Mood disorders, sleep and circadian rhythms

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Summary

Sleep disturbances and disruptions of circadian rhythms are underlying factors in most mood disorders like major depressive disorder (MDD) and bipolar disorder (BD), and their seasonal pattern or seasonal affective disorder (SAD). Decreases in sleep efficiency, total sleep time and sleep quality have all been documented in MDD. In addition to this, depressed patients of all these three categories (MDD, BD, SAD) exhibit profound disturbances in circadian rhythms including the sleep-wake rhythm. Circadian clock dysregulation has been suggested to be due abnormal circadian rhythmicity of gene expression. In particular, *CRY1* and *CRY2* polymorphisms have been shown to be associated with MDD. Similarly, variations in *CRY2*, *PER2*, *ARNTL* and *NPAS2* are associated with SAD. An antidepressant that benefits sleep quality and resynchronize disrupted circadian rhythms will be most useful in treating mood disorders. In this context, the newly introduced melatonergic antidepressant agomelatine with MT_1 and MT_2 agonistic properties with 5-HT_{2C} antagonism has been documented to be beneficial, as it improves sleep, resynchronizes the disrupted circadian rhythms, and elevates mood. This drug also manifests with fewer adverse effects and is emerging as an effective antidepressant.

KEY WORDS: insomnia, sleep, clock genes, circadian rhythms, mood disorders, agomelatine.

Introduction

The clinical picture of mood disorders such as major depressive disorder (MDD) and bipolar disorder (BD) and their form with a seasonal pattern known as seasonal affective disorder (SAD) are dominated by pathological mood and psychomotor disturbances. The cluster of signs and symptoms seen in these disorders is sustained over a period of weeks to months, and they recur often in a period or cyclical fashion (1). As mood disorders happen to be cyclical also, disturbances in circadian rhythms have been implicated in these disorders (2). By definition, circadian rhythms are endogenous and are of "self-sustaining" in nature and will generate their rhythm and persist in the absence of any external input (3). Lesion experiments conducted in hypothalamic tissue have shown that the suprachiasmatic nucleus (SCN) of the hypothalamus acts as the major circadian pacemaker (4), and this master clock has been located in the SCN of humans as well (5). Numerous studies conducted on

depressive patients have shown that functioning of the circadian time keeping system is markedly affected in patients with BD (6-8).

Malfunctioning of the circadian time keeping system is said to be the reason for marked disturbances in the timing and distribution of rapid eye movement (REM) and non-rapid eye movement (NREM) sleep stages seen in patients with MDD, and these are documented as "primary characteristics" of MDD (9). Both epidemiological and electroencephalographic studies implicate "sleep disturbances" as a frequent underlying factor for mood disorders (10). Polysomnographic studies on patients with MDD or BD have found objective findings of sleep disturbances like difficulty in falling asleep, staying asleep, early morning awakenings (11). In addition, decreases in sleep efficiency (SE) and slow-wave sleep (SWS), and increases in sleep onset latency (SOL) and nocturnal awakenings have all been reported in patients with MDD (12). REM sleep abnormalities are considered as specific symptoms of MDD (13), although similar findings characterize patients with narcolepsy. Changes in the timing of the NREM-sleep-to-REM-sleep cycle within the night-time sleep in patients with depressive disorders are interpreted as a consequence of disorganized pathways regulating sleep-wakefulness cycle (7, 14).

As the circadian system, or the SCN, is involved in timing of the sleep propensity and wakefulness and consolidation of these two states (15), the SCN is considered as significant in regulating sleep-wake rhythm (16, 17). As neurons of the SCN express high concentration of both MT_1 and MT_2 melatonin receptors and melatonin acts on these receptors to alter the neuronal firing rate (18), or phase shift the neuronal firing rates in SCN (19), the hormone has important role in the regulation of both sleep-wakefulness cycle and circadian rhythms. Desynchronization of these two is considered as one of the key triggers for development of depressive disorders (19). Existence of disturbed sleep-wake cycles coupled with abnormalities of circadian rhythms, sleep disturbances, the cyclical nature of depressive disorders, and the diurnal variations in its symptomatology all implicate dysfunction of the circadian time keeping system as the major precipitating factor for depressive illness (20).

Sleep abnormalities in mood disorders

Sleep disturbances constitute one of the core features of depressive symptomatology as evidenced from the fact that more than 80% of depressed patients suffer from poor quality of sleep (21). Whether sleep disturbances in depression are "trait-like" feature, it remains as a controversial issue (22). In the early studies, it was demonstrated that changes in sleep architecture often preceded changes in clinical state and even predicted the relapse (23). Indeed, sleep has been included as one of the diagnostic criteria for MDD (24). Patients with depressive disorders experience all major symptoms of insomnia including (a) difficulty in falling asleep, (b) difficulty in staying asleep, and (c) early morning awakenings (11). Sleep studies of slow-wave activity (SWA) in patients with MDD reveal that δ wave counts decreased as compared with sleep architecture of normal controls. Both fast-frequency β activity and elevated α activity have been noted in sleep recordings from depressive patients (9).

The temporal distribution of REM sleep is altered in patients with MDD. Decreased REM onset latency, that is the period from the onset of sleep to the appearance of first REM period, is the most common feature observed in MDD (13, 25, 26). It is suggested that reductions in NREM sleep, especially SWS, is the cause for reductions in REM sleep latency (27). A correlation between the reduced SWS and the abnormal temporal distribution associates with the increased severity of depressive symptoms and the increased risk of suicide (9). Many of the current antidepressants produce REM sleep suppression with the increase in REM onset latency prior to ameliorating the symptoms of depression (12).

It has been suggested that an ideal antidepressant should shorten the sleep latency, decrease the number of awakenings after sleep onset and increase the level of alertness during daytime (28), showing thereby the importance of "sleep disturbances in the pathogenesis of depressive disorders". But, most of the conventional antidepressants that are in clinical use today act by elevating the daytime mood of depressed patients by activating the brain with rather non-specific mechanisms and persistence of this effect in the night will result only at the expense of sleep quality (29).

The status of sleep abnormalities as a diagnostic test for differentiating MDD from other psychiatric disorders was made in one meta-analysis and literature review. Using 31 publications the authors concluded that sleep studies for the detection of MDD appear replicable with a moderate effect size, and that additional studies are required for defining sensitivity and specificity (30). In a study on patients with schizophrenia and those with MDD, it was found that REM latency and REM sleep parameters had a significant relationship to clinical symptoms in MDD as assessed with the HDRS (Hamilton Depression Rating Scale) scores. Moreover, patients with MDD also differed from healthy controls in SOL, the number of awakenings after sleep onset, SWS, REM latency, and NREM sleep stage 1 (31, 32). Abnormalities in REM density and NREM sleep have been suggested to be potential biomarkers that persist even beyond remission in patients with MDD (33). Although unipolar and bipolar types of depression can be clearly distinguished, no significant differences are observed between these two groups in terms of nocturnal sleep patterns (34-36). Polysomnographic studies on patients with bipolar disorder with either depression or mania have shown that shortened REMOL and disturbed sleep continuity occur during manic episodes (37). Bunney and his associates have found that patients suffering from bipolar depressive disorder ex-

hibited marked reductions in sleep during the night before they switched from depression to mania (38) and this finding were confirmed in other study also (39). These studies were taken as evidences to propose that bipolar disorder symptoms are the result of internal desynchronization of circadian rhythms (40).

Circadian rhythm disturbances in mood disorders

Circadian clock malfunctioning has suggested to be a contributory factor for mood disorders such as MDD, BD and SAD (40). Mood and circadian rhythms have a reciprocal relationship and share common features in neurobiology, clinical presentation and treatment methods. An interrelation between sleep, circadian rhythms and mood is illustrated in Figure 1. It is modified from the model presented by Foley et al. (41).

Disruptions of the circadian timekeeping system is said to result in neurobiological dysfunction due to changes in melatonergic system and those in the circadian clock functions, ultimately manifesting as a depressive episode and in subsequent as illness (40). The early evidence linking mood regulation and circadian rhythms was based on the phase-shift hypothesis, according to which mood disturbances arise from either a phase advance or a phase delay of the master circadian pacemaker with the rhythms of melatonin, cortisol, core body temperature, REM sleep, other circadian rhythms, and with the sleep-wake cycle (42). Kripke and his co-workers proposed in 1983 (43) that depression is due to the internal desynchronization of circadian oscillators, with a strong oscillator being linked to phase advances. Phase advances of core body temperature and REM sleep cycles in relation to the rest-activity cycles were reported in both unipolar and bipolar depressed patients (44). Similarly, a phase advance of (3 to 6 hours for) the peak of 3-methoxy-4-hydroxyphenylglycol excretion was reported in both manic and depressed patients (45). Abnormalities in the timing and distribution of REM and NREM sleep stages are suggested as primary characteristics of MDD (9). Hence, the proper study and understanding of the mechanisms involved in sleep and circadian rhythms disturbances will be helpful for explaining the pathophysiology that underlies mood disorders (46).

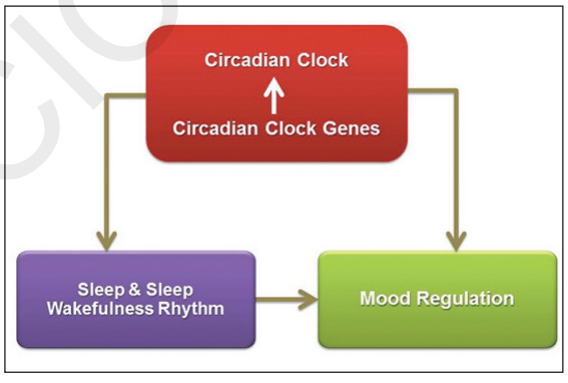

Figure 1 - Basic relationship of circadian rhythm, sleep and mood regulation.

Some studies demonstrate that suppression of REM sleep results in improvement of mood and have resorted into sleep deprivation (wake) therapy. However, the therapeutic effects of sleep deprivation therapy are influenced by the patient's characteristics and the diurnal variation in mood that contribute to the prognosis after sleep deprivation therapy (47). The relationship between mood adjustment and the circadian clock systems that regulate "diurnal preference" should also be considered while treating the patient. In this context, it has been found that the evening-type of preference to the daily activities increases the susceptibility for development of mood disorders (48, 49). Hence, the individual genetic effects that control the molecular mechanisms of circadian clocks are involved in mood disorders, and the assessment of these effects as well as response to treatment are important and need attention while treating patients with mood disorders.

A bidirectional relationship between regulation of daytime affect and night-time sleep exists, and disturbances during the day affect the night-time sleep and circadian functions (50). Most of the core symptoms of MDD exhibit circadian rhythmicity and are governed by the molecular clocks present in the SCN. The diurnal mood variation has its lowest point in the morning hours in most of the patients with MDD (42, 51). A poor coupling of the circadian oscillators to the external or the internal rhythms has been demonstrated in certain mood disorders.

Circadian clock genes and mood disorders

Polymorphisms in the core oscillator genes *CRY2, PER2, ARNTL* and *NPAS2* have been found to associate with SAD (52, 53). Sequence variations in these genes that form the functional unit at the core circadian clock have been shown to predispose to SAD, in specific to winter depression (52). Moreover, a detailed pattern of circadian gene expression was carried out with high quality post-mortem human brain samples obtained from six cortical and limbic regions (dorsolateral prefrontal cortex, anterior cingulate cortex, hippocampus, amygdala, nucleus accumbens, cerebellum) derived from 55 controls with no history of psychiatric or neurological illness, and from 34 patients with MDD (54). Among the top-ranked rhythmic genes that were covered in this study were the known clock genes *ARNTL*, *PER2*, *PER3*, *NR1D*, *DBP*, *BHLHE40* and *BHLHE41*. Findings of this study revealed the cyclical patterns for most of the known circadian genes and offered empirical evidence for molecular dysregulation of circadian rhythms across six brain regions of clinically depressed patients. Patients with MDD exhibited an abnormal phasing of circadian gene expression and disrupted phase relationships between circadian genes, which account for the disruption of regulation of a range of neural processes and behaviour that are manifested as MDD (54).

Results of this study could pave the way for identification of novel biomarkers and treatment targets for mood disorders (54).

In studies carried out on *CRY2* gene expression in depression, the effect of total sleep deprivation on the circadian oscillation of *CRY2* mRNA in human peripheral blood mononuclear cells was assessed, and it was observed that one-night total sleep deprivation led to an increase in *CRY2* mRNA levels in controls whereas in depressed patients with BD there was a decrease in *CRY2* mRNA levels (55). Further in this study, *CRY2* genetic variants were found to be significantly associated with winter depression or SAD (55). A recent study carried out on Chinese population involving 105 subjects with MDD and 485 controls reveals that MDD patients have significantly higher frequencies of C-allele and CC-genotype in *CRY1* rs2287161 and those of T-allele and TT-genotype in *TEF* rs738499 than controls (56). *CRY2* is a circadian gene that participates in regulation of the evening oscillator and its link to vulnerability for depression has been reported earlier in depressed bipolar patients (57). However, it needs to be pointed out that the Psychiatrics Genomics Consortia for schizophrenia, BD and MDD found no evidence for association of genes linked to control of the circadian rhythms and suggested that genes encoding components of molecular clock are not good candidates for harboring common variants that increase the risk to BD, schizophrenia or MDD (58). However, the genome-wide association studies that combine samples from different populations may not cover all the circadian genes and their variants and might thus have lost the relevant information.

The current understanding is that proteins encoded by the core circadian clock genes *ARNTL*, *ARNTL2*, *CLOCK* and *NPAS2* form heterodimers and bind to sites, or "boxes", to initiate the transcription of their target genes among which are the core circadian clock genes *CRY1*, *CRY2*, *PER1* and *PER2*. In turn, proteins encoded by these latter genes form heterodimers and act as repressors of the transcription-translation feedback loops of the circadian clocks. Sleep-related chronotherapies such sleep deprivations and sleep phase advances are effective in resetting the abnormal clock gene machinery and thereby correcting the abnormal circadian rhythms in terms of the phase, period and amplitude. This fact and the finding that these chronotherapies lead to improvement in mood suggest that "altered clock gene machinery" is likely to represent a core pathophysiological defect in a subset of patients with mood disorders (59).

Certain polymorphisms of *ARNTL* are said to associate with the predisposition to BD (60). Other circadian clock genes with a polymorphism reported to associate with BD include *CLOCK* (59), *NR1D1* and *Per3* (61-64). Meta-analysis of integrating data obtained from genome-wide association studies, as well as human and animal model studies, point out that other circadian genes like *RORA* and *RORB* are also associated with BD (65). Genetic variations in *ARNTL* are in addition found to associate with SAD (66). Activation of circadian gene transcription varies with the time of the day also. In day-active animals, *PER1* and *PER2* get activated in the morning hours, while *CRY1* and *CRY2* get activated in the evening hours (67). Both the dawn and dusk components, *PER2* and *CRY2* genetic variants respectively, are associated with SAD in particular (6, 57). A schematic diagram of polymorphisms of clock genes and mood disorders is presented in Figure 2.

There may be hundreds of genes in the human brain that are likely to be involved in the daily rhythmic events including the sleep-wake cycle. Daily rhythms in these genes are dysregulated in patients with mood

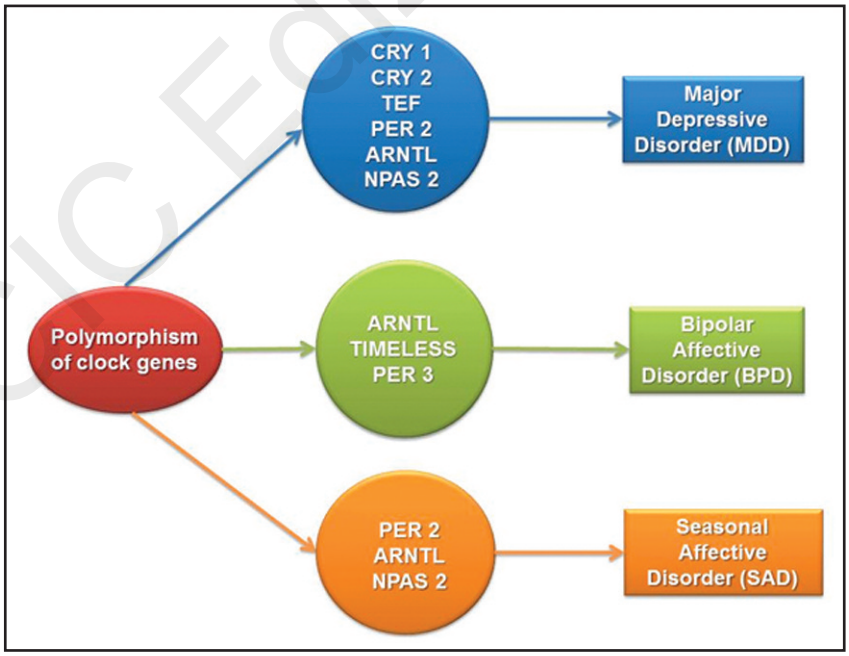

Figure 2 - Polymorphisms of clock genes and mood disorders.

disorders, suggesting thereby that mood disorders are due to dysregulation of circadian functions. This has been sufficiently substantiated by the abnormal rhythms in core body temperature, cortisol, melatonin, 3-methoxy-4-hydroxyphenylglycol, REM sleep latency, decreases in total sleep time and sleep efficiency, as has been discussed in the earlier paragraphs.

Studies of the physiological and molecular mechanisms underlying disrupted circadian rhythms and dysregulated sleep-wake mechanisms will greatly help not only in understanding the pathophysiology of mood disorders, but also will help to treat these disorders more effectively. Insomnia occurs in nearly 60 to 80% of patients with MDD (68). Antidepressant drugs that are commonly prescribed for treatment of depression may actually worsen insomnia and thus impair and postpone the full clinical remission from the illness. Tricyclic antidepressants, selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors all cause not only REM sleep suppression, but also may thereby aggravate insomnia of depressed patients (69). A comprehensive program of therapy for depression should address not only its clinical and behavioural signs and symptoms, but should focus its attention on concomitant symptoms like sleep and circadian rhythm disturbances (46, 68).

Agomelatine use for mood disorders

As depressive disorders are linked to disturbances of circadian rhythms, an antidepressant that benefits sleep quality and resets the disturbed circadian rhythms will have a superior efficacy (69, 70). An ideal anti-depressant should decrease SOL, decrease the number of awakenings after sleep onset, increase sleep quality during the night, and improve alertness during the day (71). Close to such ideal drug is the newly introduced melatonergic antidepressant agomelatine (Servier), an MT_1 and MT_2 melatonergic receptor agonist with 5-HT_{2C} antagonistic properties. This drug got its approval in November 2008 by the European Medicines Agency. A number of clinical trials involving multicenter and multinational studies has documented the clinical efficacy of agomelatine in MDD and found it having the efficacy superior over placebo in terms of response during the acute phase of treatment. The efficacy of agomelatine over sertraline, fluoxetine and escitalopram in MDD has been well documented. Agomelatine's treatment efficacy based on HDRS, CGI and Montgomery-Åsberg Depression Rating Scale (MADRS) have all been reviewed and its efficacy is equal to any other antidepressant (72-74).

Unlike other antidepressants agomelatine improves sleep continuity and sleep quality, increases sleep efficiency and the total amount of SWS (75). It also improves early NREM and REM sleep (76). A greater reduction in SOL during the night with a reduced daytime sleepiness was seen in agomelatine-treated depressed patients as compared with patients treated with escitalopram.

Agomelatine normalizes NREM sleep in depressed patients (77). Since changes in NREM sleep precede the clinical improvement, as assessed with the HDRS, it has been suggested that agomelatine's antidepressant effect is mediated through its ability to normalize sleep architecture (78). EEG analysis of the effects of agomelatine on sleep in patients with MDD shows that agomelatine (25 mg per day for 6 weeks) increases sleep efficiency with a decrease in awakenings, starting from day 7 onwards. Both SWS duration and percentage of time spent in SWS (sleep stages 3 and 4) increase significantly (78). As agomelatine did not influence REM latency or the amount of REM sleep, its antidepressant effect has been attributed to its action on correcting the abnormalities of the homeostatic system of sleep regulation (78).

Agomelatine's potential superiority over other antidepressants of the 5-HT_{2C} antagonists has been attributed to its effect of improving sleep at night and alertness during the day that is not seen with the use of other antidepressants. With agomelatine's combined mechanism of actions of preserving sleep quality at night-time and elevating mood during daytime, depressed patients experience a better quality of life (79). Agomelatine's sleep promoting melatonergic action counteracts its antihypnotic actions mediated through its 5-HT_{2C} antagonism. 5-HT_{2C} receptors are concentrated in the frontal cortex, amygdala, hippocampus and corticolimbic structures that all are involved in the regulation of mood and cognition (79).

As we have discussed in the earlier paragraphs, disruptions of circadian rhythms also correlate with the clinical severity of depression, a finding that is attributed to disturbances of sleep-wake cycle. As agomelatine is a specific agonist of MT_1 and MT_2 melatonergic receptors located in the SCN, it exerts its action by resetting the disturbed circadian rhythms including the sleep-wake rhythms seen in patients with MDD, and this action should be considered as an important component of its antidepressant effects. Agomelatine's chronobiotic effect was studied in healthy older men where this drug (50 mg per day) caused phase advances by 2 hours on average in core body temperature profiles and in the temporal organization of cortisol secretion (80). Phase delays of the circadian rhythms relative to the timing of the habitual sleep-wake cycle are an important contributing factor for the pathophysiology of SAD. Treatment with agomelatine (25 mg per day for 14 weeks) for acutely depressed patients with SAD by using *circascreen* (a self-rating scale for the assessment of sleep and circadian rhythm disturbances) demonstrated that the drug alleviated symptoms significantly from the second week of treatment onwards, and suggested that its hypnotic and resetting effects are important in the treatment of SAD. In a recent multicenter observational CHRONOS study conducted on 6,276 depressed patients agomelatine caused reduction in HAMD – score from a mean of 22.5 p6.9 at baseline to 4.7p4.7 at the end of 8 week treatment period .Improvements in sleep-wake cycle were confirmed in this study by the marked improvements in all three in-

somnia related HAMD -17 items (81).Rates of response and remission were high in both overall population and in the subgroup of ore severely depressed patients. As benefits of treatment observed in randomized studies do not always translate into clinical practice, the authors of the present study evaluated the antidepressant efficacy and tolerability of agomelatine in the naturalistic study and found agomelatine caused rapid onset of benefit across all HAMD-17 items showing agomelatine as highly effective in the treatment of depressive episodes in a "real world" clinical setting (81).

Conclusions

Disturbed sleep and disrupted circadian rhythms are two cardinal features seen in patients suffering from all three major types of mood disorders, including MDD, BD and SAD or winter depression. Sleep disturbance and depression have reciprocal relationships and influence each other. In MDD, sleep disturbances are a part of the diagnostic criteria. Besides exhibiting all major symptoms of insomnia like decreases in total sleep time and sleep efficiency, depressed patients also exhibit alteration in the temporal distribution of REM sleep. Polysomnographic studies on patients with MDD or BD yield objective findings of sleep disturbances, and these features are even used as "biologic markers" for identifying the specific type of mood disorders.

The task of a given antidepressant should be not only to improve the clinical and behavioural features, but also to improve the concomitant sleep disturbances. Hence, the effects of antidepressant on sleep should be given a main importance while prescribing a drug for treatment of depressive disorders. Second, as depression is linked to disturbances of circadian rhythms, an ideal antidepressant should reset the disrupted circadian rhythms in addition to correct the abnormalities of sleep stage dynamics. The currently used antidepressants while effective in producing a clinical remission also may exacerbate insomnia and may thus not be effective enough in tackling circadian and sleep-wake rhythm disturbances. In this context, the recently introduced melatonergic antidepressant agomelatine, with its dual mechanism of action on MT_1 and MT_2 melatonergic receptors in the SCN and other brain regions associated with sleep and circadian rhythm regulation, promotes sleep and resynchronize the disrupted circadian rhythms back to normal. These actions by themselves improve the clinical state of depressed patients having MDD, BD or SAD. In addition, agomelatine's action through 5-HT_{2C} antagonism in the prefrontal cortex, corticolimbic structures, hippocampus and amygdala, which are the key brain regions involved in mood regulation, relieves symptoms of depression and helps to achieve the clinical remission. All these events reinforce the hypothesis of direct involvement of melatonergic system in the aetiology of sleep and depressive disorders.

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