REVIEW ARTICLE

Bipolar disorder and sleep problems

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Abstract

BACKGROUND: Sleep problems are highly prevalent among patients with bipolar disorder and have a substantial impact on the course of illness.
METHOD: We conducted a series of literature searches using as key words or as items in indexed fields, bipolar disorder and sleep problems. Articles were obtained by searching MEDLINE from 1970 to 2012. In addition, we used other papers cited in articles from these searches, or cited in articles used in our own work.
RESULTS: Disturbance of the sleep/wake cycle has been a core component of bipolar disorder. Reduced total sleep time is a predictor of manic episodes Sleep is disturbed during manic episodes as well as during inter-episode period. Treatment of sleep disturbance in bipolar relies on pharmacotherapy, sleep deprivation with or without light therapy, and psychological treatments.
CONCLUSION: Multiple lines of evidence suggest that sleep disruption may be an underlying trigger for manic and depressive episodes that sleep improvement may be a clinically useful therapeutic target, and that successful prevention of relapse may rely in part on maintaining adequate sleep.

Introduction

Bipolar disorder (BD) is a common, severe, chronic, and often life-threatening condition. Treatment of bipolar disorder typically involves pharmacotherapy. Bipolar disorder is ranked in the top 10 leading causes of disability worldwid (WHO 2001), affecting as many as 1 in 25 individuals (Kessler *et al* 2005). Despite important advances in pharmacotherapy for BD, many of patients remain symptomatic between episodes (MacQueen *et al* 2003). Even in patients with continued adherence to medication regimens, the risk of relapse over a 5-year period has been estimated to be as high as 73% (Gitlin *et al* 1995). Bipolar disorder is characterized by mood disturbance, typically comprising manic episodes and depressive episodes (APA 2000). Bipolar disorder is also associated with significant sleep disturbance. During mania there is a reduced need for sleep. During depression individuals typically suffer from insomnia or hypersomnia. Surprisingly, novel evidence suggests that sleep disturbance continues even hen individuals are inter-episode (Harvey *et al* 2005; Millar *et al* 2004). The inter-episode period is also important because patients suffer from other significant symptomatology and impairment, including mood dysregulation (MacQueen *et al* 2003).

Method

We conducted a series of literature searches using as key words or as items in indexed fields, bipolar disorder and sleep problems. Articles were obtained by searching MEDLINE from 1970 to 2012. In order to explore this topic, we conducted a series of literature searches using, as key words or as items in indexed fields, bipolar disorder, mania, bipolar depression, sleep problems, insomnia, and hypersomnia. In addition, we used other papers cited in articles from these searches, or cited in articles used in our own work. Articles were selected for inclusion based on the following considerations: numbers of studied patients, using of diagnostic criteria, and validated methods of assessment.

Bipolar disorder and sleep

Reduced need for sleep is a symptom of manic and hypomanic episodes; and insomnia or hypersomnia are listed as symptoms of depressive episode, but also could appear between episodes. Systematic review of 11 studies involving 631 BD patients, sleep disturbance was the most frequent prodrome of mania (reported by 77% of patients) and the sixth most frequent prodrome of bipolar depression (24% of patients) (Jackson *et al* 2003).

Sleep in bipolar mania

One of the most striking findings in mania is the lack of need for sleep and there is evidence that sleep deprivation may be both antidepressant and promanic. During episodes of mania, the majority of patients (69–99%) experience reduced need for sleep (Harvey 2008). Polysomnography in a sleep laboratory was conducted in some studies. An association between REM sleep and mania was evident across most. This is interesting because REM sleep has been associated with affective functioning (Cartwright *et al* 2003).The interplay between bipolar mania and sleep covers the several levels (Plante & Winkelman 2008):

Disturbance of the sleep/wake cycle has been a core component of theoretical and diagnostic conceptualization of BD. Decreased need for sleep and the ability to maintain energy without sufficient sleep is one of the basic symptoms of the diagnostic criteria of mania with particular value also in differential diagnosis (APA 2000). Polysomnographic studies of unmedicated patients in mania have demonstrated shortened total sleep time, increased time awake in bed, and shortened REM latency – similar to findings seen in depressed patients (Hudson *et al* 1992). Although the ability to maintain energy without sleep is typical for mania, these patients still likely require sleep to sustain life. In the mid-19th century, Bell (1849) described several cases characterized by nearly no sleep that ended fatally. It has been hypothesized that BD patients have a genetic vulnerability that may take the form of circadian rhythm instability (Wehr *et al* 1987, Wirz-Justice *et al* 2005).

An experimentally induced sleep deprivation is associated with the onset of hypomania or mania in a considerable proportion of patients. Several authors described switches into mania occurring in situations which may be associated with sleep loss, like transmeridian travels, using street drugs or alcohol, prescribed medications, postpartum states, bereavement, and so on (Davenport & Adland 1982, Jauhar & Weller 1982, Rosenman & Tayler 1986, Young 1995, Peet & Peters 1995). Studies of therapeutic sleep deprivation in BD found evidence of "switching," properties of this strategy. Kasper and Wehr (1992), examining sleep deprivation studies estimated the risks of hypomania and mania at 12% and 7%, respectively. Colombo *et al* (1999) reviewed data from 206 patients who received total sleep deprivation as treatment for bipolar depression and found that switching into hypomania and mania occurred in only 5.8% and 4.9%, respectively. There is no available information about studies examining rates of manic induction due to sleep deprivation in euthymic bipolar patients. This potency of sleep deprivation to switching in bipolar disorder led Wehr *et al* (1987) to hypothesize that sleep deprivation is the fundamental proximal cause or "final common pathway" of mania. Authors noted that all triggers of mania, including biological causes (drugs, hormones, withdrawal syndrome, etc.), psychic effects (separation, bereavement, etc.), and direct disturbances of sleep schedules (travel, shift work, infant etc.), could be related to the ethiopathogenesis of mania through sleep reduction (Wehr 1991).

Total sleep time is a predictor of manic episodes – Wehr *et al* (1982) followed the course of 15 rapid-cycling and 52 non-rapid-cycling bipolar inpatients and found that the majority of both groups experienced one or more consecutive nights without sleep each time they switched from depression to mania. Leibenluft *et al* (1996) collected data on 11 rapid-cycling bipolar patients for 18 months. 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. Bauer *et al* (2006) 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 more predictive of hypomanic or manic symptoms. Houston *et al* (2005), using a secondary, post hoc analysis of Young Mania Rating Scale item scores of bipolar patients treated with olanzapine or lithium, found that increased motor activity and energy was a predictor 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 (Houston *et al* 2005). Perlman *et al* (2006), using a prospective, longitudinal design, also examined self-reported sleep dura-

tion at monthly intervals in bipolar I patients. Sleep deficit predicted depressive symptoms during 6-month follow-up but was not predictive of manic episodes. Jackson *et al* (2003) reviewed 11 retrospective 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. 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 (Perry *et al* 1999).

Malkoff-Schwartz *et al* (1998) studied this problem 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 euthymic periods. These results were replicated in an expanded follow-up study (Malkoff-Schwartz *et al* 2000) 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 during prodromal periods in bipolar disorder (Sclare & Creed 1990, McPherson *et al* 1993).

Nowlin-Finch *et al* (1994) found that greater total sleep time on the first night of hospitalization was associated with earlier response among patients admitted with mania. Barbini *et al* (1996) 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 (Young Mania Rating Scale).

Primary sleep disorders also may contribute to mania in BD as a result of functional sleep deprivation. For example, sleep in patients with obstructive sleep apnea is disrupted by intermittent obstruction of the upper airway, leading to repetitive brief arousals. This condition has been documented as a cause of mania or treatment resistance (Strakowski *et al* 1991).

Sleep during bipolar depression

Comparative studies found that hypersomnia is more prevalent in BP depression than in unipolar depression (Akiskal and Benazzi 2005, Bowden 2005, Benazzi 2006), and also that hypersomnia is highly recurrent across separate episodes of BP depression (Leibenluft *et al* 1995, Kaplan *et al* 2011). Estimates of hypersomnia in BD depression range from 38% (Akiskal and Benazzi 2005) to 78% (Detre *et al* 1972). A comparison of the hypersomnia in patients with BD depression with patients with narcolepsy found no evidence of excessive daytime sleepiness in BD depression (Nofzinger *et al* 1991). This result suggests that hypersomnia in patients with BD depression is probably more related to anergia and fatigue than to the real excessive sleepiness typical for the primary sleep disorders. Sleep studies of bipolar depression showed the rates of hypersomnia between 23% and 78%, and the rates of insomnia vary considerably, with one study reporting insomnia in 100% of depressed bipolar patients (Harvey 2008). Also across the polysomnography studies, a remarkable lack of consensus is evident. (Cartwright *et al* 2003). Studies of sleep quality have generally found similar abnormalities in unipolar and bipolar depression. Limited data suggest that BD patients may have more early morning awakenings and greater total REM density than unipolar subjects when matched for age, gender, and symptoms severity (Riemann *et al* 2002).

BD patients may respond better to SD (sleep deprivation) in comparison with unipolar patients. Szuba *et al* (1991), in a study of 37 either unipolar, bipolar I, or bipolar II depression patients, found that 8 of 9 BD I subjects responded to partial SD, compared with only 9 of 24 unipolar patients. Barbini *et al* (1998), using a repeated total SD in 51 patients, found that patients with BD I (n=17), BD II (n=8), and a first-episode (n=9) had more robust response than those with recurrent unipolar depression. A case series studying the role of SD during the depressed phase in 3 rapid-cycling subjects found small response to SD early in a depressive episode but more robust response as episode of depression progressed (Gill *et al* 1993). Several strategies were studied to extend the effect of SD. Some studies demonstrated that lithium administration may improve response to SD and sustain remission (Baxter *et al* 1986, Grube and Hartwich 1990, Szuba *et al* 1994, Benedetti *et al* 1999). Benedetti *et al* (1999) showed that 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) have higher probability to respond to SD than patients who are heterozygotic or homozygotic for the short variant. Smeraldi *et al* (1999) showed that a 5-HT1A/beta-adrenoreceptor blocker pindolol increased the response rates of BD depressed patients to total SD in comparison with placebo (75% versus 15%) and this response was maintained with lithium. Polymorphisms in genes related to the circadian rhythms have been linked to depressive relapse, as well as improved response to SD and efficacy of treatment with lithium (the gene coding for glykogen synthase kinase 3-β, GSK3-β) in BD subjects (Benedetti *et al* 2003, Benedetti *et al* 2004, Benedetti *et al* 2005). There is growing interest in lithium effects on the circadian rhythms through interaction with GSK3-β (Gould *et al* 2005, Yin *et al* 2006). Desynchronization of internal circadian phase and the environment through genetic polymorphisms could increase the risk of BD depression.

Manipulations of the circadian rhythms have also been used to maintain the antidepressant effects of sleep deprivation in BD patients (Wirz-Justice *et al* 2005). Morning administered bright light therapy has been shown to sustain antidepressant response to SD in BD subjects (Benedetti *et al* 2005, Colombo *et al* 2000, Benedetti *et al* 2001). Also phase advance of the sleep period after SD has been shown to sustain the antidepressant effects of SD in BD patients (Berger *et al* 1997, Reimann *et al* 1999, Neumeister *et al* 1996, Benedetti *et al* 2001).

Sleep disturbances between episodes

There is high frequency of subsyndromal inter-episode symptoms in BD patients (Sachs 2003). In terms of the sleep–mood cycle, in inter-episode bipolar disorder there is already some evidence to support the theory that sleep disturbance influences daytime mood. Sleep disturbance is associated with manic episode onset in a majority of individuals with bipolar disorder (Jackson *et al* 2003; Wehr *et al* 1987), and other study observed that sleep disturbance predicted depressive symptoms (Perlman *et al* 2006). Bauer *et al* (2006) used the cross correlation function to examine the particular time lag that maximized the sleep–mood relationship, observing that mood shifts toward depression or mania most commonly occurred the morning immediately after a sleep change. In the study of Talbot *et al* (2012) which compared participants with inter-episode bipolar disorder (n=49), insomnia (n=34), and no psychiatric history (n=52) the inter-episode bipolar and insomnia participants exhibited greater sleep disturbance than the healthy control individuals. Negative mood was equally heightened in both inter-episode bipolar disorder and insomnia, and there were no differences between the three groups in positive mood. Total wake time was associated with next morning negative mood in bipolar disorder, whereas evening negative mood was associated with subsequent total wake time in both bipolar disorder and insomnia.

A few studies have evaluated polysomnographic findings in euthymic BD patients. Knowles *et al* (1986), measured polysomnography in 10 remitted BD patients over 5 nights, found no significant differences between euthymic BD patients and age-matched controls except for more shifts to stage I and more awake or movement time in BD. Sitaram *et al* (1982) reported increased REM density during the first REM episode and higher percentage of REM sleep in a population of remitted BD patients in comparison with healthy controls, and an increased sensitivity to the REM-latency-reducing effects of arecoline. Millar *et al* (2004) compared the sleep of 19 remitted BD I patients and 19 healthy controls using sleep diaries and actigraphy. Authors reported that the remitted BP subjects had longer sleep onset latency, increased sleep duration, and more night-to-night variability of sleep patterns. Combination of actigraphy-scored variability in sleep, subjectively estimated sleep onset latency, and subjective sleep duration identified disorder status in 84% of subjects in the same study. Jones *et al* (2005), using actigraphy to compare the circadian activity patterns of bipolar patients and healthy controls, observed greater variability of activity patterns between days in BD patients, more fragmentation of the sleep/wake rhythm, but no significant differences in sleep parameters between groups. Harvey *et al* (2005) studied sleep and actigraphy data from euthymic BD subjects, patients with insomnia, and controls with good sleep and found that 70% of the euthymic BD patients exhibited a clinically significant sleep disturbance (diminished sleep efficiency, increased anxiety and fear about poor sleep, decreased daytime activity levels, and a tendency to misperceive sleep), and dysfunctional beliefs about sleep comparable to non-bipolar patients with insomnia. Approximately 25% of BD patients suffer with hypersomnia during inter-episode period (Kaplan *et al* 2011). This rate is less than the prevalence of hypersomnia in bipolar depression (Akiskal & Benazzi 2005). Hypersomnia in the inter-episode period is typically associated with future depressive symptoms.

A study aimed to clarify the association between inter-episode BD and sleep architecture (Eidelman *et al* 2010). Included were 22 adults with BD I or II (inter-episode) and 22 non-psychiatric controls. The sleep assessment was at a sleep disorders laboratory. Follow-up assessments 3 months later were conducted over the phone. At the sleep assessment, BD participants exhibited greater rapid eye movement sleep (REM) density than control participants with no other group differences in sleep architecture. Sleep architecture was not correlated with concurrent mood symptoms in either group. In the BD group, duration of the first REM period and slow-wave sleep (SWS) amount were positively correlated with manic symptoms and impairment at 3 months, while REM density was positively correlated with depressive symptoms and impairment at 3 months. The amount of Stage 2 sleep was negatively correlated with manic symptoms and impairment at 3 months. In contrast, for the control group, REM density was negatively correlated with impairment at 3 months. Study findings suggest that inter-episode REM sleep, SWS and Stage 2 sleep are correlated with future manic and depressive symptoms and impairment in BD. This is consistent with the proposition that sleep architecture may be a mechanism of illness maintenance in BD (Eidelman *et al* 2010).

Impact of sleep problem in patients with bipolar disorder

Poor sleep is known to have significant negative psychosocial, occupational, health, and economic effects (Ancoli-Israel & Roth 1999). Multiple lines of evidence suggest that sleep disturbance contributes to relapse in bipolar disorder (Harvey 2008):

Early warning signs (known as prodromes) of a mood relapse include sleep disturbance. (Lam & Wong 2005, Mantere *et al* 2008, Goossens *et al* 2010,(Latalova *et al* 2012). Disruption of social rhythms and normal sleep-wake cycle may specifically lead to provocation of manic episodes, but not depression (Malkoff-Schwartz *et al* 1998). A retrospective study found a relationship between stressful life events and the onset of manic episodes in BD patients and this relationship was particularly strong for events involving a disruption of social rhythm with sleep deprivation (Malkoff-Schwartz *et al* 2000). In a review of 73 reports of prodromal symptoms in BD and unipolar depression, Jackson *et al* (2003) found that over 80% of subjects were able to identify early symptoms. Sleep disturbance was the most common prodrome of mania and the sixth most common prodrome of depression.

Sleep deprivation in bipolar patients is associated with the onset of hypomania or mania in a proportion of BD patients (Wehr *et al* 1982). In a study of 206 depressed bipolar patients, treated with one night of total sleep deprivation followed by either a recovery night or one of the several medications (amineptine, fluoxetine, lithium, or pindolol), 4.85% of patients switched into mania and 5.83% switched into hypomania. (Colombo *et al* 1999).

Decreased or increased in sleep is followed by the episode of the disorder. Leibenluft *et al* (1996) study reported that shorter sleep duration predicted mania or hypomania the next day; this association was less consistent for depression. Barbini *et al* (1996) 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. However, Perlman *et al* (2006) found that shorter sleep duration predicted more depressive symptoms but not manic symptoms. Bauer *et al* (2006) observed that a decrease in sleep or bed rest was followed by hypomania or mania the next day and that an increase in sleep or bed rest was followed by depression the next day. All these studies reported 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.

Sleep and affect regulation

Quality of sleep and its regularity could be critical for affect regulation (Harvey 2008, Prasko *et al* 2010). Dinges *et al* (1997) observed that mood progressively decreased as sleep deprivation accumulated throughout the week. Drake *et al* (2001) compared the mood responses of participants across 4 SD conditions. More robust mood decrease 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 showed more impairment relative to the control group (no sleep loss for 4 nights). Zohar *et al* (2005) reported influence of the context for determining the direction of the effect of sleep deprivation 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 BD, who presumably have a more vulnerable affect-regulation system (Gruber *et al* 2011).

Sleep and circadian rhythms in bipolar disorder

Bipolar disorder is associated with disturbances in the body´s natural rhythms; the most clinically evident of these is the disruption of the sleep-wake cycle, but the temperature cycle, cortisol cycle, and others are also affected (Hallonquist *et al* 1986). Circadian rhythm disturbance and sleep problems have both been observed in BD (Kripke *et al* 1978, Kasper *et al* 1992, Jones et 2005, Harvey 2008). The structure and timing of sleep/wake rhythm is considered to arise from combined influences of the circadian pacemaker (designated "process C") and a homeostatic sleep process dependent on duration of prior time awakening ("process S") (Borbély and Achermann 2000, Illnerova *et al* 2000). These two processes act reciprocally to govern sleep onset and maintenance (Dijk & Lockley 2002, Richardson 2005, Wirz-Justice 2005). These systems are interconnected, influencing to some extent each other BD is known to be highly heritable although specific gene loci for BD have not yet been confirmed (Mansour *et al* 2005). Several genes known to be important in the generation and regulation of circadian rhythms and the sleep system are associated with BD, including Timeless, Clock (311 T to C), and BMal1. These associations are modest, which is consistent with the proposal that vulnerability for BD is likely to be associated with multiple genes of small effect (Mansour *et al* 2005).

BD would not be described as a simple clock gene mutation. Rather, internal desynchronization may be a major conducing factor to emotional state. The clock genes in the SCN gradually adapt to a phase shift of the light and dark cycle, whereas clock genes in muscle, liver, and lung resynchronize at their own rates (Yamazaki *et al* 2000).

This results in a double desynchronization, not only between internal (SCN) and external time, but also between different clocks and organs in the body (Schibler *et al* 2003).

It has been proposed that patients with BD have desynchronizated circadian systems (Kripke *et al* 1978, Wehr *et al* 1982, Wehr *et al* 1987, Wirz-Justice *et al* 2005). Associated with such changes is a decoupling or the major and minor oscillators located in the hypothalamus, which in healthy subjects work in a synchronized fashion. Lithium administration causes the oscillators to resynchronize (DeMet & Chicz-Demet 1987, Klemfuss 1992) The mechanism by which resynchronization

occurs is unknown; it is probably not via the inositol depletion mechanism (Lakin-Thomas 1993). A causal relation has not been established for circadian rhythm abnormalities and bipolar disorder; the changes seen in circadian rhythms could be a cause of BD or could be an effect of the disease process.

Several studies have suggested that BD is characterized by enhanced light sensitivity (Neumeister *et al* 1996, Nurnberger *et al* 2000, Wirz-Justice *et al* 2005). Sit *et al* (2007) administered bright light in the morning or at midday to nine depressed women with BD. 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. Lithium may target dysregulated circadian rhythms, slows down circadian periodicity and can modify circadian cycle length across species (Abe *et al* 2000).

Melatonin and cortisol are hormones of the circadian clock that modulate the sleep/wake cycle. BD patients experiencing pure mania exhibited higher cortisol levels during the night and an earlier nadir for plasma cortisol relative to a healthy control group (Linkowski *et al* 1994). In the Nurnberger *et al* (2000) study, euthymic BD patients exhibited lower melatonin levels and a later peak time for melatonin during the night relative to a healthy comparison group. In our study, BD patients in mania (n=11) exhibited higher melatonin levels as well as a lower level of expression of clock genes PER-1 and REV-VERB in the afternoon and in the evening than controls (n=18) and bipolar depressed patients (n=17) (Prasko *et al* 2013).

Total and partial sleep deprivation. A startling improvement in mood is observed in 40–60% of depressed BD patients after total or partial sleep deprivation (Barbini *et al* 1998). 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 (Wehr & Wirz-Justice 1981). 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 (Borbélly and Achermann 2000, Illnerova *et al* 2000, Wirz-Justice 2003).

Treatment

Pharmacotherapy

The sedating medications most frequently used in the acute phase of mania have been benzodiazepines and antipsychotics. Whether sleep induced by sedating medications only masks manic symptoms or actually reverses the underlying process responsible for mania is unclear (Wehr 1989). Benzodiazepine receptor agonists represent the treatment of choice when a medication is indicated for treating adults with insomnia (NIHSSCS 2005). The benzodiazepines clonazepam and lorazepam are as effective as antipsychotics as adjunctive medications used with lithium (which does not provide immediate antimanic effects) in the acute management of mania (Post *et al* 1996, Modell *et al* 1985, Chengappa *et al* 2000). 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. The newer benzodiazepine receptor agonists (e.g., zolpidem and eszopiclone) are less likely to be associated with rebound insomnia on discontinuation. 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 (Sharpley *et al* 2000, Cohrs *et al* 2004, Cohrs *et al* 2005). 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.

Melatonin-related approaches. 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. A positive response to melatonin (3 mg, taken at night) was reported in an open trial of 11 patients with insomnia during mania, whose insomnia was resistant to benzodiazepines (Bersani & Garavini 2000). 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. 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-HT2C receptor (Wirz-Justice 2003).

Sleep Deprivation

As noted earlier, mood rapidly improves in a proportion of depressed bipolar patients after one night of sleep deprivation (Barbini *et al* 1998). 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.

Light Therapies

Research on the role of light therapy in the treatment of bipolar disorder is needed. As already discussed, pre-

liminary data suggest that dark therapy may be helpful in reducing mood symptoms (Barbini *et al* 2005).

An Italian group developed a treatment schedule based on repeated sleep deprivation combined with light therapy and lithium (Dallaspezia and Benedetti 2011). It consists of repeated 36-h sleep deprivation, three cycles during 1 week, resulting in a lengthening of the sleep-wake period. On the first, third and fifth day patients stay awake from 7 am until 7 pm the following day. They are then allowed to sleep during the night of the second, fourth and sixth day. Sleep deprivation is carried out in normal ambient light, but patients are administered light therapy during the sleep deprivation night to counteract sleepiness, and in the morning after recovery sleep, half an hour after awakening, between 8–9 am from day 1 to day 7. If patients are not being treated with ongoing lithium salts, they start them at the beginning of the chronotherapeutic procedure, with the aim of preventing relapse (Dallaspezia and Benedetti 2011).

The same Italian group studied the effect of the catechol-o-methyltransferase (COMT) gene polymorphism (rs4680) on response to sleep deprivation combined with light therapy treatment described above. The treatment was administered to 87 bipolar depressed inpatients (Benedetti *et al* 2010). Patients who were homozygotic for the Val/Val variant showed a significantly less efficient antidepressant effect after the night awake than those who were heterozygotic and homozygotic for the Met variant. This finding supports the hypothesis of a major role for catecholamines in the mechanism of action of chronotherapeutics, and for rs4680 in modulating this effect (Benedetti *et al* 2010).

Psychological Therapies

Several of the psychological interventions for bipolar disorder include one or more components designed to help individuals with their sleep. Cognitive behavior therapy and interpersonal and social rhythm therapy include education and monitoring of the sleep/wake cycle with the aim of promoting regularity in daily activities (Frank *et al* 2000, Lam *et al* 2003).

Interpersonal therapy and social rhythm therapy includes a program to help maintain a lifestyle with regular cycles of sleep and waking, meals and social incentives (Frank *et al* 2000). A core concept of the social *zeitgeber* theory is a dysfunction in the circadian system (Frank *et al* 2005). 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 various predictions of this theory is accruing, and the treatment derived from the theory – interpersonal and social rhythm therapy – has shown effectiveness in reducing relapse in BD (Frank *et al* 2005). One goal of this treatment is to stabilize social *zeitgebers*. Patients in remission are instructed to monitor and regulate daily routines, sleep/wake cycles, and identify triggers that could provoke changes to these routines. The most important of these issues is ensuring that the patient will keep regular sleep patterns (Latalova *et al* 2012).

Cognitive behavioral therapy is focused on understanding the role of biological vulnerability to stress, managing the sleep/wake rhythm, and warning symptoms intervention. (Prasko *et al* 2013). *Cognitive-behavioral therapy for insomnia* (CBT-I) is a multicomponent treatment targeting those factors that are presumed to perpetuate sleep disturbances. Patients and their family members should be informed about the potential effects of sleep disruption on the stability of bipolar disorder. Several treatment manuals describing the implementation of CBT-I have been published (Perlis *et al* 2005). There is robust evidence that CBT-I produces reliable and durable improvements in sleep in adults with insomnia (NIHSSCS 2005). This approach to treating insomnia has not been studied in the context of BD, 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 non-pharmacological 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:

The traditional components of stimulus control involve the therapist providing the patient with a detailed rationale and help in achieving the following adaptations: 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 (Johnson 2005).

Sleep restriction involves curtailing time in bed to the actual time slept and gradually increasing it to 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.

Consideration should be given to adding a therapeutic sleep extension (or "dark therapy") procedure (Barbini *et al* 2005) if a patient begins to develop manic symptoms and exposure to natural light sources if a patient begins to develop depressive symptoms.

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 pre-sleep 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.

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