Sleep and biorhythm disturbances in schizophrenia, mood and anxiety disorders: a review

Disturbi del sonno e dei bioritmi nella schizofrenia, nei disturbi d’ansia e dell’umore: una review

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SUMMARY. Sleep problems and circadian rhythms disturbances are common in many psychiatric disorders, with the most-often-reported sleep problem in most cases being insomnia. In this paper, the main findings about sleep disturbances (features and therapy) and other biorhythm disturbances (biological timekeepers, CLOCK genes, GSK3, melatonin, hypothalamo-pituitary-adrenal axis, body temperature) are reviewed in relation to schizophrenia, mood and anxiety disorders.

KEY WORDS: sleep disturbances, insomnia, circadian rhythms, biorhythms, GSK3, melatonin, schizophrenia, depression, bipolar disorder, post traumatic stress disorder, general anxiety disorder, panic disorder.

INTRODUCTION

Since the end of the 1970s, more than 50 epidemiological studies have assessed the prevalence of insomnia symptomatology in the general population (1). Sleep problems are common in many psychiatric disorders, with he most-often-reported sleep problem in most cases being insomnia. In mania and possibly depression, insomnia can significantly worsen the disorders, and early intervention to improve sleep may help abort a relapse. Also, insomnia is often a prodromal warning sign of imminent relapse. In addition to increased insomnia, there can also be an increased incidence of parasomnias, circadian rhythm disorders, and hypersomnia (2).

Sleep disturbances are related to disturbances of circadian rhythms; in mammals, including humans, the circadian pacemaker, or biological clock, is the site of generation and entrainment of circadian rhythms (3,4). It is located in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus, on top of the optic chiasma. In the absence of temporal signals (eg, in caves or bunkers), circadian rhythms persist and express their own period that differs significantly from 24 hours. In these conditions, circadian rhythms are said to “free run.” In humans, the endogenous period of the circadian clock is estimated to have a mean value of 24.2 hours, which indicates that each day our biological clock is delayed by 12 minutes compared with the environmental light/dark cycle. In order to remain perfectly entrained to the 24-hour cyclicity of the environment, the circadian clock uses several internal and external synchronizers that are able to modify the period and the phase of circadian rhythms. The light/dark cycle is the dominant synchronizing agent for circadian rhythmicity (light is therefore
called a zeitgeber - timekeeper), although social cues and physical activity may be important too (5,6).

The SCN receive direct light information through the retinohypothalamic tract, a visual tract not linked to visual processes, and indirect light information through the thalamus, using the retinogeniculohypothalamic tract (3). The circadian oscillator adjusts its functioning by integrating various parameters of the light signal: time of presentation, duration, irradiance, and wavelength (7). The circadian pacemaker is sensitive to light throughout the 24-hour cycle in a dose-dependent manner (8). As in other species, light presented in the evening (i.e., before the circadian temperature minimum) stimulates the human circadian pacemaker to phase-delay its rhythms (i.e., schedules it later in time), whereas a light stimulus given in the morning (after this minimum) produces a phase advance. The phase response curve describes the phase shifts as a function of the circadian phase of light application. Apart from phase-shifting effects, ocular light exposure at night also directly suppresses the production of melatonin by the pineal gland (9).

The circadian pacemaker is also sensitive to the phase shifting effects of various chemical or pharmacological components, including melatonin (N-acetyl-5-methoxytryptamine), which acts on the circadian clock through specific MT1 and MT2 melatonin receptors located in the SCN (10). In normal subjects, the secretion of melatonin, the pineal hormone that regulates the rhythm of many functions, exhibits a circadian pattern. Melatonin is involved in the synchronization of the circadian clock by the day-night cycle by signaling day-night information to the endogenous circadian pacemaker. Furthermore, melatonin, through its hypothermic properties, is known to affect the circadian rhythm of body temperature directly. A striking property of the endogenous melatonin signal is its synthesis pattern, characterized by long-term elevated melatonin levels throughout the night (8).

All animals have circadian pacemakers/clocks, and their period and timing appear to be also dependent on particular genes (so-called clock genes), most of which are common to fruit flies, mice, and primates, and probably many other species (11). Mutations (polymorphisms) of these genes that lead to an altered circadian rhythm are particularly easy to identify in fruit flies, and similar variants of these genes have been found in people with certain disorders of circadian rhythm (11).

The products of some of these clock genes regulate their own expression, and the outcome of this feedback loop is an oscillation in the levels of messenger ribonucleic acids (mRNAs) and proteins. In mammals, Clock and Bmal1 encode transcription factors CLOCK and BMAL1 (11-14), which form heterodimers that activate the transcription of three Period genes (PER1, 2 and 3) and two Cryptochrome genes (CRY1 and 2) (11,15-17), Rora and Rev-Erbα (11,18-20) (Figure 1). PER and CRY proteins form complexes (21) that are translocated back into the nucleus and inhibit their own expression (11,22-25). RORα and REV-ERBα act on Bmal1 to activate and repress transcription respectively (11,18,19). NPAS2 is an alternate dimerization partner for BMAL1 that may also regulate circadian rhythm in the forebrain, but it has not been consistently found in the SCN (11,26,27). Clock proteins are phosphorylated by casein kinase I epsilon (CKI) and delta (CKI), and possibly also by the Drosophila shaggy homologue glycogen synthase kinase 3 (GSK3) (28). They are targeted for degradation by components of ubiquitin ligase complexes like FBXL3 and β-TRCP1 (11,29,30), which together regulate the period of circadian oscillation by controlling the rate of accumulation, association and translocation of PER and CRY (11,31-33).

These genes, protein products, and enzymes work together to control clock functioning, and abnormalities such as clock gene mutations can have profound consequences for the synchronization of emotional,
physiological, and behavioural processes; it seems that both how long we sleep and our preferred sleep timing (whether or not we are evening people “owls” o morning people “larks”) is partly dependant on genetic makeup, with each other and the environment (2).

DEPRESSION

Sleep disturbances

Sleep disorders have long been considered as a cardinal symptom of endogenous depression (34); subjects with insomnia exhibit symptoms of depression in 40% to 60% of the cases and have a clinical depression in 10% to 25% of cases (1). Depressive symptoms may reflect sleep disturbances, including phase shift of sleep-wake cycles (35), reduced amplitude, or disturbance of sleep-wake dependent processes (35,36).

Sleep in depressed patients resembles sleep in normal subjects whose circadian rhythms of REM sleep are phase-advanced with respect to their sleep schedules. Polysomnographic recordings of depressed subjects have evidenced that the internal sleep organization is impaired, with, specifically, a reduced latency of the first REM sleep episode of the night with increased density of rapid eye movements, an increase in total percentage of REM sleep, a reduction in deep Slow Wave Sleep (SWS), and an increase in night awakenings. These observations, together with the fact that most antidepressant drugs inhibit REM sleep, have led to the theory that short REM sleep latency is enhanced in depressed patients and are part of the pathological processes associated with depression (37).

Alterations in REM and SWS appear linked to sleep related dysfunctional arousal in primary limbic and paralimbic structures (amygdala), and hypofunction in frontal cortical areas (38). Preliminary studies in insomnia in depression indicate subcortical hyperarousal and failure of sleep to provide normal restoration of function in the prefrontal cortex, leading to chronic sleep deprivation.

Depressed patients also complain of insomnia, notably of difficulty in falling asleep, frequent nocturnal awakenings, early waking up, and nonrefreshing sleep. However, one should dissociate insomnia from decreased REM sleep latency. Indeed, while short REM sleep latency is a pathogenic process, insomnia induces an improvement in mood. In insomniac patients who are at risk for depression, sleep loss might represent an efficient adaptive mechanism to counteract the underlying depressive mood, and therefore, prolonged sleeping appears as an important risk factor for depression (39).

Treatment of sleep disturbances

From a clinical point of view, the subjective perception of sleep is more important than polysomnographic findings. In general, in most of the studies of sleep complaints during antidepressant treatment, the comparator is sleep at baseline, and there is improvement over weeks as the depression lifts. This is seen with both drug and cognitive therapies. Differences between drugs have been reported early in treatments but these differences are generally much smaller or absent after 2-6 weeks (40).

However, the ability of different drugs to improve sleep early in treatment, is often important to patients, particularly if insomnia is causing significant distress. Also, early improvement of sleep symptoms may encourage the patients to carry on with medications to the point where the mood lifting effects are apparent (2-3 weeks). 5HT2 blockers such as mirtazapine and agomelatine (5-HT2 antagonist and melatonin receptor agonist) can improve subjective sleep quickly in depression; tricyclic antidepressant (TCAs) such as trimipramine and doxepine also do this, because they are potent histamine H1 antagonists, but have more unwanted effects such as carry-over sedation and dry mouth (2).

Objectively, SSRIs, alerting TCA and mixed uptake blockers antidepressants decrease REM sleep and REM latency but can increase waking in sleep early in treatment for which a hypnotic is sometimes required (nonbenzodiazepine anxiolytics may offer advantages over traditional sedative hypnotics; long-term use of long-acting benzodiazepines should be avoided (41,42)). Mirtazapine, mianserin, trazodone and trimipramine have smaller effects on REM but decrease waking in sleep in the first week of treatment (2).

Treatment with melatonin in depression give still unclear results; melatonin, however, may be helpful when insomnia is related to shift work and jetlag (43-46).

There has been some recent evidence suggesting that electroconvulsive therapy, transcranial magnetic stimulation and antidepressant medications targeting the dopaminergic and serotonergic neurotransmitter systems, including, monoamine oxidase inhibitors (MAOIs), fluoxetine, imipramine, clozapine, risperidone, and haloperidol may have a common mode of action either via the direct inhibition or increased phosphorylation of the GSK3 enzyme (11,47-49). GSK3 is involved in many cellular functions; therefore the therapeutic action may be via a number of possible routes, including regulation of monaminergic signaling, neuroprotection, neuroplasticity, modulation of estrogen and glucocorticoid activity, regulation of brain metabolism, or regulation of the circadian system (11,50).
Exposure to bright light at appropriate times, traditionally used to alleviate the depression associated with seasonal affective disorder, can help realign the circadian rhythm in patients whose sleep-wake cycle has shifted to undesirable times (morning bright light therapy is more effective than evening therapy; the duration of administration varies from half an hour to 2 hours) (41,42,51).

The rapid, usually short-lasting improvement following total sleep deprivation and rapid return of depressive symptoms after subsequent recovery sleep, is well documented, and indicates that the depressive process is strongly sleep-dependent (39). Prolonged manipulations of the sleep-wake cycle, such as phase advancing, could maintain the effects of total sleep deprivation, both in the presence or absence of combined antidepressant drug treatment. In insomniac patients at risk for depression, sleep loss might represent an efficient adaptive mechanism to counteract the underlying depressive mood and, therefore, prolonged sleeping appears as an important risk factor for depression, as discussed above. However, the antidepressant effect of sleep deprivation is very short-lived and cannot be considered as long-term antidepressant therapy (52).

Other biorhythm disturbances

The list of physiological variables showing circadian abnormalities in depressed patients is quite extensive (53).

- **Body temperature**: several investigators have indeed demonstrated that there is reduced amplitude of circadian rhythms in depressed patients. In major depression, a flattened core body temperature rhythm has been interpreted as a reduction in circadian amplitude, with the expected drop in nighttime core body temperature being diminished (54,55). Patients with Seasonal Affective Disorder (SAD) also exhibit a significant delay in core temperature rhythm. Lewy et al. (56) have shown that morning phototherapy was effective in treating patients with SAD by phase advancing endogenous circadian rhythms of core body temperature (39).

- **Hormones**: dysregulation of the hypothalamo-pituitary-adrenal axis is common among depressed individuals. A meta-analysis of cortisol data in depression revealed evidence of overall increased glucocorticoid secretion with the largest effect at the nadir of the circadian rhythm (57). Furthermore, there is an earlier onset of the first cortisol secretory episode in depression, i.e., a phase advance of the rhythm of secretion of the hormone. An early morning rise in adrenocorticotropic secretion and a nocturnal elevation of prolactin and growth hormone release have been also found to occur earlier in depressed patients than in control subjects (58). In the course of a 4-year study in 8 patients with mania, the same team reported early timing of the nadir of the circadian curve of plasma cortisol and normal levels of growth hormone and prolactin (58). These authors hypothesized that these effects were secondary to an alteration of the sleep-wake cycle. The physiological nighttime drop in thyrotropin (TSH) is not observed in depressed patients. Nocturnal secretion of TSH is reduced in bipolar patients, and returns to normal after recovery (39).

- **Melatonin**: both decreases (59) and increases (60) in melatonin levels have been reported in depressed patients. The most consistent finding has been a lower blood concentration of melatonin in depressive patients compared with controls, including bipolar disorder (BD) and premenstrual dysphoric disorder. Brown et al. (61) reported that patients with melancholia had lower serum melatonin concentrations than healthy volunteers, as well as inverse correlations of melatonin concentration with mood depression and disturbance factors on the Hamilton scale (62). Lower nocturnal concentrations of the main metabolite of melatonin, 6-sulfatoxymelatonin, in melancholic patients were reported by Boyce et al. (63), although Rubin et al. (46) failed to confirm lower pineal function. The latter authors also reported a phase advance of melatonin rhythms (46), though a trend toward a later nocturnal melatonin peak has been also reported in patients with unipolar depression (64). A familial vulnerability has been hypothesized in the endogenous melatonin signal in subjects prone to depression, and an abnormality in the duration of the melatonin signal in those with current major depression (65). Nevertheless, melatonin has never shown antidepressant efficacy in clinical trials and shows contradictory results in terms of efficacy on other parameters (e.g., sleep), as is discussed later in this article.

- **Clock genes**: to date there has been no evidence of clock gene mutations associated with major depressive disorder. The T3111C polymorphism of CLOCK was investigated, based on its association with eveningness, but no differences were found in allelic frequencies between a group of 143 people with a history of major depression and 195 controls (11,66).

**BIPOLAR DISORDER**

**Sleep disturbances**

Sleep in BD is state-dependant, with a manic phase usually being preceded by a shortened duration of

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**Notes:**

- Bersani FS et al.
- Rivista di psichiatria, 2012, 47, 5
- 368
sleep (this can be a useful early warning). Some patients also have longer duration of sleep and an increased amount daytime sleepiness during a depressed phase. Objective sleep changes are similar to those in unipolar depression (2).

The relationship between the sleep-wake cycle and changes in mood appears to be important in patients with frequent and rapid changes in mood state, so-called “rapid cyclers,” with the switch from mania/hypomania to depression/euthymia occurring during or after sleep, while positive changes in mood from depression to hypomania/mania are more likely to occur after a period of wakefulness (67,68).

Treatment of sleep disturbances

The main psychopharmacological approaches to treat sleep disorders in bipolar patients should follow some simple guidelines: avoid the use of antidepressant medications, even those with good efficacy on sleep problems; avoid long-term use of benzodiazepines, in particular on patients with a history of substance abuse; prescribe one or more mood stabilizers (69).

Although it has been known for many years that lithium is effective as a mood stabilizer, its pharmacological mode of action has remained uncertain. However, recent evidence suggests that the therapeutic action of lithium may be related to direct effects on the circadian clock. For example, lithium has been shown to lengthen the period of circadian rhythms in rodents (70), and can lengthen the period of neuronal firing of cultured SCN neurons in a dose-dependent manner (71). A delay of the circadian rhythm of temperature and of REM sleep has also been shown in a BD patient (72). This suggests that the therapeutic action of lithium could be due, in part, to correcting a phase advance of the circadian system related to the illness.

One proposed molecular mechanism is via the inhibition of GSK3 (11,73). Although this enzyme has a number of functions that could potentially mediate the therapeutic effects of lithium (11,74), one likely possibility is via its function as a central regulator of the circadian clock. Numerous lines of evidence support this idea; both lithium and GSK3 knockdown produce a lengthening of mPer2 period in mouse fibroblasts (11,75), and GSK3 phosphorylates PER2 and REV-ERB and regulates their localization and stability, respectively (73). Even more interesting are findings that inhibition of GSK3 may be common to other mood-stabilizing agents such as valproate, and may even be a target of antidepressant therapies, including drugs which target the serotonergic and dopaminergic systems as well as electroconvulsive therapy (11,50,76). There is also evidence for effects of allelic frequency of the GSK -50 T/C SNP. Bipolar patients with the T/T allele of GSK3 show an earlier age on onset of BD and enjoy less improvement from lithium therapy than patients with the T/C or C/C alleles (11,77,78). Together these results are persuasive, making GSK3 a promising target for the future development of pharmotherapeutic agents (11).

Other biorhythm disturbances

Circadian disturbances have been reported in BD that suggest a phase advance of the master clock (SCN), including a phase advance of the diurnal rhythm of plasma cortisol (79), although negative results have been reported (80).

Beck-Friis et al. (43) reported that manicdepressive patients had lower nocturnal melatonin concentrations than healthy individuals. Lam et al. also reported a decreased baseline melatonin level in acutely ill bipolar patients. Nurnberger et al. (81) confirmed the presence of melatonin secretion abnormalities in patients with BD I. In contrast, Rubin et al. (46) found no association between melatonin concentration and bipolar depression.

The evidence for genetic abnormalities associated with clock genes is strongest in BD. Much of the work attempting to link BD to clock genes has focused on the 3111T/C polymorphism of the human CLOCK gene (11,82-85). The C/C allele of CLOCK has been associated with greater severity of insomnia during antidepressant treatment, a higher recurrence rate of bipolar episodes and reduced need for sleep. Support for a role of Clock mutation in BD has recently come from the animal literature, where behavioural studies using CLOCK mutant mice suggest a phenotype similar to mania, with an increase in the reward value of appetitive stimuli and reduced depressive and anxiety-like behaviors (11,86).

An analysis of 46 single nucleotide polymorphisms (SNP) in eight clock genes (BMAL1, CLOCK, PER1,2,3,CRY1,2,TIMELESS) using family-based samples with BD or schizophrenia has been reported (11,87). A Mendelian transmission distortion analysis revealed association of BMAL1 and TIMELESS with BD. However, these were modest associations found using a very liberal analysis. Interestingly, an independent study using haplotype analysis seems to confirm the association with BMAL1 and also finds one with PER3 (TIMELESS was not studied) (11,88). Studies examining other genes have found negative results; screening for human PER2 mutations at the CK1 binding site showed no difference in frequency between BD patients and controls (11,89), nor is there any evidence for linkage or association of CRY1 (11,90).
GENERALIZED ANXIETY

Sleep disturbances

Sleep onset insomnia is experienced by about 20-30% of patients with generalized anxiety disorders (GAD), and sometimes sleep is the main focus of anxiety. They may also have increased night-time awakening and report poor sleep quality. There are a few objective abnormalities apart from reduced sleep continuity. Some believe that primary insomnia is variant of GAD where the main focus of the worry is on sleep and the negative consequences of having too little of it. This may explain why the selective serotonin reuptake inhibitors (SSRIs) that often disrupt sleep early in the treatment of depression can improve sleep in GAD and in some case of insomnia (2).

Treatment of sleep disturbances

In large clinical trials, it has been shown that sleep improves along with other symptoms after effective antianxiety treatment involving both antidepressants and benzodiazepines. Cognitive behavioural therapy (CBT) focusing on sleep appears to be efficacious in this group, similar to its actions in patients with primary insomnia (2).

Other biorhythm disturbances

Monk et al. (91) recently assessed that behavioural circadian regularity at the age of 1 month predicts anxiety levels during school-age years (more regular=less anxious). Apart from this, there is relatively little evidence suggesting specific circadian disturbances or a role for clock genes in anxiety disorders (11). This is perhaps not surprising, given the heterogeneity of anxiety disorders and their comorbidity with other disorders such as depression (92). In contrast to studies in humans, there are a few interesting results from research on animals. One study showed a reduction of Per1 mRNA levels in mouse cerebellum by antianxiety medications (11,93), suggesting that altering circadian clock gene levels could theoretically contribute to the therapeutic action of these drugs. Also of interest is the reduction of anxiety observed in mice with a mutation of the Clock gene. For example, Clock mutant animals are much more likely to spend time in open spaces, which normal mice avoid (11,86). However, as these mice also showed behaviours associated with mania, it is unclear how to best classify this phenotype (11).

POST-TRAUMATIC STRESS DISORDER (PTSD)

Sleep disturbances

There is a high incidence of almost all sleep disturbances in PTSD. Of the patients, 70-90% have difficulty falling or staying asleep (2), and nightmares are reported by 20-70% (94). Parasomnias such as sleepwalking and night terrors are more common than that in the general population, and more recently a high incidence of sleep-disordered breathing and sleep movement disorders have also been reported (2).

In a study of car accident survivors, sleep complaints at 1 month after the trauma were higher in the group who had PTSD a year later, so there may be some predictive value in assessing sleep (95).

Objective measures of sleep disturbances are inconsistent, but most studies show decreased sleep efficiency. There is controversy about REM sleep, with some reports of REM decreases and some of increases. There does, however, seem to be a consistent trend for more awakening during REM episodes, and this plus the reduced sleep efficiency appears to indicate hyperarousal at night (2).

Treatment of sleep disturbances

Drug therapy used for PTSD symptoms such as SSRIs, trazodone and mirtazapine may improve sleep and nightmares. More recently, there have been encouraging reports of sleep improvements after prazosin, a centrally acting α1-adrenoceptor antagonist, and also with buspirone, gabapentin and tiagabine, which need to be confirmed. Evidence suggests that benzodiazepines, TCAs and monoamine oxidase inhibitors (MAOIs) are not useful for the treatment of PTSD-related sleep disorders. CBT targeting insomnia and imagery rehearsal therapy for nightmares have also demonstrated good outcomes (2).

PANIC DISORDER (PD)

There are no specific associations between PD and sleep disorders except in those patients who experience night-time panic attacks. Up to 50% of PD patients have at least one of these nocturnal panic attacks, and 30% experience them regularly. In this group, fear of falling asleep becomes a problem, and they describe onset insomnia (2).

Nocturnal panic attacks are not different in characteristics form daytime ones. When they have occurred during polysomnography, they usually follow a sudden awakening at the transition between stages 2 and 3.
sleep, that is just as the patient is descending into deep sleep. They are usually vividly recalled. Anecdotally, we have seen several patients who have described panic attacks right at the onset of sleep, and in these patients there has been a very high degree of physical awareness of heart rate and/or respiration. In healthy people, there is a slowing of heart rate and a short period of very shallow respiration at sleep onset as the autonomic system resets to its “sleep” settings. It may be that these patients are abnormally aware of these changes, or that their innate alarm system to carbon dioxide alterations is abnormal, so that the small increase in CO2 levels that occurs in the transition activates the brain stem sensors in vulnerable patients, and these provoke a panic attack (2).

Apart from the nights with panic attacks, patients with PD do not show any differences in sleep architecture from healthy controls.

Other biorhythm disturbances

Findings about the relation of circadian rhythms and PD are still fragmentary. 24 h hypothalamic-pituitary-adrenal functionality is disturbed in PD patients. Several studies found that patients with PD had elevated overnight cortisol secretion and greater amplitude of ultradian secretory episodes (96, 97, 98). Alprazolam produces substantial improvement in clinical status accompanied by nearly full resolution of pretreatment hypercortisolemia (99). Also melatonin has been found to be elevated in patients with PD (100).

Seasons seem to play a role in panic exacerbation, given the observation that panic attacks are more frequent during the summer (101-103).

Limpido et al. (104) found alterations of diurnal 24-h cycle rhythm of sleep and wake cycles sleep, appetite, and other bodily functions in patients with PD and anxiety disorders in comparison to healthy controls.

SCHIZOPHRENIA

Sleep disturbances

Patients with schizophrenia can suffer from insomnia, which is mostly described at times of acute symptoms. These include poor sleep initiation and consolidation, impaired sleep homeostasis expressed as low levels of SWS, with many subjects showing a total absence of stage 4 sleep, and shortened REM sleep latency with frequent sleep onset REM periods. Patients with schizophrenia can also have prolonged sleep or excessive napping in the day even though this is often thought to be due to the adverse effects of sedating antipsychotic medication (2). Recently, it has also been found a reduced sleep spindles in electroencephalograms (105). Taken together, these observations suggest a deficient homeostatic regulation of sleep, although sleep deprivation can lead to SWS rebound on recovery nights (106).

The disorder which has been most consistently described in schizophrenia is circadian rhythm disorder; actigraphic recordings of schizophrenic patients have revealed disturbed rest-activity cycles, showing either phase delays, longer periods of activity, or circadian rest-activity patterns. The study of schizophrenic patients by a forced desynchrony experiment revealed an abnormal circadian propensity for sleep suggesting a disturbed circadian regulation of sleep. The cause of this is unknown, but it presumably reflects some biological perturbations in the brain such that the sleep wake routine appears to lose its normal sensitivity in zeitgebers (contributing to lead to important cognitive impairment) (107,108), and in some cases, a free-running cycle can emerge, that normalizes once the acute relapse is over. Environmental factors may also play a part, because the lifestyle of many patients can lead them, for example, to spend most of the time in dim light indoors or in hospital, to not have regular periods of activity, etc; however, it is possible that at times of acute illness these patients are indeed less sensitive to external cues and this is an area of active research endeavour at present (2).

Treatment of sleep disturbances

Psychopharmacological treatment should be implemented through the administration of those medications with both antipsychotic and hypnotic action (especially 5HT2 blockers such as clozapine, olanzapine and quetiapine), with special attention to side effects (69,109-111). Recent studies found that atypical antipsychotics, including olanzapine, clozapine, quetiapine, and ziprasidone the interaction between atypical antipsychotics can regulate GSK3 and inhibit its activity of central regulator of the circadian clock (112) (see sections 2.2 and 3.2).

Treatment using normal environmental entraining processes, for example, light and exercise can be difficult in these patients, because the impetus to change lifestyle and engage in such programs is often low (2).

Other biorhythm disturbances

Circadian disturbances have been reported in schizophrenia patients, but the results are inconsistent (113). One study has measured core body temperature variation and reported desynchronization of temperature,
pulse and blood pressure rhythms, although this study was conducted under ambulatory conditions and the data influenced by masking effects (114). In some experiments, the analysis of melatonin secretion demonstrated blunted circadian variation, although uncontrolled light exposure prior to data collection may have confounded these results (115-117); this may be explained by the precox pineal calcification that occurs in patients with schizophrenia (118-121). Others have reported phase advances of body temperature (122), prolactin and melatonin (123). These advanced rhythms are surprising considering that actigraphic recordings have revealed disturbed rest-activity cycles that are often inconsistent with a phase advance, including phase delays, longer periods of activity or, occasionally, 48 hour rest-activity patterns (124-126). Levels and ultradian rhythms of nerve growth factor are also affected (127-130) and antipsychotics such as clozapine or haloperidol may regulate them (131-133). Patients with schizophrenia disorders also show a greater tendency towards eveningness (later wake and bed times and being most alert later in the day) than controls (113,134).

Evidence linking circadian clock gene polymorphisms or deregulation with schizophrenia is limited. In one study, SNP analysis of the CLOCK gene demonstrated that the T3111C polymorphism showed a transmission bias in a sample of 145 Japanese schizophrenic subjects relative to healthy controls (11,135). The authors suggested that this polymorphism, associated with aberrant dopaminergic transmission to the SCN may underlie the pathophysiology of schizophrenia. Since dopaminergic signalling through D2 receptors appears to be associated with increased CLOCK:BMAL1 (11,136) activity, this provides an interesting link between the dopaminergic hypothesis of schizophrenia (11,137) and circadian abnormalities in these patients. Post-mortem studies have shown decreased expression of the PER1 mRNA in the temporal lobe of schizophrenic subjects compared with age-matched normal controls (11,138). Associations of PER3 and TIMELESS have also been found with schizophrenia/schizoaffective disorder, as well as with BD. The association with PER3 is interesting, given the evidence of a relationship between PER3 with delayed sleep phase disorder and evening chronotype. However, the function of TIMELESS in mammals is not yet clear (11,139), making it difficult to interpret this finding. Finally, the CRY1 gene was hypothesized to be a candidate gene for schizophrenia based on its location near a linkage hotspot for schizophrenia on chromosome 12q24 (11,140). The fact that CRY1 is expressed in dopaminergic cells in the retina and that its expression influences the effects of psychoactive drugs lends further supports to this hypothesis.

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