms. *Chronobiol Int.* 2016;33(4):351–73.
59. Geoffroy PA, Curis E, Courtin C, Moreira J, Morvillers T, Etain B, Laplanche JL, Bellivier F, Marie-Claire C. Lithium response in bipolar disorders and core clock genes expression. *World J Biol Psychiatry.* 2017;1–14.
60. Geoffroy PA, Samalin L, Llorca PM, Curis E, Bellivier F. Influence of lithium on sleep and chronotypes in remitted patients with bipolar disorder. *J Affect Disord.* 2016;204:32–9.
61. De Berardis D, Marini S, Fornaro M, Srinivasan V, Iasevoli F, Tomasetti C, et al. The melatonergic system in mood and anxiety disorders and the role of agomelatine: implications for clinical practice. *Int J Mol Sci.* 2013;14(6):12458–83.
62. De Berardis D, Fornaro M, Serroni N, Campanella D, Rapini G, Olivieri L, et al. Agomelatine beyond borders: current evidences of its efficacy in disorders other than major depression. *Int J Mol Sci.* 2015;16(1):1111–30.
63. Calabrese JR, Guelfi JD, Perdrizet-Chevallier C, Group ABS. Agomelatine adjunctive therapy for acute bipolar depression: preliminary open data. *Bipolar Disord.* 2007;9(6):628–35.
64. Fornaro M, McCarthy MJ, De Berardis D, De Pasquale C, Tabaton M, Martino M, et al. Adjunctive agomelatine therapy in the treatment of acute bipolar II depression: a preliminary open label study. *Neuropsychiatr Dis Treat.* 2013;9:243.
65. Yatham LN, Vieta E, Goodwin GM, Bourin M, De Bodinat C, Laredo J, et al. Agomelatine or placebo as adjunctive therapy to a mood stabiliser in bipolar I depression: randomised double-blind placebo-controlled trial. *Br J Psychiatry.* 2016;208(1):78–86.
66. Norris ER, Burke K, Correll JR, Zemanek KJ, Leman J, Primelo RA, et al. A double-blind, randomized, placebo-controlled trial of adjunctive ramelteon for the treatment of insomnia and mood stability in patients with euthymic bipolar disorder. *J Affect Disord.* 2013;144(1–2):141–7.
67. Mahableshwarkar AR, Calabrese JR, Macek TA, Budur K, Adefuye A, Dong X, et al. Efficacy and safety of sublingual ramelteon as an adjunctive therapy in the maintenance treatment of bipolar I disorder in adults: a phase 3, randomized controlled trial. *J Affect Disord.* 2017;221:275–82.
68. Phelps J. A powerful non-pharmacologic treatment for mania—virtually. *Bipolar Disord.* 2016;18(4):379–82.
69. Phelps J. Amber lenses for virtual darkness: confirmed as a mood stabilizer. *Med Hypotheses.* 2017;98:1.
70. Phelps J. Dark therapy for bipolar disorder using amber lenses for blue light blockade. *Med Hypotheses.* 2008;70(2):224–9.
71. Henriksen TE, Skrede S, Fasmer OB, Schoeyen H, Leskauskaitė I, Bjørke-Bertheussen J, et al. Blue-blocking glasses as additive treatment for mania: a randomized placebo-controlled trial. *Bipolar Disord.* 2016;18(3):221–32. **This paper describes results from a promising recent study of virtual darkness therapy in BD.**
72. Sit DK, McGowan J, Wiltrout C, Diler RS, Dills J, Luther J, et al. Adjunctive bright light therapy for bipolar depression: a randomized double-blind placebo-controlled trial. *Am J Psychiatr.* 2017;175(2):131–9. **This paper describes results from a promising recent study of bright light therapy in BD.**
73. Hashimoto S, Kohsaka M, Nakamura K, Honma H, Honma S, Honma K. Midday exposure to bright light changes the circadian organization of plasma melatonin rhythm in humans. *Neurosci Lett.* 1997;221(2–3):89–92.
74. Sit D, Wisner KL, Hanusa BH, Stull S, Terman M. Light therapy for bipolar disorder: a case series in women. *Bipolar Disord.* 2007;9(8):918–27.
75. Keltner NL, Folks DG. Alternatives to lithium in the treatment of bipolar disorder. *Perspect Psychiatr Care.* 1991;27(2):36–7.