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Basic Sleep and Circadian Science as Building Blocks for Behavioral Interventions: A Translational Approach for Mood Disorders

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Abstract

Sleep and circadian functioning has been of particular interest to researchers focused on improving treatments for psychiatric illness. The goal of the present paper is to highlight the exciting research that utilizes basic sleep and circadian science as building blocks for intervention in the mood disorders. The reviewed evidence suggests that the sleep and circadian systems are 1) disrupted in the mood disorders and linked to symptoms, 2) open systems that can be modified, 3) the focus of interventions which have been developed to effectively treat sleep disturbance within mood disorders, and 4) intimately linked with mood, such that improvements in sleep are associated with improvements in mood. Although, significant positive treatment effects are evident, more research is needed to fill the gap in our basic understanding of the relationship between sleep and mood.

Keywords

sleep; circadian; mood disorders; cognitive-behavior therapy for insomnia; interpersonal social rhythms therapy; light therapy; sleep deprivation

The World Health Organization's study on the global burden of disease lists mental illness as the leading source of disability, accounting for nearly 40% of all medical disability (World Health Organization, 2002). The associated economic burden is estimated at $317 billion annually (Kessler et al., 2008; Insel, 2008). An analysis of mortality in 8 states indicates that individuals with serious mental illness die 13 to 32 years earlier than those without mental illness (Colton & Manderscheid, 2006).

Accordingly, there is a need for new and improved treatments for psychiatric illness (Insel, 2009). Sleep and circadian functioning has been of particular interest to researchers focused on improving treatments for psychiatric illness. Across psychiatric disorders it is clear that sleep and circadian systems are often disrupted (Benca, Obermeyer, Thisted & Gillin, 1992; Harvey, 2008a). Indeed, the accumulated evidence indicates that sleep and circadian systems are implicated in the cause and/or maintenance of psychiatric disorders (e.g. Buysse et al., 1997; Jackson, Cavanagh & Scott, 2003; Harvey, 2008a; NIH, 2005). This evidence dispels a previously widely held assumption that sleep disturbance is secondary to, or an

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epiphenomenon of, the so-called “primary” psychiatric disorder (Harvey, 2008a). Moreover, as will be discussed later in the present review, the sleep and circadian systems are modifiable.

The goal of this paper is to highlight the exciting research that utilizes basic sleep and circadian science as building blocks for interventions. Although we focus on the mood disorders, there are similar sets of findings across a wide range of psychiatric disorders including schizophrenia (Freeman, Pugh, Vorontsova, & Southgate, 2009; Myers, Startup, & Freeman, 2011) and post traumatic stress disorder (Germain et al., 2012). Perhaps not surprisingly then, the NIMH research domain criteria also highlight sleep and circadian disturbance as a key domain for research on psychiatric illness going forward (Insel et al., 2010).

Sleep and Circadian Disruption in the Mood Disorders

The mood disorders are a broad class of psychiatric disorders characterized by mood episodes, specifically depression and mania. Major Depressive Disorder (MDD) and Bipolar Disorder (BD), are two disorders that fall collectively into the mood disorder category. MDD and BD are amongst the most severe psychiatric illnesses. Estimates of the lifetime rates of suicide attempts of persons with bipolar and unipolar depression are 29.2% and 15.9% respectively (Chen & Dilsaver, 1996). Moreover, MDD is the leading global cause of disability (Insel & Charney, 2003).

MDD is characterized by depressive episodes, which are defined as periods of two weeks or longer with down or depressed mood and/or loss of pleasure and/or interest in daily activities. These mood symptoms are also accompanied by appetite changes, sleep disturbance, feelings of worthlessness or excessive guilt, psychomotor retardation or agitation, difficulty concentrating or making decisions, or suicidal ideation. Bipolar Disorder (BD) is characterized by episodes of mania or hypomania and depression. Manic episodes are periods of elevated, expansive or irritable mood lasting at least one week, or less if resulting in hospitalization. Hypomania is a less severe form of mania that can last 4 or more days. The manic or hypomanic symptoms can also include inflated self-esteem or grandiosity, decreased need for sleep (e.g., one feels rested after only 3 hours of sleep), more talking than is usual or pressured speech, racing thoughts, increased distractibility, increase in goal-directed activity (socially, at work or school, or sexually) or psychomotor agitation.

Disturbances of the sleep-wake cycle are a hallmark feature of the mood disorders, occurring in both mania and depression. These sleep disturbances arise from abnormalities in sleep-wake generating and/or timing (circadian) mechanisms. Though these disturbances are common in both MDD and BD, their presentation varies between mood disorders. Among patients with MDD, approximately 50–52% report insomnia, 27 – 30% report hypersomnia and 50% report early waking during depressive episodes (Korszun et al., 2004). During periods of remission, estimates are that between 7 and 55% continue to report sleep and circadian disturbances (Nierenberg et al., 2010). Among patients with BD, in a sample of 59 patients evidence indicates that 100% report insomnia (Winokur, Clayton, & Reich, 1969) and 78% report hypersomnia (Detre, Himmelijoch, & Swartzburg, 1972)

during depressive episodes. During manic episodes, insomnia occurs in 24–34% of patients (Winokur & Tanna, 1969). In the period between depressive and manic/hypomanic episodes, referred to as the *interepisode period* of BD, insomnia occurs in 55% (Harvey, Schmidt, Scarnà, Semler & Goodwin, 2005) and hypersomnia occurs in 25% of cases (Kaplan, Gruber, Eidelman, Talbot & Harvey, 2011). Among patients with BD and MDD, sleep disturbance is complicated and understudied.

Sleep and circadian disturbances observed among patients with mood disorders are of critical importance for at least 2 reasons. First, sleep is vital for intact emotion and mood regulation (Horne, 1985; Gruber et al., 2007; Dinges et al., 1997). Research in healthy adults has indicated that neural circuitry crucial for emotion regulation is destabilized following a night of sleep deprivation (Yoo et al. 2007; Sotres-Bayon, Bush, & LeDoux, 2004). Further, a study of naturalistic sleep loss in medical residents reported that less sleep predicted increased negative affect following a goal-thwarting event and diminished positive emotions following a goal-enhancing event (Zohar, Tzischinsky, Epstein & Lavie, 2005). Second, the adverse effects of sleep loss on cognitive functioning have been clearly demonstrated (e.g., Van Dongen, Maislin, Mullington & Dinges, 2003). Of particular importance within the mood disorders, sleep disturbance has detrimental effects on tests of cognitive flexibility and decision-making (Walker, Liston, Hobson & Stickgold, 2002). Also, sleep loss disrupts the encoding and later retention for positive emotional memory (Phelps, 2004). Hence individuals with mood disorders, who already have documented deficits in emotion-regulation (Gross & Muñoz, 1995) and cognitive processing (see Gotlib & Joormann, 2010 for review), may experience even more adverse effects from sleep disturbance than healthy populations.

Moreover, the sleep and circadian disruptions observed in MDD and BD have been identified as early indicators of the disorder and/or poor prognosis. Unipolar depressed patients with disturbed sleep have significantly worse clinical outcomes, attrition rates, and response to treatment than good sleepers (Dew et al., 1997; Thase et al., 1997). Additionally, sleep disturbances (measured via self-report and polysomnography) are associated with increased suicidal ideation, as well as slower and lower rates of remission from depression (Buysse et al., 1997; Thase, 1998). Further, two epidemiologic studies have shown that sleep problems identified 47% of the new cases of depression in the following year (Ford & Kamerow, 1989; Eaton, Badawi & Melton, 1995). Sleep disturbance has been found to be the most common prodromal symptom of manic episodes and the 6th most common prodromal symptom of depressive episodes (Jackson et al., 2003). In BD, disturbed sleep appears to be a predictor of worsening symptoms (see Harvey, 2008b for review). Indeed, in inter-episode BD shortened sleep duration predicted worsened depressive symptoms at a 6-month follow-up (Perlman, Johnson & Mellman, 2006). Similarly, interepisode sleep symptoms are correlated with future manic and depressive symptoms and impairment in BD (Eidelman, Talbot, Gruber, Hairston & Harvey, 2010; Kaplan et al., 2011).

Together, the clinical data point to the likely importance of identifying points of intervention to improve sleep and circadian functioning for patients with mood disorders. However, one particular challenge in the study of the sleep and circadian systems is the difficulty isolating

whether the dysfunction arises within the sleep system, the circadian system, or both systems, a problem we now address.

Identifying Targets for Intervention in the Sleep and Circadian Systems

The sleep/wake cycle is regulated by an interaction between two opponent processes (Borbély & Wirz-Justice, 1982). Process S regulates sleep-wake system through homeostatic self-modulation. This process regulates the duration and structure of sleep based on prior sleep and wakefulness. Specifically, sleep pressure increases during extended wakefulness and dissipates during early sleep. Sleep homeostasis influences sleep propensity; that is, sleep homeostasis results in an increased tendency to sleep when a person has been sleep-deprived, and a decreased tendency to sleep after having had a substantial amount of sleep. Process C regulates the circadian clock, arising from the endogenous pacemaker in the hypothalamic suprachiasmatic nuclei (SCN) (Reppert & Weaver, 2002). Circadian regulation of sleep is characterized by a relatively low sleep propensity during waking hours and an increase in sleep propensity during night hours. The maximal circadian propensity for sleep occurs in the early morning hours (typically 3:00 AM – 5:00 AM), near the time of peak melatonin secretion and core body temperature nadir. At the molecular level, intrinsically rhythmic cells within the SCN generate rhythmicity via an autoregulatory transcription-translation feedback loop regulating expression of circadian genes. The process by which the pacemaker is set to a 24-hour period and kept in appropriate phase with seasonally shifting day length is called entrainment, which occurs via *zeitgebers*. Zeitgeber is german for ‘time giver’; these are environmental cues that support entrainment. In sum, the sleep and circadian processes work in concert to facilitate consolidated nighttime sleep in humans.

However, while the sleep and circadian processes are interrelated, they are also independent (Borbély & Wirz-Justice, 1982). The independent actions of Process C and Process S can be most clearly isolated using laboratory-based manipulations. Forced desynchrony (FD) protocols are currently the gold standard method for distinguishing the influences of Process S and Process C. Specifically, FD protocols hold participants to a non-24 hour day outside of the range of entrainment of the biological clock. This forces the endogenous clock to free-run to its intrinsic 24–25 hours period, thus decoupling the circadian clock from the build up of homeostatic sleep drive (Hanneman, 2001). Such experimental manipulations revealed that the sleep and circadian processes can be unpaired. Moreover, this work indicates that the phase relationship between the sleep and circadian systems during a 24-hour day is crucial for enabling consolidated periods of sleep and wakefulness. Disruption to the phase relationship between these systems results in poorly consolidated sleep and daytime fatigue or sleepiness.

From an intervention perspective, it is particularly exciting that process C and S are *open systems* susceptible to modification. The endogenous period generated in the SCN is close to, but generally not equal to, 24 hours. As a result, entrainment to a 24-hour day is achieved through a combination of internal cues from the sleep homeostat (Process S) and exogenous inputs (zeitgebers). The phase, period and amplitude of the internal clock can be adjusted via changes to the timing/regularity of zeitgebers and manipulations of the sleep homeostat.

Process S contributes to entrainment primarily through modulation of the sleep homeostat. When sleep deprivation occurs, sleep pressure builds, thereby causing the individual to feel sleepy earlier than is typical for their circadian clock. Likewise, if an individual takes an afternoon nap, sleep pressure decreases, resulting in the individual being less tired at their usual bedtime. Through changes in sleep timing, the sleep homeostat can affect regulation of the circadian system. Experimental evidence supports this link between the two processes. In hamsters, sleep deprivation was shown to rapidly reset the circadian clock and alter gene expression within the circadian system (Antle & Mistleberger, 2000). Sleep loss also appears to modulate the response of the hamster circadian system to light (Mistleberger, Landry & Marchant, 1997; Challet, Turek, Laute, & Van Reeth, 2001). In humans, a study of 10 free-running patients demonstrated that endogenous circadian rhythm (measured via core body temperature) is intimately linked to sleep propensity; the increase in circadian sleep tendency that occurs as the night progresses counteracts the decrease in sleep propensity associated with accumulated sleep and allows humans to maintain a consolidated 8 hour sleep episode (Dijk & Czeisler, 1994).

With regard to Process C, entrainment occurs via exogenous inputs or zeitgebers, which are environmental events that can affect the phase and period of the clock. Cycles of alternating light and darkness are one of the most powerful exogenous inputs of circadian rhythms in humans (Roenneberg & Foster, 1997; Czeisler & Wright, 1999). In mammals, there are specialized photoreceptive ganglion cells whose exclusive purpose is believed to be entrainment of the circadian rhythm via light intensity measurement (Klerman et al., 2002). Light is detected by ocular photoreceptors and information regarding light intensity is then transmitted to the brain via the retinohypothalamic tract. This tract terminates in the suprachiasmatic nuclei (SCN), lying just above the optic chiasm. Retinal light exposure early in the night will delay the timing of the clock, while light exposure later in the night and early in the morning will advance the timing of the clock (Czeisler et al. 1989; Johnson, 1990). Humans are highly responsive to the phase-delaying effects of light during the early biological night. According to Zeitzer, Dijk, Kornauer, Brown and Czeisler (2000), even small changes in ordinary light exposure during the late evening hours can significantly affect both plasma melatonin concentrations and the entrained phase of the human circadian pacemaker.

Nonphotic cues can also exert a powerful influence on the SCN. Social cues, such as the timing of social interactions, meals and exercise, are a dominant nonphotic cue (Mistlberger, Antle, Glass & Miller, 2000). The best evidence for social entrainment in humans is from a small sample of subjects with total blindness (inability to perceive light of any intensity) who synchronized to the 24 h day, or to near-24 h sleep-wake schedules under laboratory conditions with regular social interactions (Mistleberger & Skene, 2005). In healthy adults, higher daily regularity in social rhythms (social interactions, mealtimes, etc., occurring at about the same time each day) is associated with a biomarker of stronger circadian function (deeper nocturnal body temperature trough) and better subjective sleep quality (Monk, Petrie, Hayes & Kupfer, 1994). Work with animal models complements and extends findings in humans. In the absence of photic cues, female rats living in isolation show a greater delay in their circadian relative to those living in groups (Cambras, Chiesa, Araujo &

Díez-Noguera, 2004), suggesting that cohabitation helps to stabilize circadian rhythmicity. In a study by Sulzman, Fuller and Moore-Ede (1977), only light-dark cycles and cycles of food availability were shown to be entraining agents in a sample of monkeys. Moreover, feeding period restriction has been shown to modulate the expression of peripheral circadian clock genes (Jang & Lee, 2012). Objective body temperature data has confirmed marked differences in the effects of varied restricted feeding schedules on circadian rhythms (Nelson & Halberg, 1986). Exercise and activity can also serve as exogenous inputs that entrain the circadian system, with several studies reporting that increased nocturnal physical activity can phase delay human circadian rhythms (Buxton et al., 1997; Van Reeth et al., 1994; Edgar & Dement, 1991).

As we move to the next section and think more about the interaction between the sleep and circadian systems, we need to be cognizant of the difficulty in truly differentiating between the sleep and circadian processes. Though they are independent processes they are also overlapping and difficult to tease apart.

How do the sleep and circadian systems become dysregulated in the mood disorders?

Popular early theories linking sleep and circadian rhythms to mood episodes proposed that, in mood disorders, the endogenous circadian pacemaker becomes misaligned with sleep timing (Frank, Kupfer, Ehlers & Monk, 1994; Kripke et al., 1994; Wehr, Wirz-Justice, Goodwin, Duncan & Gillin, 1979) and sleep disturbance serves as a psychobiological marker of mood disorder (Kupfer, 1976; Benca et al., 1992). In the past 30 years, researchers have begun to elaborate upon early hypotheses to better understand how the sleep and circadian systems become dysregulated in mood disorders. Below is a summary of a selection of the most well investigated sleep and circadian disturbances and what we know about why these sleep and circadian disturbances develop in the mood disorders. As will become evident, there are many open questions and domains for future research.

Insomnia is highly prevalent in the mood disorders. Insomnia is defined as difficulty initiating or maintaining sleep or non-restorative sleep for at least 1 month that causes significant impairment or distress in social, occupational, or other areas of functioning. Estimates from large epidemiological studies observed a 50–75% comorbidity rate between insomnia and other psychiatric illnesses (Ford & Kamerow, 1989; Lichstein, Wilson & Johnson, 2000). Despite limited information concerning insomnia's underlying pathophysiology, there is a general agreement that insomnia is perpetuated by the interplay of cognitive and behavioral mechanisms, which serve to alter homeostatic and circadian regulation. For example, daytime napping or spending extra time in bed in pursuit of elusive, unpredictable sleep may only serve to interfere with the body's homeostatic mechanisms that operate automatically to increase sleep drive in the face of increasing periods of wakefulness (i.e., sleep debt). Alternately, the habit of remaining in bed well beyond the normal rising time following a poor night's sleep may disrupt the body's circadian system by delaying circadian phase (Edinger & Wohlgemuth, 1999; Webb, 1988). Indeed, experiments in which bedtime (clock time at which participants went to sleep) was manipulated to occur at different phases of the circadian rhythm demonstrated that an

uninterrupted 8 hour sleep episode can only be achieved when sleep is initiated approximately 6 hours before the core body temperature minimum (which is linked to the bodies' circadian rhythm; Dijk & Czeisler, 1994). Moreover, there is likely to be a cyclical influence of sleep disturbance and mood disorder, with worsening sleep problems leading to a decline in mood as well as the maintenance of daytime distress and symptoms and, conversely, daytime distress and symptoms worsening the sleep problems (Harvey, 2008a).

While insomnia has been established as a core symptom across mood disorders, much less is known about hypersomnia in mood disorders. Across diagnostic nosologies, such as the DSM-IV, ICD-10 and ICSD-2, hypersomnia is broadly defined by a combination of prolonged nighttime sleep episodes, increased nighttime wakefulness, frequent daytime napping, and excessive daytime sleepiness (Kaplan & Harvey, 2009). Epidemiologic data suggest hypersomnia is present in 10–40% of patients with various mood disorders (Baldwin & Papakostas, 2006). Despite its prevalence, very little research has been done describing how hypersomnia develops in the mood disorders. Billiard, Dolenc, Aldaz, Ondze and Besset (1994) compared individuals with hypersomnia with and without mood disorders. While excessive sleepiness and prolonged sleep length were evident in a subset of individuals with mood disorders, for others the reports of hypersomnia were more closely associated with illness-related lethargy. Billiard et al. (1994) further noted that many individuals in the mood disorders group, as compared to the idiopathic hypersomnia group, spent a good deal of time in bed without any actual sleep. Excessive time in bed or long sleep could stymie build up of homeostatic sleep pressure and destabilize sleep timing, contributing to disrupted sleep regulation. Thus, akin to insomnia, it is hypothesized that hypersomnia disrupts both the homeostatic and circadian systems (Kaplan & Harvey, 2009).

Inadequate, irregular, or inappropriate timing of exposure to light and dark is hypothesized to play a role in the mood disorders (Boivin, 2000). For example, seasonal affective disorder, a depressive episode occurring in winter or fall when light exposure is lowest and spontaneously remits in spring or summer when light exposure is higher (Rosenthal et al., 1984). Moreover, studies have shown that insomnia complaints and depressed mood are associated with low light exposure (Kripke et al., 1994; Wallace-Guy et al., 2002). In addition, MDD and BD are commonly accompanied by circadian phase shifts such that exposure to light decreases (Emens, Lewy, Kinzie, Arntz & Rough, 2009; Liebenluft, Feldman-Naim, Turner, Schwartz& Wehr, 1995). Researchers have also postulated that an increased sensitivity to light exposure may be a marker of BD (Lewy, Wehr, Goodwin, Newsome & Rosenthal, 1981; Phelps, 2008) although subsequent research has failed to replicate this finding (Nurnberger et al., 2000).

Reduced physical activity and unstable social rhythms are also implicated in sleep and circadian disruptions within the mood disorders (Frank et al., 1994). Indeed, lower activity levels that are characteristic of the mood disorders are hypothesized as contributors to sleep disturbance (e.g., Harvey et al. 2005). Similarly, depression and and interepisode BD have been associated with lower social support (Moos, Cronkite & Moos, 1998; Eidelman et al., 2010) and more social strain (Franks et al. 1992). Two studies highlight that the onset of manic episodes are associated with life events that involve disruption of social rhythms (Malkoff-Schwartz, et al., 1998; Malkoff-Schwartz, et al., 2000).

Taken together, the sleep and circadian disruptions observed in mood disorders point to specific deficiencies in entrainment.

How does the basic science inform intervention?

Because sleep and circadian processes are open systems, disturbances in the sleep and circadian systems are modifiable. In the section that follows, several treatment breakthroughs are described that draw directly from the basic science provided by sleep and circadian researchers.

Cognitive Behavioral Therapy for Insomnia (CBT-I)

Cognitive Behavioral Therapy (CBT) was originally designed to target problematic thoughts and behaviors, which are characteristic of individuals with psychiatric disorders (Beck, 1964). Its effectiveness in altering negative thought and behavior patterns has been demonstrated across psychiatric disorders (see Beck, 2005 for a review).

Cognitive Behavioral Therapy for Insomnia (CBT-I) is a modification of classic CBT. CBT-I aims to change sleep habits and scheduling factors, as well as misconceptions about sleep and insomnia, that perpetuate sleep difficulties. CBT-I is a multi-component treatment. It is a short treatment, typically unfolding over 2 to 8 50-minute sessions, delivered individually or in groups. As demonstrated in Table 1, the treatment components of this intervention are directly drawn from basic science research.

CBT-I is currently the recommended first-line treatment for insomnia. Though hypnotic medications are effective for the short-term management of insomnia, there is limited evidence about sustained efficacy with long-term use (Krystal, 2009). In contrast, a review of CBT-I outcomes by the Standards of Practice Committee of the American Academy of Sleep Medicine found that CBT-I is highly effective in achieving both short-term improvements in sleep and sustained gains over long-term follow-up (Morin et al., 2006). Comparing short-term effects of pharmacological treatments for insomnia and CBT-I, a meta-analysis of 21 RCTs concluded that treatment effects for the two treatment modalities were generally comparable, though CBT-I is more effective in decreasing time to initiate sleep (Smith et al., 2002). Another study by Sivertsen et al. (2006) compared CBT-I, zopiclone and placebo. The results clearly favored CBT-I, which resulted in improved short and long-term functioning relative to zopiclone.

As insomnia is a pervasive problem across psychiatric conditions (Lichstein, Wilson, & Johnson, 2000; Ohayon & Roth, 2001), adaptations of CBT-I have been increasingly evaluated in the context of comorbid psychiatric illness in an effort to improve outcomes. Consistent with the growing evidence that insomnia and comorbid psychiatric disorders mutually maintain one another, accruing evidence suggests that CBT-I results in improvements not only in insomnia symptoms, but also psychiatric symptoms (Smith, Huang, & Manber, 2005). Recent studies have explored the application of CBT-I to MDD and BD.

In a sample of patients with MDD prescribed escitalopram, Manber et al. (2008) randomized half to CBT-I while the other half received placebo psychotherapy. Relative to placebo psychotherapy, the addition of CBT-I to pharmacologic anti-depressant treatment resulted in significantly higher rates of remission from both insomnia (7.7% vs. 50%) and depression (33.3% vs. 61.5%). In a later study, Manber et al. (2011) evaluated whether response to CBT-I treatment differed in patients with severe versus mild depression, comorbid with insomnia. Results indicated that improvement in insomnia, perceived energy, productivity, self-esteem, and overall treatment satisfaction did not differ by depression severity. Moreover, following CBT-I patients with more severe depressive symptoms experienced significant reductions in suicidal ideation and depression severity.

As discussed earlier, sleep complaints are common across all phases of BD (Jackson et al., 2003). Importantly, insomnia persists between episodes in 55% of patients (Harvey et al., 2005). In a recent case series, Kaplan and Harvey (2013) reported that CBT-I has a positive impact on sleep in patients with inter-episode BD and comorbid insomnia. Regularizing bedtimes and rise times was often sufficient to bring about improvements in sleep. This finding indicates that circadian disruptions in BD may be a key factor maintaining comorbid insomnia. Moreover, when changes in mood and daytime sleepiness were carefully monitored, CBT-I was found to be a safe and efficacious treatment for insomnia in BD.

Interpersonal and Social Rhythm Therapy (IPSRT)

The social zeitgeber hypothesis proposes that major life events (e.g., loss of a significant relationship or a job) not only have psychological salience, but also destabilize key zeitgebers, such as daily activities and light exposure (Frank et al., 1997). Social Rhythm Therapy is a psychotherapy based on the social zeitgeber hypothesis designed to increase stability in social rhythms. In the treatment of BD, Social Rhythm Therapy is typically integrated with principles from interpersonal psychotherapy in a treatment known as Interpersonal and Social Rhythm Therapy (IPSRT; E. Frank, et al., 1994).

IPSRT has 3 main goals 1) to help patients with BD stabilize their daily routines, 2) to assist patients in noticing the bi-directional relationship between mood and interpersonal interactions and 3) to ameliorate interpersonal difficulties (Frank, 2007; Miklowitz, 2006). The beginning of IPSRT involves the tracking of daily sleep timing, activities, social interactions and mood. After several weeks of tracking their daily activities, patients begin to see the connections between their sleep and daily activities and mood. The therapist and patient collaboratively create a plan to stabilize the patients' social schedule and sleep timing in order to regularize the circadian system.

The effectiveness of IPSRT for BD has been demonstrated in several studies (Frank, et al., 1997; Frank et al., 2005; Miklowitz, et al., 2007). A study by Frank et al. (1997) randomly assigned patients with BD to medication, active clinical management (a conventional clinic approach of medication combined with counseling), or IPSRT. When compared with active clinical management, patients receiving IPSRT experienced greater stability in daily routines and more time prior to recurrences of mood episodes. IPSRT was most effective in delaying mood episodes in patients who succeeded in stabilizing their daily routines. Patients who received IPSRT were also more likely to remain well through a 2-year follow-up (Frank et

al., 2005). This effect was mediated by the substantially increased regularity of social routines among subjects receiving IPSRT. Another study (Miklowitz et al., 2007) compared a combined treatment of IPSRT and Family Focused Therapy (FFT) to brief psychoeducational crisis management in a medicated sample of patients with BD. During one year, patients who received IPSRT combined with FFT experienced longer periods of remission.

Taken together, the literature suggests that psychosocial intervention designed to improve biological rhythm regularity, such as IPSRT, has beneficial effects on various psychiatric symptoms associated with a range of disorders (Malkoff-Schwartz et al., 2000).

Light and Dark Therapy

In 1984, Rosenthal and colleagues published a case series on recurrent depression with a seasonal pattern (seasonal affective disorder),. The experimental treatment of a sample of these depressed patients with artificial bright light resulted in remission from depression (Rosenthal et al., 1984). The researchers ability to modify the circadian system through the manipulation of a powerful zeitgeiber, light, laid the groundwork for the development and refinement of light therapy.

Light therapy attempts to reset the phase of the endogenous circadian clock relative to the light-dark cycle and/or increase its amplitude. The goals of light therapy include 1) synchronizing the sleep-wake cycle with the subjective night, 2) shifting the circadian clock to facilitate sleep at a desired time of day/night, and 3) advancing the circadian clock to attain indirect effects on mood (Wirz-Justice, Benedetti & Terman, 2009; Shirani & Louis, 2009). Light treatment involves the patient sitting in front of on a light therapy unit at a prescribed distance yielding an intensity of light ranging from 2,500–10,000 lux (Terman, Amira, Terman & Ross, 1996). The optimal dose and timing of bright light therapy is a matter of ongoing interest (Anderson, Glod, Dai, Cao, & Lockley, 2009), particularly in individuals who are light sensitive (Liebenluft et al., 1995). Effective timing of light administration is best predicted by an individuals' circadian timing (Terman, Terman, Lo, & Cooper, 2001). The patient is not required to look directly at the unit, indeed most patients read or eat while undergoing light exposure. Side effects associated with light therapy may include eyestrain, headache, nausea, and agitation. As some patients are resistant to sitting in front of a light box, clinicians often use management of natural light for similar therapeutic effects. Managing exposure to light in the evening can help patients down regulate sufficiently and allow the biology governing sleep onset to take over (Wallace-Guy et al., 2002). For example, turning down lights, turning off television, computers and cell phones an hour before bedtime can be a simple but powerful intervention for some patients.

While bright light exposure is a first line treatment for depression with a seasonal pattern, a few studies have also demonstrated effectiveness in non-seasonal depression (Even, Schröder, Friedman, & Rouillon, 2008; Golden, et al., 2005). A meta-analysis of placebo-controlled bright light studies found support for the use of bright light treatment in non-seasonal MDD and in seasonal affective disorder, with effect sizes of 0.53 and 0.84, respectively (Golden et al., 2005). Interestingly, bright light therapy delivered as an adjunct to antidepressant pharmacotherapy for non-seasonal depression was not effective (Golden et

al., 2005). Limited trials of light therapy have also demonstrated the effectiveness of light therapy in post-partum depression (Oren, et al., 2002) and chronic fatigue syndrome (Terman, Levine, Terman, & Doherty, 1998). Light therapy has also been associated with reduced suicidal ideation in 45% of patients with seasonal affective disorder (Lam, Tam, Shiah, Yatham & Zis, 2000). Notably, the presence of pre-treatment hypersomnia has been associated with favorable bright light treatment outcome (Terman et al., 1996; Avery et al., 1991)

There is a dearth of research investigating light therapy in patients with BD, as some reports have suggested that individuals with BD may be hypersensitive to the antidepressant effects of light. Indeed, hypomania or mania can occur as a potential adverse effect of light exposure in BD (Tuunainen, Kripke & Ende, 2004). For example, in a sample of women with bipolar depression, Sit, Wisner, Hanusa, Stull & Terman (2007) examined dosing of bright light, varying intensity and frequency of exposure across 2-week intervals. Three out of 4 of the women developed mixed mood states (including irritability, elevated energy and racing thoughts), while one entered a sustained period of remission. Thus, researchers have investigated light restriction (or dark therapy) as a treatment for mania (Wehr et al., 1998). Barbini et al. (2005) randomly allocated bipolar patients in a manic episode to 14 hours of darkness over three consecutive days or treatment as usual. Patients who received dark therapy exhibited a greater decrease in manic symptoms relative to the treatment as usual group. In a case report of two severely manic patients who were asked to enter a dark room for a daytime nap, both patients were asleep within ‘seconds following eye closure’ (Van Sweden, 1986). This may indicate that ‘reduced need for sleep’ experienced during mania may be associated with light hypersensitivity rather than a truly reduced sleep need. The few studies of dark therapy that exist are promising, and more research is needed in this domain for patients with BD.

Sleep Deprivation

Thirty years ago, the first experimental sleep deprivation study in a depressed patient with severe insomnia revealed an unexpected and paradoxical improvement in depression the following day (Pflug & Tölle 1971). The rapid overnight remission of severe depression following sleep deprivation remains one of the most striking phenomena in psychiatry, though depressive symptoms generally return after recovery sleep (Wu & Bunney, 1990).

Sleep deprivation, or wake therapy, generally consists of total sleep deprivation for one night or for the second half of one night (referred to as partial sleep deprivation). Because depressive symptoms rapidly return after subsequent sleep, sleep deprivation is not widely used alone (Wirz-Justice & Van den Hoofdakker, 1999). A combination of sleep deprivation (or partial sleep deprivation) with other treatments, including pharmacotherapy and light therapy, shows promise in achieving a rapid and maintained therapeutic response (Benedetti et al., 1997, Barbini, Colombo, Barbini, Campori & Smeraldi, 1999; Colombo, Benedetti, Barbini, Campori & Smeraldi, 2000). In order to verify that exposure to light during the night is not the active mechanism of sleep deprivation, researchers investigated whether sleep deprivation was also effective in the dark (Wehr, Rosenthal, Sack, & Gillin, 1985). Indeed, although patients’ experienced much more difficulty staying awake, sleep

deprivation in the dark was also effective. Although the mechanisms are not well-understood, one theory posits that the antidepressant effects of sleep deprivation may be due to an enhancement of process S, and the relapse of depression following recovery sleep to return to baseline levels of the abnormal S process (Borbely & Wirz-Justice, 1982). In support of this hypothesis, a recent investigation reported that selectively deprived slow wave sleep (thus enhancing process S without disrupting total sleep time) in a small sample of unmedicated depressed patients led to an acute reduction in depressive symptomatology (Landsness, Goldstein, Peterson, Tononi & Benca, 2011).

Sleep deprivation in BD has potential benefits and risks. There is some evidence that, following partial sleep deprivation, bipolar depressed patients show a greater decrease in negative affect than recurrent unipolar depressed patients (Szuba, Baxter, Fairbanks, Guze, Schwartz, 1991; Barbini et al 1998). However, a risk when treating bipolar depression is a switch from depression into mania. In patients with BD, a close relationship has been observed between sleep loss and the onset of mania (e.g. Barbini et al., 1998). Indeed, an investigation of 3 cycles of sleep deprivation (alone or in combination with heterogeneous medications) in a sample of 206 patients with bipolar depression observed a 4.85% switch rate into mania and a 5.83% switch rate into hypomania (Colombo et al. 1999). Although, these percentages are low and comparable to those observed with antidepressant drug treatments, these results highlight the importance of careful monitoring of the sleep and wake patterns of patients with BD.

There are few studies investigating the consequences of sleep deprivation on the circadian system. One study found that after repeated partial sleep deprivation, the circadian rhythm of melatonin was delayed by 45 minutes (Lo et al., 2012). In total sleep deprivation conditions, because the circadian process is independent from the sleep process, circadian rhythms appear to modulate the timing but not the amount of accumulated total sleep rebound (Mistleberger et al., 1983). The circadian effects of sleep deprivation will be import to consider and manage in future research, particularly if this treatment becomes more widely used.

Overall, sleep deprivation has been described as the most rapid antidepressant available today. Data on hundreds of depressed patients of all diagnostic subcategories show marked improvement within hours in approximately 60% of patients (see Wirz-Justice et al., 2005 for review). Lack of antidepressant response to the first dose sleep deprivation does not mean that the patient will not respond to later doses of sleep deprivations (Fahndrich, 1988; Gordijn et al., 1995). However, the question of how to sustain the remarkable antidepressant response that occurs after sleep deprivation in some depressed patients remains an open domain for further investigation.

Conclusions

We have reviewed evidence suggesting that the sleep and circadian systems are 1) disrupted in the mood disorders and linked to symptoms, 2) open systems that can be modified, 3) the focus of interventions which have been developed to effectively treat sleep disturbance within mood disorders, and 4) intimately linked with mood, such that improvements in sleep

are associated with improvements in mood. Treatment of sleep and circadian disturbances within mood disorders are an exciting domain of research. Although, significant positive treatment effects are evident, more research is needed. Significant gaps include 1) our basic understanding of the relationship between sleep and mood, 2) the modification of existing treatments for sleep disturbance in mood disorders for children, adolescents, and the elderly, 3) improving existing treatments and/or developing novel treatments, and 4) dissemination research focusing on improving access to these efficacious treatments.

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Table 1

How Behavioral Change Components of CBT-I Map onto Basic Sleep and Circadian Science.

Behavior Changes Targeted with CBT-I	How Maps Onto Basic Science
Go to bed only when sleepy	Allows for adequate build-up of sleep drive prior to bedtime (Process S)
Wind down before bed	Decreases hyperarousal, and when done regularly, conditions the body to prepare for sleep (Process C and Process S)
Getting out of bed during nighttime awakenings	Conditioning bed as cue for sleep
Restricted time in bed	Sleep restriction increases sleep drive (Process S)
Regular risetime	Entrainment of circadian phase (Process C); If a poor night of sleep, allows for greater build-up of sleep drive the following day (Process S)
Sunlight or bright light on awakening	Entrainment of circadian phase (Process C)
No naps	Serves to increase sleep drive (Process S)