Sleep Disturbance in Bipolar Disorder: Therapeutic Implications

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In this review, the authors detail our current understanding of the crucial role that sleep and its disturbances play in bipolar disorder. Multiple lines of evidence suggest that impaired sleep can induce and predict manic episodes. Similarly, treatment of sleep disturbance may serve as both a target of treatment and a measure of response in mania. The depressive phase of bipolar illness is marked by sleep disturbance that may be amenable to somatic therapies that target sleep and circadian rhythms. Residual insomnia in the euthymic period may represent a vulnerability to affective relapse in susceptible patients. Given the importance of sleep in all phases of bipolar disorder, appropriate evaluation and management of sleep disturbance in patients with bipolar illness is further detailed.

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Sleep disturbance is recognized as an essential aspect of affective illness. A substantial literature exists on this relationship in depressive disorders, and both insomnia and hypersomnia are diagnostic criteria for major depressive episode in DSM-IV-TR (1). Decreased rapid eye movement (REM) latency and slow-wave sleep abnormalities are among the most robust physiological markers of depression, although it is clear that these are nonspecific disturbances seen in many other psychiatric disorders (2). Many reports have suggested the potential causal role of insomnia in the development of depression in patients who have no previous history of depression and in predicting relapse in patients with depression in remission (3–15). Less attention has been paid to impaired sleep in bipolar disorder than in unipolar depression, although its importance has long been recognized, particularly during manic episodes. As Kraepelin noted nearly a century ago:

> The attacks of manic-depressive insanity are invariably accompanied by all kinds of bodily changes. By far the most striking are the disorders of sleep and general nourishment. In mania sleep is in the more severe states of excitement always considerably encroached upon; sometimes there is even almost complete sleeplessness, at most interrupted for a few hours, which may last for weeks, even months… In the states of depression in spite of great need for sleep, it is for the most part sensibly encroached upon; the patients lie for hours, sleepless in bed, … although even in bed they find no refreshment (Kraepelin E, Manic-Depressive Insanity and Paranoia, Edinburgh, Livingstone, 1921 [translated by Barclay RM], p. 44).

Although Kraepelin's observations regarding the sleep-wake cycle in bipolar patients are still applicable in modern psychiatry, our understanding of the biology of sleep regulation and its relationship to bipolar disorder continues to advance. The current understanding of the sleep-wake rhythm posits that it is the product of the combined influences of a circadian oscillation and a homeostatic sleep drive, which act reciprocally to govern sleep onset and maintenance (Figure 1) (16–18). Given the interaction between sleep and circadian processes, it is difficult to discuss one separately from the other, and particularly so in bipolar patients, a population in which disruption of both sleep and circadian rhythms are well-documented phenomena (19, 20).

In this review, we focus primarily on the observable sleep-wake disturbance in the manic, depressed, and euthymic phases of bipolar disorder, with the caveat that it is often unclear whether circadian or homeostatic factors are ultimately responsible for observed sleep disturbances in bipolar patients, as abnormalities in the underlying circadian rhythm or sleep homeostat may manifest as disturbances in the sleep-wake cycle (16, 17). We also discuss various methods of maintaining adequate sleep quality and quantity in individuals with bipolar disorder.

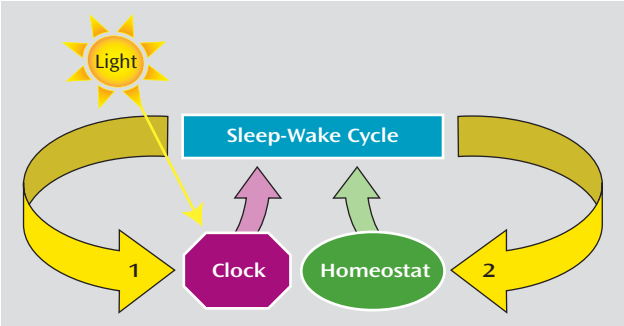
Sleep in Mania

Our current understanding of the relationship between sleep and bipolar mania involves the following aspects: 1) decreased need for sleep is a fundamental marker of the manic state; 2) sleep deprivation is one cause of mania and may in fact be a fundamental etiological agent in mania; 3) total sleep time is a predictor of future manic episodes; and 4) total sleep time may be a marker of response as well as a target of treatment in mania. Each of these relationships is addressed in turn.

Decreased Need for Sleep as a Marker of Mania

Decreased need for sleep is one of the seven diagnostic criteria of bipolar mania, and it may be of particular value in differential diagnosis, since the ability to maintain en-

FIGURE 1. Components of the Sleep-Wake Cycle[a]



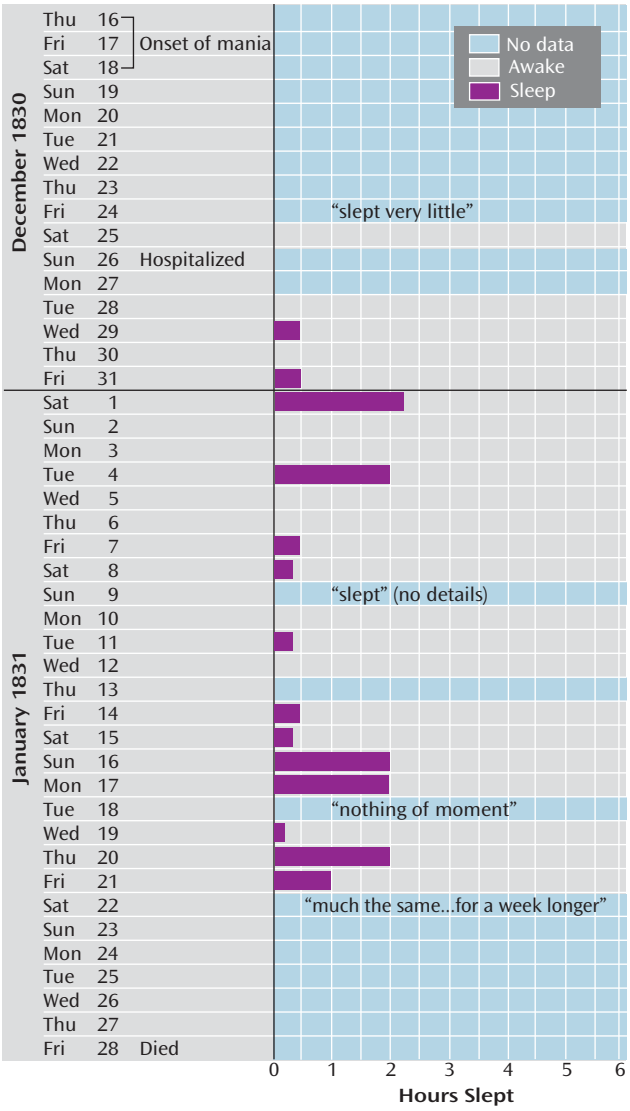
[a] Adapted from Dijk and Lockley (17) with permission from the publisher.

ergy without sufficient sleep is seen in few other disorders (1). Using data from the National Comorbidity Survey, Kessler et al. (21) found that the only manic symptom profile that could be validly assessed with the Composite International Diagnostic Interview, a fully structured interview developed to generate diagnoses according to the definitions and criteria of DSM-III-R and ICD-10, is characterized by euphoria, grandiosity, and the ability to maintain energy without sleep, which described approximately one-half of all clinically validated bipolar I cases in the survey.

Although the ability to maintain energy without sleep is characteristic of mania, manic patients still likely require sleep to sustain life, and thus the nomenclature "decreased need for sleep" may be inaccurate. In the mid-19th century, Bell (22) documented several cases of florid mania characterized by nearly no sleep that typically ended fatally for the patient; one of the notable cases he reported is presented in Figure 2. Such mortality in the presence of sleeplessness is similar to animal models of sleep deprivation, in which death is the outcome of prolonged total sleep deprivation, despite increased food intake (23). In modern times, with improved treatments, manic patients are unlikely to die from prolonged sleeplessness during hospitalization. Historical data do, however, suggest that manic patients, despite prolonged sleeplessness, ultimately have a physiological need for sleep.

That decreased sleep is also characteristic of mania is corroborated by objective measures, such as polysomnography. Although polysomnography in manic patients can be technically quite difficult, polysomnographic studies of unmedicated manic patients have demonstrated shortened total sleep time, increased time awake in bed, and shortened REM latency—similar to polysomnographic parameters seen in depressed patients (24, 25). Polysomnographic measures in manic patients may be affected by motor hyperactivity during the day, since sleep architecture can be affected by increased daytime activity in normal subjects (26). Thus, it is unclear whether polysomnographic abnormalities seen in mania are caused by the manic state per se or are secondary to other features of mania, such as increased levels of physical or mental activity, changes in metabolism, and so forth.

FIGURE 2. Diminished Sleep Duration of a 30-Year-Old Manic Patient Admitted to the McLean Asylum for the Insane, Near Boston, in December 1830, Eventually Resulting in Death[a]

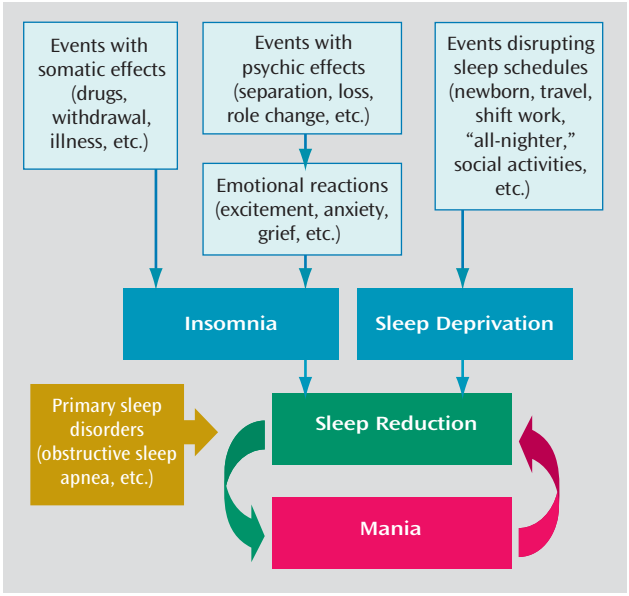


[a] Data originally published in 1849 by Bell (22). The comments in the figure are quoted from Bell's report; in these instances, Bell gave some indication of the patient's sleep status but provided no quantitative data.

Sleep Reduction as a Cause of Mania

The literature posits various triggers in the genesis of mania. Reports describe switches into mania occurring with drugs of abuse, prescribed medications, transmeridian travel, postpartum states, bereavement, and so on, all of which may be associated with sleep loss (27–33). In most such anecdotal reports, it is unclear whether sleeplessness was a cause of the mania or a prodromal symp-

FIGURE 3. Sleep Reduction as a "Final Common Pathway of Mania," Revisited[a]



[a] Adapted from Wehr et al. (39).

tom of mania, and hence we are unable to infer cause and effect from these cases. In some instances, early manic symptoms may have spurred the behavior (e.g., drug use, travel, etc.), which then produced sleep deprivation.

On the other hand, studies of therapeutic sleep deprivation in unipolar and bipolar depression provide clearer evidence of the potential causal, or "switching," properties of sleep deprivation. In the past two decades, work in this area has been performed with well-characterized patients with either rapid-cycling or non-rapid-cycling bipolar disorder. However, the older literature (predating the establishment of definitions of rapid cycling) includes mixtures of patients with both rapid and non-rapid cycling patterns as well as those with unipolar depression. Wu and Bunney (34) reviewed much of the literature from the 1970s and 1980s and found that 29% of bipolar depressed patients and 25% of unspecified depressed patients became hypomanic or manic after one night of total sleep deprivation. Unfortunately, the majority of early sleep deprivation studies were not designed to detect mania; moreover, depressed unipolar and bipolar patients were not distinguished from one another in reported results, and hypomania and mania were often reported post hoc (35, 36). Kasper and Wehr (37), examining sleep deprivation studies whose designs were better suited to predicting the frequency of switching into mania, estimated the risks of hypomania and mania at 12% and 7%, respectively. More recently, Colombo et al. (38) reviewed data from 206 patients who received total sleep deprivation as treatment for bipolar depression (frequently with supplemental medication treatments intended to extend the duration of antidepressant response) and found that switching into hypomania and mania occurred in only 5.8% and 4.9%, respectively, of such patients. One-third of those who switched into mania had resolution of manic symptoms within 3–5 days with nocturnal benzodiazepines, and the remaining patients required mood stabilizers or antipsychotic medications (38). We know of no studies examining rates of manic switching due to sleep deprivation in euthymic bipolar patients, although these patients may theoretically be at greater risk of switching than depressed bipolar patients.

The potency of sleep deprivation as a catalyst to switching in bipolar disorder led Wehr et al. (39) to hypothesize that sleep deprivation is the fundamental proximal cause or "final common pathway" of mania. Wehr et al. noted that all triggers of mania, including biological causes (drugs, hormones, withdrawal, etc.), psychic effects (separation, bereavement, etc.), and direct disturbances of sleep schedules (from newborn infants, shift work, travel, etc.), could be related to the genesis of mania through sleep reduction (Figure 3) (39). This theory posits that sleep deprivation is both a cause and a consequence of mania, and thus mutually self-reinforcing sleep loss perpetuates the manic state. Although prospective testing of this hypothesis is logistically complicated by the fact that sleep deprivation is both a cause and an early symptom of mania, cases of bipolar inpatients who switch into mania after sleep deprivation (from various causes) have been reported, supporting the final common pathway hypothesis (40).

Primary sleep disorders also may contribute to mania in bipolar patients as a result of functional sleep deprivation. In particular, cases of obstructive sleep apnea, in which sleep is disrupted by intermittent obstruction of the upper airway during sleep, leading to repetitive brief arousals, have been documented as a cause of mania or treatment resistance (41–43). Thus, primary sleep disorders may be an additional cause of functional sleep deprivation leading to mania that was not originally included in Wehr's "final common pathway" hypothesis (Figure 3).

Sleep as a Predictor of Mania

If sleep deprivation is a potential trigger for mania, then sleep duration may also be a predictor of mania over the course of the illness. There have been few longitudinal studies of the relationship between sleep and mood in bipolar patients. Wehr et al. (44) followed the course of 15 rapid-cycling and 52 non-rapid-cycling bipolar inpatients (using actigraphy and nurse observation, respectively, for the two groups) and found that the majority of these patients experienced one or more consecutive nights without sleep each time they switched from depressive to manic phases of illness. Leibenluft et al. (45) collected data on 11 rapid-cycling bipolar patients who had filled out sleep logs and twice-daily mood ratings for 18 months. Of the eight patients who had a sufficient number of manic or hypomanic episodes to allow data analysis, sleep duration

predicted the subsequent day's mood in five patients, with increased sleep associated with a decreased probability of hypomania or mania the following day. Similarly, Bauer et al. (46) found that 41% of a mixed population of 59 bipolar I and II outpatients showed a significant correlation between sleep plus bed rest and mood the night before a mood change, with decreased sleep (particularly <3 hours) more predictive of hypomanic or manic symptoms.

Klein et al. (47), in a small, nonrandomized, double-blind crossover study of lithium discontinuation using actigraphy to monitor daytime and nighttime activity patterns in bipolar patients, found that patients who relapsed did not differ from those who did not relapse in estimated sleep efficiency or sleep activity either before or after lithium discontinuation, although significant differences were found in daytime motor activity. Houston et al. (48), using a secondary, post hoc analysis of Young Mania Rating Scale (YMRS) item scores of bipolar patients treated with olanzapine or lithium as part of a maintenance trial, found that increased motor activity and energy was a relatively strong marker of initial manic symptoms. However, the authors also found that a decreased need for sleep occurred in 25% and 10.5% of patients maintained on olanzapine and lithium, respectively, in the 2-week period preceding manic relapse (48). Recently, Perlman et al. (49), using a prospective, longitudinal design, also examined self-reported sleep duration at monthly intervals in bipolar I patients. They found that sleep deficit predicted depressive symptoms during 6-month follow-up but was not predictive of manic episodes. The authors noted several possible reasons for the lack of an association between sleep and mania: manic patients were less likely to complete the sleep measure and were more likely to drop out of the study, and the self-reports of sleep duration were made at monthly intervals, which may not have been frequent enough to detect a relationship between sleep and mania.

Patients' retrospective reports, although they lack the rigor of prospective studies, may also provide insight into the role of sleep in the genesis of manic symptoms. Jackson et al. (50) reviewed 11 such studies of prodromal symptoms in mania and found that sleep disturbance was by far the most commonly reported prodromal symptom (77% of patients) prior to a manic episode. This finding is important, because there is evidence that teaching patients to recognize early symptoms of a manic relapse and to seek early treatment is associated with an increased time to a manic episode and an improvement in occupational and social functioning (51).

Malkoff-Schwartz et al. (52) approached this issue from another perspective, hypothesizing that stressful life events associated with social rhythm disruption (in particular, sleep deprivation) would be commonly observed in prodromal periods prior to an affective episode. In a prospective study of 39 bipolar patients, social rhythm disruption was observed in about two-thirds of manic prodromal periods, which was significantly greater than the frequency observed prior to depressive episodes or control (i.e., euthymic) periods (52). These results were replicated in an expanded follow-up study (53) that included unipolar depressed and rapid-cycling bipolar patients and found that social rhythm disruptions occurred more frequently prior to mania than to other affective episodes. However, other authors have not observed an excess of such stressful life events (although these were generally not assessed for their effects on sleep) during prodromal periods in bipolar disorder (54, 55). Thus, disruption of the daily rhythm may often occur before episodes of mania in bipolar patients, but at present it is not possible to infer a cause-and-effect relationship between sleep disruption stemming from social rhythm disruption and subsequent mania.

Sleep as a Marker of Response and a Therapeutic Target in Mania

If disturbed sleep is a marker of impending or developed mania, is improved sleep an early marker for mania resolution? Using a blinded chart review, Nowlin-Finch et al. (56) found that greater total sleep time on the first night of hospitalization was associated with faster response and earlier discharge among those admitted to an inpatient setting with mania. Barbini et al. (57) compared the duration of nighttime sleep and clinical symptoms in 34 manic inpatients and found a significant correlation between duration of sleep and ratings of cooperation and irritability on the Nurses' Observation Scale for Inpatient Evaluation but no significant correlation with the YMRS. Both of these studies suggest that improved sleep in the inpatient setting may be a harbinger of positive outcomes; a causal relationship has not been demonstrated, however.

Although causality is debatable, clinicians have long used therapeutic agents that target disordered sleep in manic patients. Sedative-hypnotics such as bromides, chloroform, alcohol, and opium were used a century ago to manage agitated psychiatric states. Sedation is still used to treat acute mania, and clinical experience suggests that sedation alone is valuable in managing manic behavior. Whether sleep induced by sedating medications only masks manic symptoms or actually reverses the underlying process responsible for mania is unclear (36). Unfortunately, no systematic studies have been conducted to examine the effects of sedation alone (i.e., with or without induced sleep) on the course of mania.

In recent years, the sedating medications most frequently used in the acute phase of mania have been benzodiazepines and antipsychotics. The literature suggests that the benzodiazepines clonazepam and lorazepam are as effective as neuroleptics as adjunctive medications used with lithium (which does not provide immediate antimanic effects) in the acute management of mania (58, 59). This is further supported by the frequent use of benzodiazepines in clinical trials as rescue medications early on, before the medication of interest has had an opportunity to work. In fact, it is possible that a "placebo" response

in some trials may in fact be the result of benzodiazepine use during the early phases of these trials (60). Atypical antipsychotics are also commonly used to treat acute mania, and indeed, olanzapine, quetiapine, and ziprasidone have all been reported to increase total sleep time in healthy subjects (61–63).

A more novel pharmacological approach to improving sleep in manic patients is the use of melatonin. Melatonin is an endogenous neurohormone secreted by the pineal gland in a circadian fashion under conditions of darkness, whereas light inhibits its secretion. It is theorized to exert its effects through interactions with the suprachiasmatic nucleus, the site of the circadian pacemaker. Bersani and Garavini (64) used melatonin as a hypnotic in 11 outpatients with mania whose insomnia was resistant to benzodiazepines. No other medication changes were allowed during the 30-day open study. A dramatic improvement in subjective sleep duration was observed, concurrent with a marked improvement in manic symptoms. Melatonin is a relatively poor hypnotic, but it seems to influence sleep patterns through its effects on phase-shifting the circadian rhythm, which suggests that this result may be mediated through the circadian system rather than the sleep homeostat (65).

Besides medical management, behavioral interventions that may improve or extend sleep have been used in the treatment for mania for more than a century (66). In the 19th century, before the advent of pharmacological management, prolonged bed rest—the "rest cure" initially advocated by S. Weir Mitchell—was widely used for a variety of neuropsychiatric disorders (66). More recently, investigators have used similar behavioral techniques with some success. Wehr et al. (67) used 14 hours of bed rest as a means of stabilizing a patient with treatment-refractory rapid-cycling bipolar disorder. Although prolonged bed rest did not appear to increase total sleep time, the variability of sleep durations was reduced. Similarly, Barbini et al. (68) found that adding 14 hours of enforced darkness to the treatment regimen of hospitalized manic patients resulted in significant decreases in YMRS scores when treatment occurred within 2 weeks of onset of the manic episode and that patients treated with dark therapy also had shorter hospital stays and required lower doses of antimanic agents. According to nursing observation of sleep duration, manic patients treated with enforced darkness did have more sleep than their counterparts who did not receive this treatment; a caveat to this finding, however, is that nursing observation often overestimates sleep duration (68, 69). The improvements seen with bed rest and enforced darkness may occur through circadian manipulation, since light is the primary *zeitgeber* (timegiver) of the circadian clock, and patients may become better without clear improvement in sleep per se. Moreover, regulated light-dark cycles on inpatient units as a component of milieu therapy may be partly responsible for the therapeutic effects of hospitalization for manic patients.

In summary, multiple lines of evidence suggest that sleep disruption may be an underlying trigger for manic episodes, that sleep improvement in mania may be a clinically useful therapeutic target, and that successful prevention of relapse in mania may rely in part on maintaining adequate sleep. However, the data regarding sleep and mania are limited in several spheres. First, there is a dearth of studies that prospectively assess sleep duration in outpatients with bipolar disorder as a predictor of relapse. Second, outpatient studies have predominantly examined subjective rather than objective measures of sleep duration. Third, there is considerable individual variability in the response to sleep disturbance in patients with bipolar disorder, which suggests that some but not all bipolar patients may be subject to relapse caused by sleep impairment. Finally, there is no prospective evidence that treatment of sleep disturbance in the prodromal period does in fact prevent manic episodes.

Sleep in Bipolar Depression

Differences in sleep in bipolar and unipolar depression could conceivably be of use clinically, for example, in distinguishing between a unipolar and a bipolar depressive episode. Unfortunately, objective studies of sleep quality (using polysomnography, for example) in bipolar depression have generally found similar abnormalities in unipolar and bipolar depression, although limited data suggest that bipolar patients may have more early morning awakenings and greater total REM density than unipolar comparison subjects when matched for age, gender, and severity of symptoms (70). Some clinicians believe that hypersomnia, rather than insomnia, is more indicative of bipolar than unipolar depression (71, 72). However, a comparison of the hypersomnolence of bipolar depression with that of narcolepsy, using the Multiple Sleep Latency Test, an objective measure of excessive sleepiness, found no evidence of excessive daytime sleepiness in bipolar depression, which suggests that bipolar hypersomnolence is more reflective of anergia/fatigue than the true excessive sleepiness seen in other primary sleep disorders (73).

As discussed previously, the use of sleep deprivation as an antidepressant greatly enhanced our understanding of the relationship between sleep and mania. Currently there is little interest in using sleep deprivation to treat depression, either unipolar or bipolar, most likely because of frequent relapse after recovery sleep and the dominance of other areas in mood disorders research, such as pharmacotherapy, neurochemistry, and genetics (74). Still, there are interesting correlates between sleep and bipolar depression that merit discussion.

Although Wu and Bunney (34) found no difference in response to sleep deprivation in bipolar versus unipolar depression when reviewing the older literature, some more recent small studies suggest that bipolar patients may respond more robustly to sleep deprivation. Szuba et al.

(75), in a small prospective study of 37 patients with either unipolar, bipolar I, or bipolar II depression, found that eight of nine (89%) bipolar I subjects responded to partial sleep deprivation, compared with nine of 24 (38%) unipolar subjects. Barbini et al. (76), using a repeated total sleep deprivation protocol in a larger prospective study of 51 patients, found that although all patients had improvement in depressive symptoms, those with bipolar I disorder (N=17), bipolar II disorder (N=8), and a first-episode unipolar disorder (N=9) had significantly greater response to total sleep deprivation than unipolar patients with a history of prior depressive episodes. A small case series examining the role of sleep deprivation during the depressed phase in three rapid-cycling bipolar patients found little response to sleep deprivation early in a depressive episode but more robust responses as the depressive episode progressed, suggesting the possibility that neurobiological substrates underlying bipolar depression might change over the course of the illness, making the depressed phase more amenable to treatment with sleep deprivation (77).

Although sleep deprivation may be an efficacious antidepressant in bipolar depression, its clinical utility as monotherapy is limited by relapse to depression after recovery sleep. Various pharmacological approaches have been studied as potential augmentation strategies to improve or extend the antidepressant effect of sleep deprivation. Numerous reports demonstrate that lithium, the mainstay of treatment of bipolar disorder, may improve response to sleep deprivation and sustain remission in both unipolar and bipolar depressed patients (78–81).

There is evidence that bipolar depressed patients who are homozygotes for the long variant of a functional polymorphism in the transcriptional control region upstream of the coding sequence of the serotonin transporter 5-HTTLPR are more likely to respond to sleep deprivation than those who are heterozygotic or homozygotic for the short variant (82). Smeraldi et al. (83) demonstrated that pindolol, a 5-HT_{1A}/beta-adrenoreceptor blocking agent, significantly improved the response rates of bipolar depressed patients to total sleep deprivation compared with placebo (75% [15/20] versus 15% [3/20]) and that complete response could be maintained with lithium salts alone in 65% of cases.

Besides pharmacological approaches, manipulation of the circadian system has also been used to maintain the antidepressant effects of sleep deprivation in bipolar patients. Bright light in the morning has been shown to sustain antidepressant response to sleep deprivation in bipolar patients and may decrease hospitalization time (84–86). Furthermore, phase advance (e.g., moving the sleep period several hours earlier than usual) of the sleep period after sleep deprivation has been shown to sustain the antidepressant effects of sleep deprivation in both unipolar and bipolar subjects (87–90).

It has been suggested that genetic factors may confer an underlying chronobiological vulnerability for depression, including bipolar depression (18). Polymorphisms in genes related to the circadian mechanism have been linked to depressive relapse (e.g., the CLOCK gene), as well as improved response to sleep deprivation and efficacy of long-term lithium treatment (the gene coding for glycogen synthase kinase 3-β, GSK3-β) in bipolar patients (91–93). Although the mechanism through which lithium provides mood stabilization remains unclear, there has been growing interest recently in its effects on the circadian system through its interaction with GSK3-β (94, 95). Theoretically, desynchronization of internal circadian phase and the environment through genetic polymorphisms could increase the risk of depression in some bipolar patients. This remains speculative at this point, though, and further research is needed to advance such hypotheses.

Despite data suggesting that sleep deprivation in the treatment of bipolar depression may be efficacious, APA's practice guideline on the treatment of bipolar disorder (96) lists it as a novel approach. This is appropriate given limited data comparing it with conventional treatments, concern about switching patients into mania, the logistical difficulties of sleep deprivation on inpatient psychiatric units, and the return of depressive symptoms after recovery sleep. Still, because sleep deprivation is the fastest method known of alleviating depressive symptoms, and because recent data suggest that use of specific adjunctive treatment may prolong its antidepressant response, some have called for renewed interest in the study of sleep deprivation as a somatic therapy (97).

Sleep in Euthymic Bipolar Patients

Although modern classification systems are able to describe diagnostic criteria for bipolar mania and depression, they fail to accurately capture the pathology of the euthymic state. Bipolar disorders are characterized in part by a high frequency of subsyndromal interepisode symptoms (98). Thus, it is not surprising that sleep in bipolar patients may continue to be disturbed during euthymic periods.

A limited number of studies have evaluated polysomnographic anomalies in euthymic bipolar patients. Knowles et al. (99), using polysomnography to follow 10 remitted bipolar patients over 5 nights, found no significant differences between euthymic bipolar patients and age-matched controls except for slightly more frequent arousals in the former. Sitaram et al. (100) found increased REM density and percentage of REM sleep in a population of remitted bipolar patients relative to healthy comparison subjects, as well as an increased sensitivity to the REM-latency-reducing effects of arecoline (an acetylcholine agonist).

More recently, Millar et al. (101), using sleep diaries and actigraphy, compared the sleep of 19 remitted bipolar I patients and 19 age- and gender-matched healthy comparison subjects and found that the remitted bipolar patients had greater sleep onset latency, increased sleep duration,

FIGURE 4. Components of Clinical Interview for Sleep Complaints

Sleep history and assessment
- Nature of complaint (pattern, onset, history, course, duration, severity)
- Predisposing and precipitating factors
- Factors that exacerbate insomnia or improve sleep pattern
- Etiologic factors
- Sleep-wake pattern
- Daytime symptoms (sleepiness, hyperarousal)
- Perceived impact (consequences, impairment)
- Maladaptive conditioning to bedroom environment
- Physiologic or cognitive arousal at bedtime
- Symptoms of other primary sleep disorders
- Sleep environment (bedtime routines, sleep-incompatible behaviors)
- Sleep hygiene practices
- Lifestyle (daily activity, exercise pattern)
- Treatment history (self-help attempts, coping strategies, response to previous treatments)
- Treatment expectations

Medication and substance use
- Sleep medication, home or herbal remedies
- Prescription medications
- Over-the-counter medications (diet pills, antihistamines)
- Alcohol, tobacco, caffeine
- Illicit substances

Medical history and examination
- Medical disorders associated with sleep disruption
- Chronic pain
- Menopausal status (women)
- Prostate disease (men)
- Laboratory testing if indicated

Psychiatric history
- Depressive symptoms
- Anxiety symptoms
- Other mental health disorders (bipolar disorder, schizophrenia, etc.)
- Stress level

[a] Adapted from Edinger and Means (105) with permission from the publisher.

and more night-to-night variability of sleep patterns. Jones et al. (102), using actigraphy to compare the circadian activity patterns of bipolar patients and healthy comparison subjects, found greater variability of activity patterns between days in bipolar patients but no significant differences in sleep parameters (e.g., sleep onset latency) between the two groups. Study subjects were asked to record only their bedtime and getting-up time, and the remaining sleep parameters were calculated from actigraphic measures, which may underestimate sleep latency and waking after sleep onset and overestimate sleep efficiency (102). Finally, recent work by Harvey et al. (103) examining sleep and actigraphy data from euthymic bipolar patients, patients with insomnia, and subjects with good sleep found that 70% of the euthymic bipolar patients exhibited a clinically significant sleep disturbance. Compared with the other groups, the remitted bipolar patients exhibited diminished sleep efficiency, increased anxiety and fear about poor sleep, decreased daytime activity levels, and a tendency to misperceive sleep, with levels of dysfunctional beliefs about sleep comparable to those of nonbipolar patients with insomnia.

Thus, although the number of studies is limited and the results conflicting, bipolar patients do seem to exhibit sleep disturbance in the euthymic period. The observations in these studies lend credence to the notion that impaired sleep may represent vulnerability to relapse into pathological phases of illness. Although this hypothesis is unproven, given the information previously presented connecting both mania and bipolar depression to sleep, sleep disturbance may be a potential therapeutic target in the clinical management of the bipolar patient during the euthymic period.

Evaluation of Sleep Complaints in Bipolar Patients

Given the potential importance of disturbed sleep in stimulating manic episodes and the fact that persistent sleep disturbance is common in euthymia, managing sleep complaints is a fundamental priority in bipolar disorder. It is thus essential that clinicians have an understanding of the disparate causes of sleep problems in bipolar patients and develop a systematic approach to managing sleep complaints. In the following sections, we review the evaluation of sleep disturbances in bipolar disorder and briefly review treatment options.

The comprehensive evaluation of sleep complaints in patients with bipolar disorder is similar to the approach taken with other patients. A thorough sleep history that outlines the nature of the complaint and screens for primary sleep disorders (such as obstructive sleep apnea and restless legs syndrome) as well as other medical and neurological causes of sleep disturbance is crucial (Figure 4) (104, 105). When possible, treatment should be directed toward the underlying cause of the sleep complaint.

We have already alluded to the importance of primary sleep disorders as potential causes of sleep deprivation and manic relapse in bipolar patients. Given that obstructive sleep apnea and restless legs syndrome, two primary sleep disorders associated with sleep impairment, are common in the general population (roughly 2%–4% and 2%–7%, respectively) and potentially more so in psychiatric patients, we recommend screening for these disorders in all patients with sleep complaints and referring them for further evaluation and management as needed (106, 107). A brief screening for obstructive sleep apnea includes attention to the risk factors of excessive weight and large neck circumference (collar size >16.5 inches in men) and whether the patient snores, has difficulty breathing during sleep, or has unexplained excessive daytime sleepiness. Restless legs syndrome can be screened for by inquiring whether the patient experiences an urge to move his or her legs when at rest (often associated with uncomfortable sensations) that is at least temporarily relieved by movement and is most prominent at night.

Little is known about prevalence rates of obstructive sleep apnea in bipolar patients. One large telephone-based survey found that both bipolar disorder and obstructive sleep apnea occurred significantly more fre-

quently in populations with severe (6% and 6.7%, respectively) and moderate daytime sleepiness (3.9% and 4.8%, respectively) than in populations with no daytime sleepiness; rates of co-occurring bipolar disorder and obstructive sleep apnea, however, were not reported (108). Sharafkhaneh et al. (109) found that in a sample of patients in the Veterans Health Administration diagnosed with obstructive sleep apnea, 4.06% also had bipolar disorder, whereas the prevalence of bipolar disorder in the nonapnea (comparison) population was 1.88%. We know of no studies that have examined the rate of restless legs syndrome in patients with bipolar disorder.

Obesity, although not required for the diagnosis of obstructive sleep apnea, is a major risk factor for the development of the disorder and may be critically important in bipolar populations. Fagiolini et al. (110) found that obese patients experienced a greater number of lifetime manic and depressive episodes, and their index affective episodes tended to be more severe and more difficult to treat. One hypothesis was that obesity produced sleep apnea, which disrupted sleep and caused mood destabilization. Obesity in bipolar patients may be iatrogenic, since many of the psychotropic medications used in bipolar disorder are associated with significant weight gain (111). There is evidence to suggest that obesity, male gender, and chronic use of antipsychotic drugs are risk factors for obstructive sleep apnea in psychiatric patients, which may be relevant for patients with bipolar disorder, given the increasing use of atypical antipsychotics in this patient population (112).

Management of Insomnia in Bipolar Patients

Insomnia symptoms, which include difficulty falling asleep, multiple or prolonged awakenings from sleep, inadequate sleep quality, or short overall sleep duration when given enough time for sleep, are common across the spectrum of psychiatric illness, including bipolar disorder. When these symptoms cause impairment, it becomes important to address them; insomnia has been independently associated with significant morbidity, functional impairment, and health care costs (113). The multitude of treatments for insomnia can be broadly grouped into psychotherapeutic and pharmacologic treatments. We discuss each in the context of bipolar disorder.

Psychotherapy for Bipolar Insomnia

The primary psychotherapeutic treatment of insomnia is cognitive-behavioral therapy for insomnia (CBT-I). The efficacy of CBT-I in primary insomnia (insomnia not related to another medical or psychiatric disorder) is well established, and there is some suggestion that it may be more effective than pharmacotherapy (114, 115). Strategies of CBT-I can include sleep restriction therapy, sleep hygiene education, stimulus control therapy, and relaxation training (Table 1) (116). Unfortunately, there are no studies of CBT-I in bipolar insomnia, although most of these techniques could probably be applied without fear of negative outcome in bipolar patients. The exception is sleep restriction therapy, in which time in bed is limited to the number of hours the patient believes he or she is sleeping, which could increase the chances that a bipolar patient will switch to mania (117). Unfortunately, sleep restriction is considered one of the most efficacious CBT-I techniques, and hence the overall value of CBT-I may be limited in bipolar disorder (118). Management of insomnia in bipolar patients using CBT-I also may be complicated by the fact that bipolar patients (particularly those who are rapid cycling) often complain of difficulty arising in the morning and can have mild hypomanic symptoms that intensify over the course of the day, potentially disrupting their ability to sleep at night or adhere to prescribed CBT-I interventions (119, 120).

Psychotherapies used successfully in the treatment of bipolar disorder utilize psychoeducational components that emphasize identification of prodromal symptoms (e.g., sleep disturbance) and the importance of lifestyle regularity, including stabilization of sleep-wake rhythms (121). Colom et al. (122) found that group psychoeducation significantly reduced the number of patients who relapsed and the number of recurrences per patient, as well as the time to recurrences (depressive, manic, hypomanic, and mixed). Interpersonal and social rhythm therapy, which is based on the notion that management of life

TABLE 1. Cognitive and Behavioral Techniques for Insomnia[a]

Stimulus control therapy	A set of instructions designed to reassociate the bed/bedroom with sleep and to re-establish a consistent sleep-wake schedule: (1) Go to bed only when sleepy; (2) get out of bed when unable to sleep; (3) use the bed/bedroom for sleep only (no reading, watching TV, etc.); (4) arise at the same time every morning; (5) no napping.
Sleep restriction therapy	A method designed to curtail time in bed to the actual amount of sleep time. For example, if a patient reports sleeping an average of 6 hours per night out of 8 hours spent in bed, the initial recommended sleep window (from lights out to final arising time) would be 6 hours. Periodic adjustments to this sleep window are made contingent on sleep efficiency until an optimal sleep duration is reached.
Relaxation training	Clinical procedures aimed at reducing somatic tension (e.g., progressive muscle relaxation, autogenic training) or intrusive thoughts at bedtime (e.g., imagery training, meditation) interfering with sleep.
Cognitive therapy	Psychological methods aimed at challenging and changing misconceptions about sleep and faulty beliefs about insomnia and its perceived daytime consequences. Other cognitive procedures may include paradoxical intention or methods aimed at reducing or preventing excessive monitoring of and worrying about insomnia and its correlates/consequences.
Sleep hygiene education	General guidelines about health practices (e.g., diet, exercise, substance use) and environmental factors (e.g., light, noise, temperature) that may promote or interfere with sleep. This may also include some basic information about normal sleep and changes in sleep patterns with aging.

[a] Adapted from Morin et al. (149) with permission from the publisher.

stressors that disrupt patterns (e.g., social patterns, sleep-wake patterns) may improve outcomes in bipolar disorder, has been shown to prolong maintenance and decrease affective relapse (123, 124). Similarly, cognitive-behavioral treatments for bipolar disorder often stress maintenance of sleep-wake patterns through psychoeducational and/or cognitive-behavioral approaches and have been shown to be an efficacious modality in bipolar disorder (125, 126).

Pharmacotherapy for Bipolar Insomnia

The empiric pharmacological treatment of insomnia in bipolar disorder includes benzodiazepines, benzodiazepine receptor agonists (BzRAs), sedating antidepressants, anticonvulsants, sedating antipsychotics, and melatonin receptor agonists. Here we briefly discuss the pros and cons of these medications in the context of bipolar disorder, with the caveat that no medication has been specifically approved for management of insomnia in bipolar disorder.

Benzodiazepines, long considered first-line therapy for insomnia, offer several benefits in the treatment of insomnia, including known efficacy and a wide range of half-lives. No studies have directly demonstrated that using benzodiazepines to improve sleep also improves mood stability in bipolar patients, nor have any controlled trials examined the use of benzodiazepines in prodromal phases of mania. However, in both an uncontrolled retrospective chart review and a prospective open trial at the same institution, clonazepam was found to be effective as a replacement for neuroleptics used adjunctively with lithium in the maintenance treatment of bipolar disorder, although two other trials did not have success with this approach (127–130).

The potential for abuse, tolerance, withdrawal, daytime sedation, and motor/cognitive impairment is often a limiting factor in the use of benzodiazepines for the treatment of insomnia. BzRAs (e.g., zolpidem, zaleplon, and eszopiclone) are similar to traditional benzodiazepines in that they work at the γ-aminobutyric acid (GABA) receptor, but they are more specific to $GABA_A$ receptors containing α-1 subunits. All have short to intermediate half-lives, which reduces the likelihood of daytime carryover and the resultant side effects. Although BzRAs also have potential for tolerance and withdrawal, there is evidence that non-nightly use of BzRAs over 8–12 weeks is not associated with such sequelae (131, 132). Furthermore, newer agents have been studied for extended durations (up to 6 months) without evidence of tolerance or rebound insomnia on discontinuation (133, 134). Although BzRAs are clinically used as hypnotics in bipolar insomnia, we know of no studies to date examining their use as adjunctive medications in the management of bipolar disorder.

Despite evidence that benzodiazepines and BzRAs are effective for insomnia, the agents most commonly prescribed to treat chronic insomnia are sedating antidepressants at low dosages (135). Their use in insomnia has increased dramatically since the early 1990s, probably as a result of concerns about long-term use of BzRAs (including label restrictions on duration of use), widespread use of selective serotonin reuptake inhibitors (SSRIs) in treating depression (which, in contrast to the older antidepressants, are not sedating and may in fact be alerting), and restrictions on access to branded BzRAs by health maintenance organizations. Trazodone and other antidepressants, particularly tricyclics, are known to have the capacity to induce mania in bipolar patients, and there is limited evidence that trazodone may somewhat paradoxically induce manic switching more rapidly than SSRIs (136–138). Thus, we recommend that sedating antidepressants, even at low dosages, be used with caution in patients with bipolar disorder.

Anticonvulsants that are not approved for the treatment of bipolar disorder (gabapentin, topiramate, and tiagabine) are also sometimes used off-label as hypnotics in bipolar patients. This is likely because they are sedating and are not associated with manic switching, and because some other anticonvulsants have demonstrated mood-stabilizing properties. Again, there is little direct evidence to support this strategy specifically in bipolar patients. However, there is some suggestion that gabapentin can improve subjective sleep quality, decrease light sleep, increase REM sleep, and possibly increase slow-wave sleep (139). Similarly, tiagabine may increase slow-wave sleep, although its usefulness as a hypnotic in primary insomnia is limited (140). These agents are probably less effective than benzodiazepines and BzRAs in the treatment of insomnia, and their side effects (cognitive impairment, daytime sedation, etc.) should be considered before prescribing them as hypnotics in bipolar disorder.

Antipsychotics, in particular atypical antipsychotics, are frequently used as adjunctive or primary agents in bipolar disorder, often with the intention of improving sleep, and these agents have gained popularity as off-label sedative-hypnotics in the general population. However, use of antipsychotics solely as hypnotics is controversial, especially given their propensity to cause metabolic abnormalities, daytime sedation, and weight gain and their risk of extrapyramidal symptoms (141). The antipsychotic most commonly used in clinical practice as a sedative-hypnotic is quetiapine, typically in low doses (25–100 mg), which has been shown to increase total sleep time and improve subjective sleep quality in healthy subjects (62). However, clinicians should be cautious in using antipsychotics in the management of bipolar insomnia because antipsychotics may induce or worsen sleep-related movement disorders, such as restless legs syndrome and periodic limb movements of sleep, which may paradoxically diminish quality of sleep (62, 142, 143).

Drugs that act on the melatonin receptor, such as ramelteon and exogenous melatonin, may be useful in the management of bipolar insomnia, particularly in patients

with comorbid substance use, as these agents are not associated with any risk of abuse (144, 145). Although melatonin has shown some promise in treatment-refractory mania in rapid-cycling patients, melatonin and melatonin receptor agonists have not been carefully studied in maintenance treatment of bipolar disorder (64). A case series of five euthymic rapid-cycling patients suggested that exogenous melatonin had little effect on mood or sleep, although melatonin withdrawal delayed sleep onset time and may have had mild mood-elevating effects (146). Thus, the use of agents that target the melatonin receptor in bipolar patients requires further investigation.

Conclusions

It is clear that sleep disturbance, regardless of the underlying mechanism, is of import in the management of patients with bipolar disorder. However, specific cause-and-effect relationships have proven difficult to elucidate. Some researchers have argued that reducing the complex behavioral and symptom patterns seen in bipolar disorder into putative endophenotypes, which would include sleep-wake-related phenotypes, such as circadian rhythm instability, cholinergic sensitivity (and its effects on REM sleep), and response to sleep deprivation, may help tease out any underlying genetic susceptibility and the pathophysiology of the disease spectrum (147, 148). For the time being, however, a pragmatic approach to the management of sleep-related issues in patients with bipolar disorder is warranted. Careful assessment of the quality and quantity of sleep, thoughtful application of behavioral and pharmacological therapy to improve sleep, and screening for co-occurring sleep disorders are critical in the management of this patient population. Further research will no doubt provide a broader evidence base for specific sleep-related modalities in the treatment of bipolar disorder.

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