Sleep and Circadian Rhythms in Bipolar Disorder: Seeking Synchrony, Harmony, and Regulation

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Despite advances in the treatment of bipolar disorder, a significant proportion of patients experience disabling symptoms between episodes, and relapse rates are high. These circumstances suggest that there is a critical need to achieve a mechanistic understanding of triggers of relapse and to target them with specific, empirically derived treatments. Sleep disturbances are among the most prominent correlates of mood episodes and inadequate recovery, yet sleep has been minimally studied in ways that integrate mechanistic understanding and treatment. In this article, the author seeks to define the limits of current knowledge and to specify preliminary clinical implications. Sleep disturbance is important because it impairs quality of life, contributes to relapse, and has adverse consequences for affective functioning. While sleep disturbance and circadian dysregulation are critical pathophysiological elements in bipolar disorder, many questions about the mechanisms that underpin the association remain. The author presents a model that recognizes a role for genetic vulnerability and suggests that there is a bidirectional relationship between daytime affect regulation and nighttime sleep such that an escalating vicious circle of disturbance in affect regulation during the day interferes with nighttime sleep/circadian functioning, and the effects of sleep deprivation contribute to difficulty in affect regulation the following day.

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Despite important advances in pharmacological treatments for bipolar disorder, a high proportion of patients remain highly symptomatic between episodes, and the risk of relapse over 5 years is high (1). This is the case even in patients receiving treatment with both pharmacological and psychological interventions (2). Given these circumstances, there is a critical need to identify the mechanisms that sustain interepisode dysfunction and trigger relapse and to develop methods to target these mechanisms with specific, empirically derived treatments. Sleep disturbance is among the most prominent correlates of mood episodes and inadequate recovery, yet sleep has been minimally studied in ways that integrate mechanistic understanding and treatment.

Methodological Considerations

Several methodological issues should be clarified from the outset. First, *sleep disruption* and *circadian rhythm disturbance* have both been implicated in bipolar disorder. However, they are not identical processes. Although there is an interaction between them, the amount and patterning of sleep depends on many factors, of which the circadian rhythm is only one. Much of the literature on bipolar disorder tends to blur this distinction. The most direct measure of the circadian system is melatonin, which is released by the pineal gland. The most direct measure of the sleep system is the combination of subjective and objective estimates of sleep. Because these systems are interconnected, each is influenced, at least to some extent, by the other.

Second, a distinction can be drawn between insomnia (a subjective perception of inadequate sleep) and sleep deprivation (an objectively measured decrement in sleep). Few studies have adopted a multimethod approach to measuring sleep in bipolar disorder so as to capture both insomnia and sleep deprivation. In this review, I use the umbrella term "sleep disturbance" to encompass both of these manifestations of sleep disturbance as well as other types of sleep disturbance that are characteristic of bipolar disorder, particularly hypersomnia.

Finally, given that research on a medication-free group of bipolar patients is often unfeasible, unethical, and unrepresentative, most studies are based on participants who are taking medications prescribed for bipolar disorder. Several of these medications have sedating or alerting effects and may alter sleep architecture. Strategies for reducing the potential confounding effects of medications are briefly discussed below.

Bipolar Disorder and Sleep Disturbance Often Coexist

Sleep in Episodes

DSM-IV-TR lists three bipolar disorder-related diagnoses: bipolar I, bipolar II, and cyclothymia. Sleep distur-

TABLE 1. Summary of Studies Reporting Sleep Disturbance Across Manic, Depressive, and Mixed Episodes in Bipolar Disorder

Authors and Reference Number	Sleep Disturbance	Polysomnography or Self-Report
Mania		
Clayton and Pitts (3)	Reduced need for sleep in 94%	Self-report
Winokur and Tanna (4)	Reduced need for sleep in 90%, initial insomnia in 34%, terminal insomnia in 24%	Self-report
Loudon et al. (5)	Reduced need for sleep in 69%	Self-report
Carlson and Strober (6)	Reduced need for sleep in 78%	Self-report
Cassidy et al. (7)	Decreased sleep present but of minimal severity in 90%, indisputably present in 78%	Self-report
Serretti and Olgiati (8)	Bipolar I: reduced need for sleep in 99%; bipolar II: reduced need for sleep in 97%	Self-report
Hudson et al. (9)	Relative to healthy non-patients, decreased time spent asleep, increased time awake in the last 2 hours of recording, shortened REM sleep latency, increased REM activity, increased REM density	Polysomnography
Linkowski and Mendlewicz (10)	Relative to healthy comparison subjects, later time of sleep onset (mean of 12:34 a.m. compared with 11:50 p.m.), reduced time from sleep onset to final morning awakening (378 minutes vs. 457 minutes); trend for short REM latency	Polysomnography
Hudson et al. (11)	Relative to healthy non-patients, bipolar and unipolar patients exhibited disturbed sleep continuity, increased percentage of stage 1 sleep, shorter REM latency, increased REM density	Polysomnography
Bipolar depression		
Winokur et al. (12)	Insomnia in 100%, difficulty falling asleep in 58%, early morning awakening in 27%; hypersomnia in 23%	Self-report
Detre et al. (13)	Hypersomnia in 78%, hyposomnia in 17%, restless sleep in 29%	Self-report
Casper et al. (14)	Global sleep disturbance in 85%, early morning awakening in 77%, difficulty falling asleep in 60%, hypersomnia in 23%	Self-report
Duncan et al. (15)	Relative to unipolar patients and healthy nonpatients, greater fragmentation of REM periods	Polysomnography
Gillin et al. (16)	Relative to healthy nonpatients, lower REM latency	Polysomnography
Giles et al. (17)	No differences between bipolar I and bipolar II patients; relative to patients with unipolar depression, longer REM latency and greater total sleep time in bipolar II patients	Polysomnography
Jernjaczyk (18)	Reduced REM latency, greater standard deviation in activity and density of eye movements	Polysomnography
de Maertelaer et al. (19)	Compared with patients with unipolar depression, longer sleep onset latency; trend toward greater number of spindles	Polysomnography
Thase et al. (20)	Relative to healthy non-patients, fewer minutes in stage 1; did not observe shorter mean REM latency, poor sleep continuity, or low stages 3 and 4	Polysomnography
Lauer et al. (21)	Relative to healthy non-patients, both unipolar and bipolar patients exhibited prolonged slow-wave sleep latency, reduced REM latency, and increased REM density	Polysomnography
Fossion et al. (22)	Relative to patients with unipolar depression, trend toward higher percentage of awakenings in bipolar I patients; relative to bipolar II patients, trend toward greater fragmentation of REM sleep in bipolar I patients	Polysomnography
Mixed mood state		
Cassidy et al. (7)	Decreased sleep present but of minimal severity in 100%, indisputably present in 91%	Self-report

bance is listed as a symptom of each; reduced need for sleep is a symptom of manic and hypomanic episodes; and insomnia or hypersomnia are listed as symptoms of major depressive episode.

Shortcomings of the Diagnostic Criteria

Several aspects of the sleep-related diagnostic criteria for bipolar disorder create problems for researchers. For a manic episode, "reduced need for sleep" is not operationalized. Should this be a subjective judgment made by the patient? Should quantitative criteria be adopted, such as the example given in DSM-IV-TR, "feels rested after only 3 hours of sleep"? For a major depressive episode, it is not clear how "insomnia or hypersomnia nearly every day" should be operationalized. Does the patient need to meet DSM-IV-TR criteria for insomnia or hypersomnia most nights for 2 weeks (the duration requirement for the mood symptoms)? What would "nearly every day" equate to? Or should the patient meet the full DSM-IV-TR criteria for insomnia and hypersomnia? The latter both require a duration of 1 month. The hypersomnia criteria are also vague on a critical point, namely, how much sleep would qualify as "excessive sleep." These shortcomings likely arise from the absence of data related to sleep in bipolar disorder.

Sleep Disturbance in Bipolar Episodes

The sleep symptoms are one of a choice of symptoms that may be present for any of the bipolar diagnoses (i.e., they are not required for diagnosis). Hence, we need to establish the proportion of patients who experience sleep problems. The data available to address this question are summarized in Table 1. As shown in the first part of the table, during episodes of mania, the majority of patients (69%–99%) experience reduced need for sleep. Polysomnography in a sleep laboratory, the current gold-standard method for assessing sleep disturbance, was conducted in some studies. While the sample sizes for these studies were small, an association between REM sleep and mania was evident across most. This is interesting because REM sleep has been associated with affective functioning (23).

Studies of sleep during bipolar depression are summarized in the second part of Table 1. The rates of hypersomnia vary between 23% and 78%, and the rates of insomnia vary considerably, with one study reporting insomnia in 100% of depressed bipolar patients. Across the polysomnography studies, a remarkable lack of consensus is evident (23). Only one study was identified that monitored sleep during a mixed episode (third part of Table 1); reduced need for sleep was the common sleep disturbance.

Interepisode Sleep

Significant sleep disturbance is also a feature of the period between episodes. In one study, the sleep pattern exhibited by the bipolar group more closely resembled that of an insomnia comparison group than a group of subjects with normal sleep (24). In another study, Jones et al. (25) observed that the bipolar group exhibited more fragmentation of the sleep/wake rhythm and less day-to-day stability relative to comparison subjects. Millar et al. (26) reported longer sleep onset latency and more night-to-night variability relative to comparison subjects. In the same study, a combination of actigraphy-scored variability in sleep, subjectively estimated sleep onset latency, and subjective sleep duration identified disorder status in 84% of subjects. Sitaram et al. (27) reported higher REM density during the first REM episode and higher percentage of REM sleep in their bipolar group relative to healthy comparison subjects. Finally, Knowles et al. (28) observed more shifts to stage I and more awake or movement time relative to comparison subjects.

Is Sleep Disturbance a State or a Trait?

Is sleep disturbance in bipolar disorder a stable feature in and out of episodes (i.e., trait-like), or does it vary across mood states (i.e., state-like)? Longitudinal data are not available to answer this question. However, taking evidence across studies, it appears that although sleep is significantly impaired during the interepisode period, sleep disturbance escalates just before an episode and worsens still further during an episode.

Focus on REM or Non-REM Sleep, or Both?

Given the findings across the studies published to date (summarized in Table 1), it is not yet clear which aspects of sleep architecture will be of greatest importance in bipolar disorder. This is in contrast to the unipolar depression literature. Abnormalities in the distribution of REM and non-REM sleep, particularly a reduction of REM latency, have been consistently observed in unipolar depression (29). Given the intriguing association between REM sleep and mood regulation in healthy subjects (30) and in unipolar depression (23), as well as the existing data in bipolar disorder (Table 1), it seems likely that REM sleep will be of primary interest in the context of bipolar disorder.

Does Sleep Disturbance Matter?

The data indicating pervasive sleep disturbance in bipolar disorder are of considerable concern for at least three reasons. First, sleep disturbance impairs quality of life. In the absence of bipolar disorder, poor sleep is known to have significant negative psychosocial, occupational, health, and economic effects (31). For example, relative to good sleepers, individuals with chronic sleep disturbances report more psychological distress and impairments in daytime functioning, take sick leave more frequently, and utilize more health care resources. Poor sleep has adverse consequences for mood, motivation, and cognitive functioning (31). It seem highly likely that these negative sequelae of poor sleep have significant functional consequences in individuals with bipolar disorder.

Second, sleep disturbance contributes to relapse. Multiple lines of evidence suggest that sleep disturbance contributes to relapse in bipolar disorder. While any one study alone does not provide strong evidence, the convergence of results is compelling:

Prodromes of episodes. In a systematic review of 73 reports of prodromal symptoms in bipolar disorder and unipolar depression, Jackson et al. (32) found that the majority of patients (over 80%) were able to identify early symptoms. In patients with bipolar disorder, sleep disturbance was the most common prodrome of mania and the sixth most common prodrome of depression.

Sleep deprivation in bipolar patients. A small handful of experimental studies and case studies have reported that induced sleep deprivation is associated with the onset of hypomania or mania in a proportion of patients (e.g., reference 33). In a study of 206 depressed bipolar patients, Colombo et al. (34) treated patients with one night of total sleep deprivation followed by either a recovery night or one of several medications (lithium salts, fluoxetine, amineptine, or pindolol). The results indicated that 4.85% of patients switched into mania and 5.83% switched into hypomania. It seems possible that with more than one night of full or partial sleep deprivation, the proportion of patients relapsing might be much greater.

Prospective monitoring of sleep and mood in bipolar disorder. Table 2 provides a methodological summary of four studies that prospectively monitored sleep and episode status. The study by Bauer et al. (35) found that a decrease in sleep or bed rest was followed by a shift toward hypomania or mania the next day and that an increase in sleep or bed rest was followed by a shift toward depression the next day. The latency between the shifts tended to be about 1 day. Perlman et al. (36) found that shorter sleep duration predicted greater depressive symptoms but not manic symptoms. The Leibenluft et al. (37) study found that shorter sleep duration predicted mania or hypomania the next day; this association was less consistent for depression. Finally, Barbini et al. (38) observed that shorter sleep duration was associated with higher levels of manic symptoms (as reflected in scores on cooperation and irritability scales) the next day. These studies all report an association between sleep disturbance and mood, although the nature of the association—particularly whether it is stronger for manic or depressive symptoms—is less consistent. This variation may be related to differences across the studies in the measures used and the time frames studied.

The third reason for concern about pervasive sleep disturbance in bipolar disorder is that sleep is critical for affect regulation. The three studies summarized in Table 3

TABLE 2. Methodological Summary of Studies That Prospectively Monitored Sleep and Mood in Bipolar Disorder

Authors and Reference Number	N	Subtype	Mood Status	Period of Monitoring	Frequency of Monitoring	Sleep Measure	Mood Measure
Bauer et al. (35)	59	Bipolar I: 37%, bipolar II: 22%	Various	100 days	Daily for mood, hourly for sleep	Endorsed one of "awake," "asleep," or "bed rest"	100-unit scale from mania to depressed
Perlman et al. (36)	54	Bipolar I	30% manic, 43% depressed, 20% mixed or cycling, 7% interepisode	6 months	Once for sleep, monthly for mood	Sleep duration subscale from the Pittsburgh Sleep Quality Index	Modified Hamilton Depression Rating Scale, Bech-Rafaelsen Mania Scale
Leibenluft et al. (37)	11	Not reported	Rapid cycling	18 months	Daily	Daily diary of sleep duration; time of sleep onset; time of wake onset	100-mm line, from 1 ("most depressed ever felt") to 100 ("most manic ever felt")
Barbini et al. (38)	34	Not reported	Manic	3 days	Daily for mood, hourly for sleep	Nurse assessment every 60 minutes	Young Mania Rating Scale

examined the hypothesis that mood is adversely affected by sleep deprivation. Dinges et al. (39) found that mood progressively declined as sleep deprivation accumulated throughout the week. Drake et al. (40) compared the mood responses of participants across four sleep deprivation conditions. Greater mood impairment was evident in the rapid sleep loss group (0 hours in bed) as opposed to the slow, cumulative sleep loss group (6 hours in bed for 4 nights), who experienced more impairment relative to the control group (no sleep loss for 4 nights). Zohar et al. (41) found that context is important for determining the direction of the effect of sleep disturbance on affective functioning: sleep loss appears to intensify negative emotions following a goal-thwarting event as well as to diminish positive emotions following a goal-enhancing event. Although these studies were conducted with healthy volunteers, the observed effects may be greater in patients with bipolar disorder, who presumably have a more vulnerable affect-regulation system.

Mechanisms

The previous section summarized evidence for the importance of sleep for quality of life and for optimal affect regulation. Moreover, the evidence suggests that sleep disturbance can trigger mood episodes in bipolar disorder. In this section, three sets of evidence are presented that address possible mechanisms by which sleep and/or circadian functioning may contribute to bipolar disorder. As Figure 1 suggests, the mechanisms reviewed are not mutually exclusive. Indeed, they are likely to interact in complex and bidirectional ways. The groupings of evidence presented in this section on circadian versus sleep-related mechanisms could be criticized as being arbitrary given the interconnectedness between these systems. However, for clarity to emerge, it is important that we cease the current blurring of the two systems in the bipolar literature by parsing out domains of independence as well as interactions between the two systems. The criterion used to group the evidence was whether the measures or methods used were more likely to be tests of the circadian system (e.g., light, melatonin) or more likely to capture the sleep system (e.g., subjective or objective measures of sleep).

Genetic Vulnerability/Endophenotype

Bipolar disorder is known to be highly heritable. Given that specific gene loci for bipolar disorder have not yet been confirmed, it has been argued that complex psychiatric diagnoses like bipolar disorder need to be decomposed into endophenotypes for genetic analysis to progress (42). Several genes known to be important in the generation and regulation of circadian rhythms and the sleep system are associated with bipolar disorder, including Timeless, Clock (311 T to C), and BMal1. These associations are modest, which is consistent with the proposal that bipolar disorder is likely to be associated with multiple genes of small effect (42).

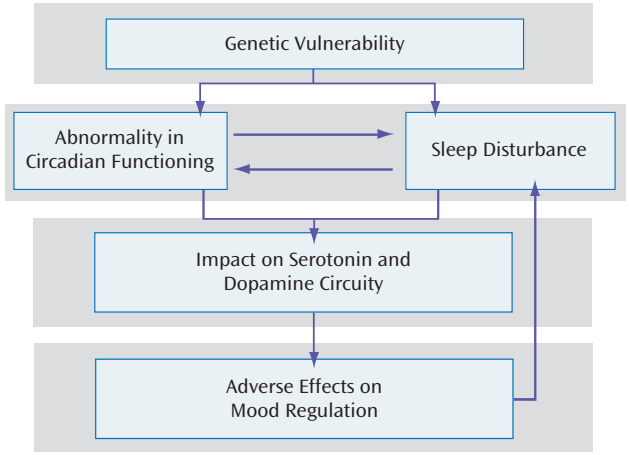
Circadian System

It has been proposed that patients with bipolar disorder have abnormally shifted or arrhythmic circadian systems. The term "circadian" refers to a time frame of "about 1 day" and captures an interesting feature of the circadian clock, namely, that it runs slightly longer or shorter than 24 hours. Evolution has endowed us with a biological system that is highly responsive to *zeitgebers* ("timegivers")—stimuli in the environment that cue the system so that our circadian rhythms become synchronized with the activity in the world around us. Our system is particularly sensitive to the zeitgeber light. An active process known as entrainment keeps our system aligned with external time and allows it to shift as the balance of light and dark varies across the seasons and as we travel from one time zone to another. It is an incredibly simple yet intricately orchestrated system. The "master clock" is located in the suprachiasmatic nucleus (SCN) in the anterior hypothalamus. The SCN governs all circadian rhythms and is supplemented by a large number of peripheral clocks across organs and cells (43). When the system is in harmony, it is fully synchronized by the SCN. But this harmony across systems

TABLE 3. Methodological Summary of Studies of the Impact of Sleep Deprivation on Mood in Healthy Subjects

Authors and Reference Number	Participants	N	Design
Dinges et al. (39)	Healthy young adults	16	Restricted sleep to 5 hours per night for 1 week; tests administered 3 times per day
Drake et al. (40)	Healthy individuals ages 21–35 years	12	All participants completed each of these conditions: no sleep loss for 4 nights, slow sleep loss (6 hours in bed) for 4 nights, intermediate sleep loss (4 hours in bed) for 2 nights, rapid sleep loss (0 hours time in bed) for 1 night; tests administered daily
Zohar et al. (41)	Medical residents	78	Sleep measured with actigraphy; emotion reactivity measured via three phone calls per day; frequency of measurement, 5–7 days every 6 months for 2 years

FIGURE 1. Bidirectional Relationships Between Sleep, Circadian Functioning, and Mood Regulation in Bipolar Disorder



can be easily lost at various junctures, including between the SCN and external time and between the SCN and different organs in the body (43). For the latter, each clock is differentially sensitive to zeitgebers. The SCN is very responsive to light, the clock in the liver is very sensitive to food, and clocks in muscle are sensitive to exercise. So there are many inputs that can influence and contribute to harmony and dysregulation (43).

In the sections below, the evidence implicating the circadian system is reviewed. Again, although any one study or line of evidence is not strong on its own, the convergent evidence is compelling.

Light. Several studies have suggested that bipolar disorder is characterized by enhanced light sensitivity. For example, in a recent study (44) light was administered in the morning or at midday to nine depressed women with bipolar disorder. Three of the four who received light in the morning developed a mixed state, and the other responded well. Four of the five who received midday light responded well. It is possible that the greater impact in the morning reflects an increased sensitivity of the photoreceptors in the eye (44).

Melatonin and cortisol. Melatonin and cortisol are "hands" of the circadian clock that modulate the sleep-wake cycle. In one study, euthymic bipolar patients exhibited lower melatonin levels and a later peak time for melatonin during the night relative to a healthy comparison group (45). In another study, bipolar patients experiencing pure mania exhibited higher cortisol levels during the night and an earlier nadir for plasma cortisol relative to a healthy control group (46).

Lithium. Lithium is an effective mood-stabilizing treatment, but its mechanism of action is not certain. Given evidence across species that lithium slows down circadian periodicity and can modify circadian cycle length (47), it may target dysregulated circadian rhythms. Indeed, in a case series of seven rapid-cycling bipolar patients, five exhibited a circadian rhythm that ran fast, and in these participants lithium slowed the rhythm (48).

Interpersonal and social rhythm therapy. A core concept of the social zeitgeber theory is dysfunction in the circadian system (49). This theory suggests that episodes of depression and mania or hypomania arise as a consequence of life events. These begin a causal cascade of processes: a life event disturbs social zeitgebers such as mealtimes and bedtimes, and these changes then derail the circadian rhythm, triggering relapse. Evidence for the various predictions of this theory is accruing, and the treatment derived from the theory—interpersonal and social rhythm therapy—has been shown to be effective in reducing relapse in bipolar disorder (49). One goal of this treatment is to stabilize social zeitgebers.

Total and partial sleep deprivation. A startling improvement in mood is observed in 40%–60% of depressed bipolar patients after total or partial sleep deprivation (50). However, symptoms of depression quickly return after the patient has slept. Two of the leading explanations implicate a circadian mechanism.

The internal coincidence model proposes that depressed patients are sleeping at the wrong biological clock time because the phase angle between the biological clock and the sleep-wake cycle is out of alignment (51). According to this theory, sleep deprivation is therapeutic because it prevents sleep at the critical phase. But with recovery sleep, the misalignment is reinstated.

The therapeutic effect of sleep deprivation has been proposed to increase homeostatic pressure and thereby counteract the hyperaroused state in depression (43). The two-process model proposes that sleep is modulated by the interaction of a homeostatic process (known as process S) and a circadian process (known as process C). It has been proposed that depression is characterized by a

deficiency in the building up of process S. Sleep deprivation may cause a short-term increase in process S to normal levels (43). Relapse then occurs because process S returns to low levels.

Sleep

At the neural systems level, circuits involved in affect regulation and circuits involved in sleep regulation are known to interact in bidirectional ways (52). For example, in one study (53), healthy participants who were sleep-deprived for 35 hours and those who had slept normally completed an emotional stimulus viewing task (100 images varying in emotional intensity) in an event-related functional MRI design. As expected, both groups exhibited amygdala activation in response to negative stimuli. However, relative to those who slept normally, those who were sleep-deprived exhibited more than 60% greater amygdala activity. This large increase was associated with a loss of activity in the medial-prefrontal cortex, which exerts top-down control on the limbic area (including the amygdala) and functions to modulate emotional responses so they are appropriate for the context. This finding suggests that sleep contributes to maintaining the connectivity between the medial-prefrontal cortex and the amygdala, which is critical for responding appropriately to emotional challenges the next day. Although the study used healthy participants, it is certainly tempting to speculate that this finding is particularly relevant to patients with bipolar disorder, whose emotion regulation system is likely to be even more vulnerable to the adverse consequences of sleep deprivation.

Studies of therapeutic sleep extension also suggest the potential importance of sleep. A promising case study showed that increasing and stabilizing sleep reduced rapid cycling (54). In a preliminary trial of "dark therapy" by Barbini et al. (55), 16 bipolar patients in a manic episode were treated with 14 hours of enforced darkness for 3 consecutive days and 16 others received treatment as usual. Those who received dark therapy exhibited a decrease in manic symptoms compared with the those in the treatment-as-usual group.

Critical Link: How Do Circadian Dysregulation and Sleep Disturbance Trigger Affective Disturbance?

As already noted, although the circadian system and the sleep system are potentially separable, they are interconnected. Several researchers have implicated the serotonin and dopamine systems as the critical links between abnormalities in the sleep and circadian systems and affective functioning in bipolar disorder. Since it would be premature to cite this evidence as more pertinent to circadian versus sleep-related mechanisms, the evidence will be discussed here as likely to be relevant to both.

Evidence for the involvement of the serotonin system includes the finding that serotonin turnover increases immediately after light exposure, and the highest concentrations of CNS serotonin are in the suprachiasmatic nucleus and the raphe nucleus, part of the serotonergic pathway. In addition, there is increased sensitivity of 5-hydroxytryptamine (5-HT) neuronal firing under conditions of sleep deprivation (43). Finally, in patients with bipolar disorder, those who were homozygotic for the long variant of the 5-HT transporter gene were shown to have better mood amelioration after sleep deprivation than those who were heterozygotic and homozygotic for the short variant (56).

Evidence implicating limbic dopaminergic pathways includes the finding that administration of amineptine (a dopamine agonist) before therapeutic sleep deprivation prevented the improvement in depressive symptoms that would typically have been observed. Also, sleep deprivation seems to activate limbic dopamine pathways (indexed by increased limbic blood flow, increased dopamine D_2 receptor occupancy, and increased eye blink rates after total sleep deprivation) (57). Finally, a dopamine reuptake inhibitor has been shown to prevent the antidepressant effect of sleep deprivation (58).

Clinical Implications

The evidence reviewed here suggests that sleep disturbance is commonly comorbid with bipolar disorder, that sleep is important for quality of life and optimal affect regulation, and that onset of sleep disturbance predicts episodes of bipolar disorder. An important direction for future research is to devise new methods of supplementing standard treatment for bipolar disorder to improve sleep and regularize the circadian cycle without interfering with standard therapy. The potential of several such treatment approaches is described below.

Pharmacotherapy

Insomnia. Several classes of medications are used to treat insomnia (e.g., benzodiazepine receptor agonists, sedating antidepressants, and antihistamines). Benzodiazepine receptor agonists represent the treatment of choice when a medication is indicated for treating adults with insomnia (59). However, all hypnotic medications carry some risk of daytime residual effects (e.g., cognitive and psychomotor impairments) as well as risks of tolerance and dependence. These risks vary with dosage, half-life, duration of use, and individual factors (e.g., age, gender). Short-acting medications have fewer residual next-day effects than the long-acting agents (59). When used on a regular and prolonged basis, there are also risks of tolerance and dependence, which vary across individuals. Rebound insomnia is a common problem associated with rapid discontinuation of benzodiazepine hypnotics, particularly after prolonged use. In general, the newer benzodiazepine receptor agonists (e.g., zolpidem and eszopiclone) are less likely to be associated with rebound insomnia on discontinuation. However, few

TABLE 4. Elements of Sleep-Related Content of Cognitive-Behavioral Therapy (CBT) for Insomnia and Other Psychosocial Treatments for Bipolar Disorder

Therapy Component	CBT for Insomnia	Family-Focused Intervention	CBT for Bipolar Disorder	IPSRT[a]
Reduce tension and conflicts (e.g., stressful family relationships) that might disrupt circadian rhythm		Y		
Sleep hygiene	Y	Y	Y	Y
Daily tracking of mood, sleep, and routines	Y	Y	Y	Y
Goal setting to regularize times of going to bed and waking up	Y	Y	Y	Y
Functional analysis of a recent typical night of poor sleep	Y			
Stimulus control	Y			
Sleep restriction	Y			
Cognitive therapy for dysfunctional beliefs about sleep	Y			
Cognitive therapy for sleep-related worry	Y			
Exposure to natural sources of light	Y			Y
Activity scheduling to reduce disruptions of circadian rhythm			Y	
Identifying and coping with prodromes (which may include sleep)			Y	

[a] IPSRT=Interpersonal and Social Rhythm Therapy.

studies have included a follow-up to determine whether gains are sustained after cessation of treatment. Thus, the durability of sleep improvement associated with pharmacological treatment is not well documented. No clinical trials of pharmacological interventions for insomnia in patients with bipolar disorder have been conducted yet, and the interaction of hypnotics and mood-stabilizing medications has not yet been studied.

Hypersomnia. Frye et al. (60) recently reported on a double-blind placebo-controlled study for adjunctive use of modafinil in depressed patients with bipolar disorder. Compared with the placebo group, those who received modafinil had significantly greater improvements in depressive symptoms by week 2, and these gains remained throughout the 6 weeks of administration. Note that response and remission rates were only 44% and 39%, respectively, compared with 23% and 18%, respectively, in the placebo group, and adverse effects included headache, nausea, insomnia, and rapid heart rate. No posttreatment follow-up was reported, so long-term outcomes remain unknown.

Melatonin-related approaches. A positive response to melatonin (3 mg, taken at night) was reported in an open trial of 11 patients with insomnia during mania (61). The melatonin agonists, such as agomelatine and ramelteon, are particularly interesting in the context of bipolar disorder. Agomelatine is promising as it is both an agonist of the melatonin receptors and an antagonist of the serotonin 5-HT_{2C} receptor (43).

Light Therapies

Research on the role of light therapy in the treatment of bipolar disorder is needed. As already discussed, preliminary data suggest that dark therapy may be helpful in reducing mood symptoms (55).

Sleep Deprivation

As noted earlier, mood rapidly improves in a proportion of depressed bipolar patients with one night of sleep deprivation (50). Given that symptoms of depression quickly return after the patient has slept, several approaches are being studied in the hope of extending the therapeutic effects of sleep deprivation by combining it with antidepressant medications, lithium, and light therapy. The initial results are promising (62).

Psychological Therapies

Insomnia. Cognitive-behavioral therapy for insomnia (CBT-I) is a multicomponent treatment (Table 4 lists the specific treatment components) targeting those factors that are presumed to perpetuate sleep disturbances. Several treatment manuals describing the implementation of CBT-I have been published (63). There is robust evidence that CBT-I produces reliable and durable improvements in sleep in adults with insomnia (59).

This approach to treating insomnia has not been studied in the context of bipolar disorder, but with some adaptations it has some potential advantages, including minimal potential for adverse interactions with mood-stabilizing medications, minimal adverse effects, and the likelihood of high acceptability to patients as a nonpharmacological intervention for sleep disturbance. With careful adaptation, this approach has considerable promise in the treatment of insomnia in patients with bipolar disorder. Examples of the type of adaptations that may be necessary include the following:

1. The traditional components of stimulus control involve the therapist providing a detailed rationale for and helping the patient achieve the following: using the bed and bedroom only for sleep (e.g., no television watching); going to bed only when sleepy; getting out of bed and going to another room when unable to fall asleep or return to sleep within 15–20 minutes, and then returning to bed only when sleepy again; and arising in the morning at the same time each day. For patients with bipolar disorder, the second of these—going to bed only when sleepy—may be omitted for those who need to get into bed even though not yet sleepy in order to begin the process of down-regulating sufficiently to fall off to sleep. The

third item—getting out of bed when sleep has been elusive—may need to be adapted to set a minimum time in bed of 6.5 hours to avoid sleep deprivation during the early phase of treatment. It may also need to be adapted for patients at risk of getting caught up in rewarding and arousing activities when they get out of bed. This is likely to be important for those in whom hypomania and mania are often related to elevated achievement motivation, ambitious goal setting, and excessive goal pursuit (64).

2. Sleep restriction involves curtailing time in bed to the actual time slept and gradually increasing it to an optimal sleep duration. The goal is to maximize sleep efficiency (defined as [total sleep time divided by time in bed] × 100) to more than 85%–90%. Because this treatment component is associated with a potential for a small amount of short-term sleep deprivation, a minimum prescription of 6.5 hours in bed may be a wise safety measure.
3. Consideration should be given to adding a therapeutic sleep extension (or "dark therapy") procedure (55) if a patient begins to develop manic symptoms and exposure to natural light sources if a patient begins to develop depressive symptoms.
4. The component targeting dysfunctional beliefs about sleep may need adaptation because some beliefs held by bipolar patients may be true (e.g., sleep deprivation can have serious consequences, such as triggering a manic episode). Hence, this component will need to strike a balance between valuing sleep and reducing fear of poor sleep (because fearfulness/anxiety in the presleep period is antithetical to sleep onset).

Hypersomnia. It is possible that psychological mechanisms contribute to the maintenance of hypersomnia. These include difficulties related to motivation or maintaining interest or sleeping to avoid difficulties. It remains to be determined whether a psychological intervention for hypersomnia would benefit patients with bipolar disorder.

Existing approaches. Several of the psychological interventions for bipolar disorder include one or more components designed to help individuals with their sleep. Table 4 summarizes the similarities and differences in the sleep-related content of the three main psychosocial treatments for bipolar disorder as well as CBT-I, based on a careful review of the treatment manuals for each approach. There are several components in common across all of the treatments, including daily tracking of sleep, regularizing the sleep-wake cycle via goal setting, and education about sleep hygiene. There are also features that are unique to each approach.

Unresolved Issues

Given the data reviewed, advancement of knowledge about the role of sleep and circadian influences on sleep holds promise for providing a scientific basis for new theories of bipolar disorder and developing novel adjunctive interventions that have the potential to improve quality of life, improve affective functioning, and reduce the risk of relapse in bipolar patients. Studies in the small pool of research published to date have tended to be based on small samples and have often used suboptimal indices of sleep. More informative methods would include systematic longitudinal research of daily subjective and objective estimates of sleep following recently published guidelines (65), as well as analyses of the macroarchitecture (e.g., sleep onset latency, REM variables, stages 1, 2, 3, and 4, and wakenings) and microarchitecture (quantitative EEG) of sleep. Data for the latter are particularly scarce in bipolar patients.

As noted earlier, a key challenge in conducting research in this area is the potential confound of mood medications that affect sleep. Strategies to manage this confound include keeping medication use constant, as long as clinically indicated, for the duration of the study; adopting within-subject or prospective designs to minimize intersubject variability in medication use; and excluding patients who are taking highly sedating medications.

Natural history data on sleep in bipolar disorder are needed to improve our understanding of the similarities and differences in sleep across mood states (euthymia, mania, depression, and mixed) and across the diagnostic subtypes (bipolar I, bipolar II, and cyclothymia). The variable presentations of "sleep disturbance" include sleeping too much (hypersomnia), difficulty getting to sleep (sleep onset latency insomnia), difficulty staying asleep (wake after sleep onset insomnia), waking up too early (early morning waking insomnia), delayed circadian phase, and difficulty regularizing the circadian cycle. Each of these may be driven by different mechanisms, and interventions for each are also likely to be different.

The mechanisms underlying the association between sleep and affective functioning in bipolar disorder are not yet understood. Some of the evidence may be accounted for in a simple framework of an escalating, bidirectional vicious circle of disturbance in mood regulation during the day interfering with nighttime sleep and the effects of sleep deprivation contributing to difficulty in affect regulation the following day (Figure 1). However, the role of other systems, such as the hypothalamic-pituitary-adrenal axis and the distribution of REM and non-REM sleep, remain to be understood.

Progress is also needed to parse out the relative contributions of sleep disturbance and circadian dysregulation to bipolar symptoms. Progress on understanding the role of the circadian system in bipolar disorder is hampered by several challenges (43). Cortisol is influenced by stress. Melatonin is suppressed by light (even indoor room light). State-of-the-art methods for delineating the differential contributions, such as constant routine and forced desyn-

chrony, have been developed, but these are practically challenging to carry out with patient groups.

Finally, it will be critical to consider a developmental approach. The emergence of bipolar disorder during childhood and adolescence is of particular concern because early-onset illness appears to have a more severe presentation and course. Minimal data are available on the prevalence and course of sleep disturbance in youths with bipolar disorder. Moreover, research and clinical questions related to the possible link between sleep disturbance and mood have yet to be addressed (see reference 66 for a review). Given the compelling evidence for sleep in learning and motivation, research on and development of interventions targeting sleep in these younger age groups are a high priority.

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