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Circadian Rhythms and Psychiatric Illness

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Abstract

Purpose of review—The present review provides a conceptual introduction to sleep and circadian research in psychiatric illness, and discusses recent experimental and intervention findings in this area.

Recent Findings—In this review, studies published since January 2011 on circadian disturbance and psychiatric illness have been summarized.

Summary—Exciting new results have increasingly utilized objective and validated instruments to measure the circadian system in experimental studies. Since 2011, treatment research has still predominantly utilized self-report measures as outcome variables. However, research in the treatment domain for sleep/circadian disturbances comorbid with psychiatric illness has advanced the field in its work to broaden the validation of existing sleep treatments to additional patient populations with comorbid sleep/circadian disruptions, address how to increase access to and affordability of treatment for sleep and circadian dysfunction for patients with psychiatric disorders, and how to combine psychosocial treatments with psychopharmacology to optimize treatment outcomes.

Keywords

Sleep; circadian; psychiatric; psychosocial intervention

INTRODUCTION

It is clear that sleep and circadian processes are disrupted across psychiatric disorders (1–3). While the prevalence of sleep and circadian disorders varies across psychiatric conditions, the most common are insomnia, hypersomnia, delayed sleep phase, and nightmares. Sleep and circadian disturbances are risk factors for the onset of psychiatric disorders (4), precursors of relapse (5), associated with residual symptoms (6) and treatment resistance (7).

The present review provides a conceptual introduction to sleep and circadian research in psychiatric illness, and discusses recent experimental and intervention findings in this area. It is based upon searches of U.S. National Library of Medicine databases covering the period from January 2011 –June 2013.

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CONFLICTS OF INTEREST
None

CONCEPTUAL FRAMEWORK

According to a popular model proposed by Borbély & Wirz-Justice (8), two opponent processes govern the sleep-wake cycle. The first is a clock-like *circadian* system (known as Process C), arising from the endogenous pacemaker in the hypothalamic suprachiasmatic nuclei (9). The process by which the pacemaker is set to a 24-hour period and kept in phase with seasonally shifting day length is called entrainment, which occurs via *zeitgebers*. The primary zeitgeber is the daily alteration of *light* and *dark*. The suprachiasmatic nuclei is also responsive to *non-photic* cues such as arousal/locomotor activity, social cues, feeding, sleep deprivation, and temperature (10).

The second factor, known as Process S, is sleep homeostasis (or Process S, 11). Sleep pressure increases during wakefulness and rapidly dissipates during sleep. This process regulates the duration and structure of sleep based on prior sleep and wakefulness. Sleep homeostasis results in an increased pressure to fall asleep when a person has been sleep-deprived, and a reduced pressure to sleep following a sleep period.

Distinguishing the circadian from the sleep system is an important domain for current and future research, yet it can be methodologically challenging to achieve.

MEASUREMENT

Sleep and circadian processes are interrelated, but also independent (8). The gold standard method for distinguishing the influences of Process S and Process C is the forced desynchrony (FD) protocol. FD protocols hold participants to a non-24 hour day outside of the range of entrainment of the biological clock, thus forcing the endogenous clock to free-run to its intrinsic period of 24–25 hours (12). This serves to decouple homeostatic and circadian regulatory processes to more clearly isolate their constituent functions. However, given that FD protocols manipulate the sleep-wake cycle, this methodology could exacerbate some psychiatric conditions, thus posing a safety risk.

There are a range of other methods that can be used to estimate the independent and overlapping contributions of the circadian and sleep processes. Several of the measures that fall into this category will now be described, although it is emphasized that none represent direct methods for differentiating the sleep vs. circadian processes.

Dim Light Melatonin Onset (DLMO) is a popular and accurate method of assessing endogenous circadian phase (13). Melatonin is a hormone produced by the pineal gland; its levels remain low during the daytime, begin to increase before sleep, and peak in the first part of the night. Synthesis and production of melatonin is predominantly regulated by the light-dark cycle (14). Bright light in the evening can suppress, or “mask”, melatonin production (15), which necessitates its measurement in dim light conditions. Melatonin can be assessed via its concentration in plasma or saliva, and its metabolite (aMTS6S) in plasma or urine (16, 17).

The circadian rhythm of core body temperature, particularly the temperature minimum (T_{min}), is also a well-established reliable method for measuring circadian phase (18). Body

temperature fluctuates throughout the day; reaching its minimum in the early morning prior to awakening and reaching its maximum near mid-day. Core body temperature can be measured by a variety of methods, such as intravascular, tympanic, bladder, rectal, esophageal (19).

Cortisol has a diurnal profile that is characterized by a substantial increase in cortisol concentration peaking approximately 30 minutes after awakening, called the cortisol awakening response (CAR), followed by a subsequent decline over the remainder of the day (20). CAR is typically measured via saliva or plasma samples (21). The frequency of sampling can differ between studies, ranging from continuous to every 30min for several hours or for the whole day (21, 22).

Rest-Activity pattern can be assessed via actigraphy (23). Actigraphs are small, wristwatch – like devices, which measure physical motion via a sensor located within the device. Based on actigraphy data, sleep timing (Midsleep, Bedtime, Risetime) can be calculated. Midsleep, bedtime and rise-time are estimates of circadian phase which are moderately correlated with markers of the biological clock, such as DLMO and T_{min} (24).

CIRCADIAN DYSRUPTION AND PSYCHIATRIC DISORDERS

The methods just described have paved the way for researchers to understand the contributions of the circadian process in psychiatric illness. Although the bulk of circadian research has focused on healthy adult populations and shift workers, the body of research assessing circadian functioning in psychiatric populations is growing.

Wulff et al. (25)* found significant sleep/circadian disruptions in a sample of outpatients who met diagnostic criteria for schizophrenia as compared to controls. Although all of the patients with schizophrenia showed disruptions in sleep/circadian functioning, half displayed severe circadian misalignment in melatonin cycles while the other half showed normally timed melatonin production. Similarly, results from another study (26), indicate that endogenous melatonin's sleep-promoting action seems to be compromised in patients with schizophrenia as compared to healthy controls. While both studies are preliminary and medication effects are difficult to tease apart, these studies suggest that melatonin irregularities could be a potential treatment target for patients with schizophrenia and that further research, particularly in patients at risk for developing schizophrenia, is warranted.

Recently, researchers (27)** demonstrated that young people with major depression have significantly lower salivary melatonin levels and a shorter period between melatonin onset and habitual sleep time than those who had symptoms of depression, but did not meet diagnostic criteria for depression. Similarly, in a small sample of pregnant mothers with a history of major depressive disorder (but no current diagnosis), findings from Sharkey et al. (28)** using actigraphy data, suggest that changes in perinatal circadian rhythms may contribute to the development of postpartum mood disorders. Although these data are preliminary and the sample size was small, these findings warrant further research on circadian rhythms in samples at risk for developing depression.

In the small pool of studies on circadian rhythms in bipolar disorder published to date, research has been based on small samples and has often used suboptimal indices of the sleep/circadian systems. However, recent research has begun to emerge using validated objective measures for the study of circadian rhythms. Using actigraphy data, research among patients with a current depression diagnosis suggests that patients with bipolar depression are particularly likely to have a delayed sleep phase (29). Moreover, even during periods of euthymia, actigraphy data from St. Amand et al. (30) suggests that patients with bipolar disorder report sleep complaints.

TREATMENTS THAT TARGET THE CIRCADIAN AND SLEEP SYSTEMS

Given the circadian/sleep disruptions evident across psychiatric conditions described, interventions that target the sleep and circadian disruptions comorbid with these conditions have been developed. In this section we briefly review the empirical basis for these interventions and describe outcomes from recent intervention trials.

Cognitive Behavioral Therapy for Insomnia

The primary goal of Cognitive Behavioral Therapy for Insomnia (CBT-I) is to reverse the cognitive and behavioral mechanisms maintaining insomnia. CBT-I is currently considered the treatment of choice for insomnia (31). It is a multi-component treatment, which typically combines stimulus control, sleep restriction, sleep hygiene, cognitive restructuring, and relaxation. This treatment often begins with a reduction of time spent in bed so that time in bed is equivalent to the time the patient estimates he or she spends sleeping. This serves to increase nighttime homeostatic sleep pressure, consolidate sleep, and realign the circadian clock. Also, the recommendation to wake at the same time each day may assist in entraining the circadian system.

CBT-I has been validated as a treatment for insomnia in major depressive disorder (32), alcohol dependence (33) and other medical conditions (34). As insomnia is a feature observed transdiagnostically (3), recent research has widened the use of CBT-I and clarified its benefit for patients with schizophrenia, bipolar disorder, post-traumatic stress disorder (PTSD), and a mixed sample of psychiatric outpatients.

As there is a strong association between insomnia and paranoia (35), a recent program of research evaluated the treatment of insomnia in individuals with persecutory delusions. Myers et al., (36) conducted an open trial evaluating a 4-session CBT-I intervention in an outpatient sample with persistent persecutory delusions and insomnia in the context of a psychotic disorder. Patients reported significant reductions in insomnia severity, persecutory delusions, anxiety and depression. These findings provide preliminary support for the safety and efficacy of CBT-I in psychotic disorders.

As discussed earlier, sleep complaints are common in patients with bipolar disorder (3) and insomnia is a particularly prevalent symptom even during periods of euthymia (37). In a series of patients with bipolar disorder and comorbid insomnia who underwent behavioral treatment for insomnia, Kaplan and Harvey (38)** indicate that CBT-I has a positive impact on sleep. The authors suggest that regularizing bedtimes and rise times was often sufficient

to bring about improvements in sleep, indicating that circadian disruptions in bipolar disorder may be a key factor in comorbid insomnia. This study also demonstrated that, when changes in mood and daytime sleepiness are carefully monitored, CBT-I appears to be a safe and efficacious procedure for treating insomnia in patients with bipolar disorder.

CBT-I for PTSD has been previously validated as an efficacious treatment for sleep symptoms (39). Recently, researchers (40) replicated these findings in a small sample of military veterans. When compared with a treatment as usual condition, CBT-I combined with image rehearsal therapy produced substantial reductions in PTSD symptoms and insomnia severity. In another sample of military veterans with PTSD and sleep complaints, Germain et al. (41)* conducted a trial testing the comparative efficacy of an 8 week trial of 8.9mg prazosin, CBT-I targeting nightmares and insomnia, and a placebo pill control condition on sleep and daytime symptoms. Relative to placebo, both CBT-I and prazosin achieved significantly greater reductions in insomnia symptoms, nightmare frequency and a decrease in PTSD symptoms when compared with the placebo condition. However, the active treatments did not differ from one another.

Recent research has focused on creating abbreviated forms of CBT-I (42)*, which can be disseminated more easily and used within a mixed sample in psychiatric outpatient settings. Two studies (43, 44) compared a treatment as usual condition to a treatment as usual plus abbreviated CBT-I (4 and 2 sessions respectively) in a psychiatric outpatient setting. Patients receiving abbreviated CBT-I experienced significant reductions in depression and insomnia symptoms at post treatment and follow-up when compared to controls in both studies.

Interpersonal Social Rhythm Therapy

Interpersonal Social Rhythm Therapy (IPSRT) is a validated treatment for bipolar disorder (45). Research has shown that IPSRT has several important effects: increased time to recurrence of a bipolar episode, reduced long-term remission (45, 46), and reduced number of suicide attempts (47). IPSRT targets zeitgebers, which have a powerful impact on the circadian/sleep systems (48). As these zeitgebers are modifiable, regularizing daily rhythms such as meals, exercise and social contact, is a primary goal of IPSRT.

In the period under review, two new studies on IPSRT were published. A recent paper (49) investigated the feasibility and effectiveness of modifying individual IPSRT for a group setting for medicated individuals with bipolar depression. The six-session group format was indeed feasible and effective in reducing depression symptoms when coupled with medication. Also, Swartz et al. (50)* conducted a randomized trial in a small sample comparing 12 weeks of IPSRT versus flexibly dosed quetiapine (between 25–300mg) in patients with BP-II depression. Both IPSRT and quetiapine significantly reduced mood and anxiety symptoms at post-treatment, though no significant differences were observed between the two treatments.

Chronotherapy

Traditional chronotherapy for patients with late bedtimes involves progressively delaying or advancing bedtimes and waketimes until reaching the desired alignment (51–53). The addition of bright light exposure (using either a light box or exposure to morning light) is a

well established first line treatment for depressions with a seasonal pattern (54), and has also proven effective in purely nonseasonal depression (55–57).

In the period under review, two studies investigated the use of chronotherapy in combination with total sleep deprivation and medication in order to improve treatment outcomes. Echizenya et al. (58)* investigated the efficacy of chronotherapy combined with an antidepressant regimen in treatment-resistant depression. The treatment protocol included a night of total sleep deprivation, 3 days of sleep phase-advance, 5 days of bright light therapy and ongoing antidepressant treatment. The results demonstrated a clinically significant improvement in depressive symptoms. Another study (59)* investigated whether a chronotherapeutic could shorten the response time to antidepressant medication treatment for major depressive disorder. Patients with major depressive disorder were randomized to duloxetine plus 9 weeks of an exercise intervention or duloxetine plus 9 weeks of a chronotherapeutic intervention. Both the control and chronotherapeutic treatments led to a clinically significant reduction in depression, however patients treated with the chronotherapeutic intervention had an augmented and sustained antidepressant response when compared to the control condition.

Melatonin Receptor Agonists—Melatonin receptor agonists are analogues of melatonin, which bind to and activate the melatonin receptor. In comparison to melatonin, melatonin receptor agonists have better pharmacokinetics and a longer half-life. Agonists of the melatonin receptor have a number of therapeutic applications including treatment of sleep disorders and depression (60).

In the period under review, two small clinical trials evaluated the melatonin agonist ramelteon for sleep disturbance in bipolar disorder. In one trial, while ramelteon did not significantly differ from placebo in reducing symptoms of insomnia, mania, and global severity of illness in a sample of patients with bipolar disorder, it was tolerable and associated with improvement in a global rating of depressive symptoms (61). Another recent study of ramelteon focused on treating sleep disturbance in euthymic bipolar disorder patients (62). Relative to the placebo group, participants receiving ramelteon had marginally better sleep quality, and overall risk for depression and mania relapse was cut nearly in half during the treatment period.

CONCLUSIONS

Recently published studies provide evidence to support the importance of consideration of sleep and circadian rhythms in the study of potential prevention, causes, mechanisms, maintaining factors, and treatment of psychiatric illnesses. Exciting new results have increasingly utilized objective and validated instruments to measure the circadian system in experimental studies. Since 2011, treatment research has still predominantly utilized self-report measures as outcome variables as opposed to validated objective measures. However, research in the treatment domain for sleep/circadian disturbances comorbid with psychiatric illness has advanced the field in its attempt to a) broaden the validation of existing sleep treatments for additional patient populations with comorbid sleep/circadian disruptions, b) address how to increase access to and affordability of treatment for sleep and circadian

dysfunction for patients with psychiatric disorders, and c) how to combine psychosocial treatments with psychopharmacology to optimize treatment outcomes. Future research is needed in larger samples with more objective measures of the sleep/circadian systems to deepen our understanding of how and why these systems are so important in the study of psychiatric illness.

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KEY POINTS

- Recently published studies provide evidence to support the importance of consideration of sleep and circadian rhythms in the study of potential prevention, causes, mechanisms, maintaining factors, and treatment of psychiatric illnesses.
- Exciting new results have increasingly utilized objective and validated instruments to measure the circadian system in experimental studies.
- Psychosocial treatments for sleep and circadian disturbance comorbid with psychiatric illness is being increasingly used transdiagnostically to improve sleep/circadian and psychiatric outcomes.