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Review

Pathophysiology of depression: Role of sleep and the melatonergic system

Venkataramanujan Srinivasan [a,1], Seithikurippu R. Pandi-Perumal [b,*], Ilya Trakht [b], D.Warren Spence [c], Ruediger Hardeland [d], Burkhard Poeggeler [d], Daniel P. Cardinali [e]

[a] *Department of Physiology, School of Medical Sciences, University Sains Malaysia, Kubang Kerian, Kota Bharu, Kelantan, Malaysia*
[b] *Division of Clinical Pharmacology and Experimental Therapeutics, Department of Medicine, College of Physicians and Surgeons of Columbia University, 630 West 168th Street- Rm # BB813, New York, NY 10032, USA*
[c] *Sleep and Alertness Clinic, 750 Dundas Street West, Toronto, Canada ON M6J-3S3*
[d] *Johann Friedrich Blumenbach Institute of Zoology and Anthropology, University of Goettingen, D-37073 Goettingen, Germany*
[e] *Departamento de Fisiología, Facultad de Medicina, Universidad de Buenos Aires, Paraguay 2155. 1121 Buenos Aires, Argentina*

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Abstract

Profound disturbances in sleep architecture occur in major depressive disorders (MDD) and in bipolar affective disorders. Reduction in slow wave sleep, decreased latency of rapid eye movement (REM) sleep and abnormalities in the timing of REM/non-REM sleep cycles have all been documented in patients with MDD. It is thus evident that an understanding of the basic mechanisms of sleep regulation is essential for an analysis of the pathophysiology of depressive disorders. The suprachiasmatic nucleus (SCN), which functions as the body's master circadian clock, plays a major role in the regulation of the sleep/wakefulness rhythm and interacts actively with the homeostatic processes that regulate sleep. The control of melatonin secretion by the SCN, the occurrence of high concentrations of melatonin receptors in the SCN, and the suppression of electrical activity in the SCN by melatonin all underscore the major influence which this neurohormone has in regulating the sleep/wake cycle. The transition from wakefulness to high sleep propensity is associated with the nocturnal rise of endogenous melatonin secretion. Various lines of evidence show that depressed patients exhibit disturbances in both the amplitude and shape of the melatonin secretion rhythm and that melatonin can improve the quality of sleep in these patients. The choice of a suitable antidepressant that improves sleep quality is thus important while treating a depressive disorder. The novel antidepressant agomelatine, which combines the properties of a 5-HT_{2C} antagonist and a melatonergic MT_1/MT_2 receptor agonist, has been found very effective for resetting the disturbed sleep/wake cycle and in improving the clinical status of MDD. Agomelatine has also been found useful in treating sleep problems and improving the clinical status of patients suffering from seasonal affective disorder.

Keywords: Depression; Sleep; Melatonin; Agomelatine; Suprachiasmatic nucleus; Chronobiotics; Seasonal affective disorder

Contents

* Corresponding author. Tel: +1 917 455 7147; fax: +1 212 342 2969.
E-mail address: sleepresearch@gmail.com (S.R. Pandi-Perumal).
[1] Current address for V. Srinivasan is: Prof. of Physiology, SRM Medical College & Research Centre SRM University Kattankulathoor -603203 Kancheepuram District INDIA.

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1. Introduction

According to the World Health Organization, depression affects nearly 121 million people worldwide. It is also one of the top 10 causes of morbidity and mortality (Rosenzweig-Lipson et al., 2007). Depression is a heterogeneous syndrome rather than a single disease, and has been characterized as a collection of "physiological, neuroendocrine, behavioral and psychological symptoms" (Nestler et al., 2002; Fuchs et al., 2006). Due to its complexity, many gaps remain in our understanding of the etiology and pathophysiology of depression. However, an increasing amount of evidence is now pointing to the possibility that chronobiological difficulties may underlie or at least accompany the condition. Numerous studies undertaken in depressive patients have suggested that a common comorbidity of depression is a dysregulation of the circadian timing system. This seems to occur in various types of depression, but is particularly evident in bipolar affective disorder (Bunney et al., 1970; Sitaram et al., 1978; Wehr and Goodwin, 1979).

In nearly 80% of depressed patients, including those with major depressive disorders (MDD) or bipolar affective disorder, profound disturbances in sleep architecture have been documented (Wehr and Goodwin, 1979; Reynolds and Kupler, 1988; Armitage and Hoffmann, 2001). It should be stressed that a marked overlap exists in the neuronal pathways regulating the sleep/wake cycle and those presumably altered in depressive illness (Lustberg and Reynolds, 2000). A particular feature of MDD is the abnormality in the timing and distribution of rapid eye movement (REM) and non-REM (NREM) sleep stages that can be regarded as a primary characteristic of the disease (Armitage, 2007). Studies of sleep in depressive and affective disorders have been useful in supporting theoretical considerations about their pathophysiology (Srinivasan et al., 2006).

The introduction of tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors in the 1960s prompted a host of studies on the possible neurotransmitter abnormalities in depressed patients. Those studies demonstrated that functional alterations in brainstem noradrenergic or serotonergic systems were involved in both the regulation of mood and affective behaviors and in the regulation of the sleep/wake cycle. Various imaging studies (Drevets, 2001; Mayberg, 2003; Berton and Nestler, 2006) have now shown that several brain areas such as the prefrontal cortex, cingulate cortex, hippocampus, striatum, amygdala and thalamus are active during the experience of sleep disorders (insomnia, fatigue) as well as of disorders of mood (including depressed mood, feelings of worthlessness, diminished ability to concentrate, recurrent thoughts of death or suicide, as well as other symptoms as per the DSM-IV criteria for depressive disorders (American Psychiatric Association, 1994).

Other studies have shown that an increased incidence of depressive symptoms correlates with poor sleep quality or chronic insomnia, disturbances which appear to be major risk factors for depression (Lustberg and Reynolds, 2000). Hence, an understanding of the physiological mechanisms of sleep regulation, and especially of the sequellae of their breakdown can assist in unraveling the complexities of the pathophysiology of depressive disorders.

Of particular importance in sleep regulation is the activity of the hypothalamic suprachiasmatic nucleus (SCN). The SCN determines the sleep/wake rhythm, consisting in the timing of sleep propensity and wakefulness, and, further, it helps to consolidate both states (Borbely, 1982; Edgar et al., 1993; Klerman et al., 1999; Zee and Manthena, 2007). Inasmuch as neurons of the SCN express high levels of MT_1 and MT_2 melatonin receptors (Dubocovich and Markowska, 2005), and, further, since exogenous melatonin has been shown to depress SCN neuronal activity (Liu et al., 1997) and to phase-shift the neuronal firing rate (McArthur et al., 1997), melatonin is assumed to be a key regulator of the sleep/wakefulness rhythm.

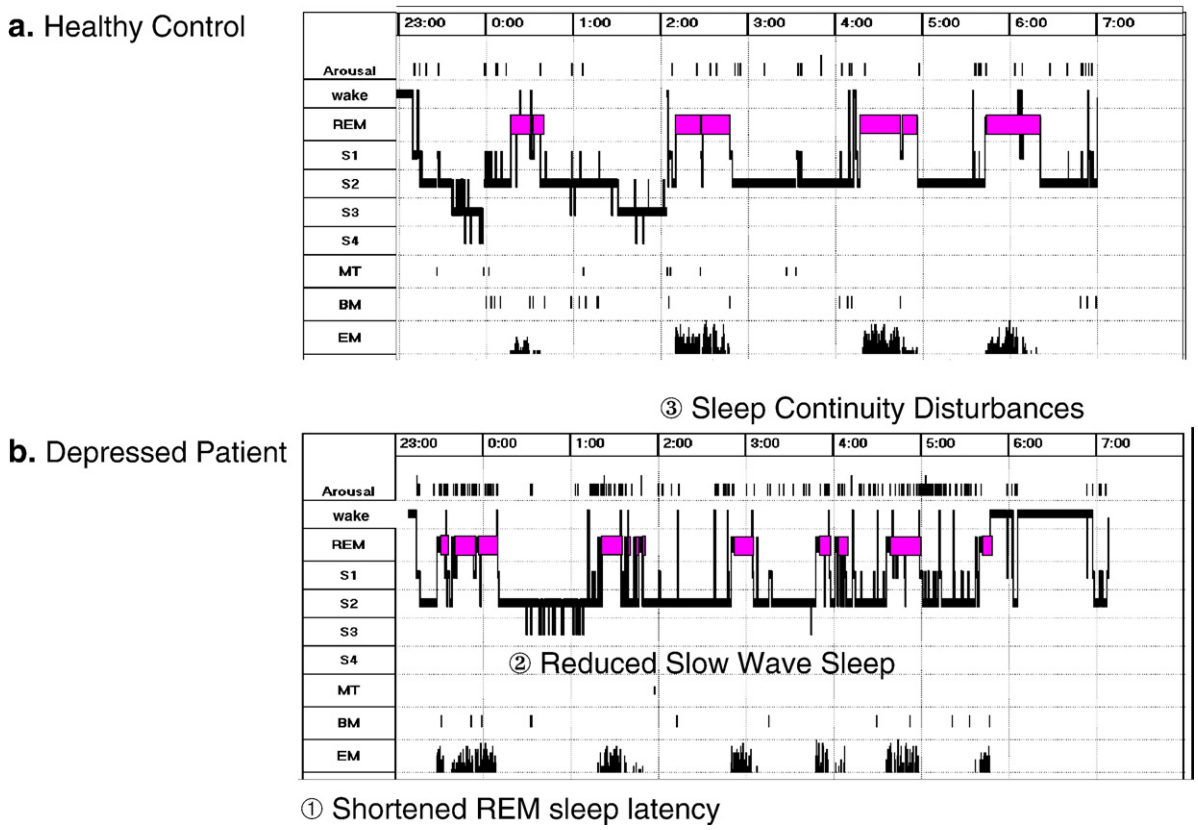

Fig. 1. The two polysomnograms show the characteristics of healthy sleep (a) in comparison with sleep in a depressed patient (b). (1) In depression, the period between sleep onset and the first occurrence of REM sleep, shown in gray, is markedly reduced (reduced REM latency). (2) The depressed patient spend less time in sleep stages 3 and 4 (reduced NREM sleep). (3) In depression, the number of awakenings and arousals is increased and the patient awakens early in the morning (disturbed sleep continuity). The sleep stages (REM, S1–4, sleep stages 1–4) are given across the time. BM, body movement; EM, eye movement (reproduced with permission from Nissen, C., Nofzinger, E.A., 2007. Sleep and depression: a functional neuroimaging perspective, In: Pandi-Perumal, S.R., Ruoti, R.R., Kramer, M. (Eds.), Sleep and Psychosomatic Medicine, Informa Healthcare, London, figure 5.1, pp. xxiii (color plate).

Moreover, the close association between sleep and mood disorders suggests that melatonin may also be important in the regulation of mood (Srinivasan et al., 2006).

2. Prevalence of sleep disorders in depression

Chronic insomnia is considered to be one of the most frequent and prominent factors that trigger depression and is often viewed as a predictor of a depressive disorder. In one study self-reported sleep disturbance was a major prodromal symptom 5 weeks prior to the recurrence of a depressive episode (Perlis et al., 1997). Depressed patients often complain of difficulties in falling asleep, frequent nocturnal awakenings and early morning wakefulness. Further, more than 90% of depressed patients suffer from impairment of sleep quality (Mendelson et al., 1987).

Sleep disturbances in depressed patients have been analyzed by polysomnography (PSG) (Fig. 1). A reduction in slow wave sleep, shortening of REM onset latency (REMOL), increased REM sleep, and sleep continuity disturbances were among the symptoms found in an assessment of untreated depressed patients (Kupfer et al., 1981). Indeed, REM sleep abnormalities are considered specific for MDD although there are some controversies on this issue. In a retrospective study of 67 male depressive patients and 67 carefully age-matched male healthy control subjects Hubain et al. (2006) found that the influence of age, severity, adaptation and gender were strongly associated with depressive symptoms. (Hubain et al., 2006). In contrast to most studies in this area, REM sleep was found to be reduced. Further, aging was found to influence most sleep variables, but not the order of their association with depression. One of the main markers of depression was the absence of sleep, a finding

that was interpreted to support the authors' conclusion that a possible linkage between hyperarousal and stress underlies its physiopathology (Hubain et al., 2006).

It is interesting to note that although unipolar and bipolar types of depression can be clearly distinguished, no significant differences between the two groups of patients are observed in terms of nocturnal sleep patterns (Duncan et al., 1979; Berger et al., 1982; Feinberg et al., 1982; Lauer et al., 1992). Further, the sleep abnormalities exhibited by manic patients are similar to those found in unipolar and bipolar depressed individuals (Hudson et al., 1992; Riemann et al., 2001). However, patients with seasonal affective disorder (SAD) do not show the sleep patterns seen in MDD (Anderson et al., 1994).

3. Sleep changes as markers for depression

Both epidemiological and electroencephalographic studies implicate sleep disturbance in the pathogenesis of depression (Lustberg and Reynolds, 2000). PSG studies in depressed patients show a reduction in the absolute number of delta waves during the first NREM sleep period and a general decrease in delta activity throughout the night (Fig. 1). Additionally, an alteration in the temporal distribution of REM sleep with impairment of the timing of the REM/NREM sleep cycle was documented (Buysse et al., 1997). It has been suggested that patients with decreased REMOL prior to treatment are prone of developing subsequent episodes of depression and experiencing rapid relapses after remission (Rush et al., 1989). The presence of sleep abnormalities in the first degree relatives of depressed patients (even those who never experienced the illness) suggests that these sleep changes can be viewed as "markers" of depression (Giles et al., 1990; Lustberg and Reynolds, 2000). The decrease in slow wave activity during the first NREM period and the increase of REM sleep occur more frequently in early depression although the significance of this is not clear (Kupfer and Ehlers, 1989).

Functional neuroimaging studies using positron emission tomography have indicated that MDD patients have higher rates of brain glucose metabolism during the first NREM sleep period as compared to non-depressed controls, a change associated with decreased slow wave activity (Gillin et al., 1996). Despite this associational evidence, whether sleep disturbance has a causal role on depression is still not completely resolved. However, the clinical management of depression should entail an awareness of the reciprocal relationship between insomnia and the depressive episodes (Lustberg and Reynolds, 2000). It has been suggested that the existence of abnormalities in the timing of REM/NREM sleep cycle in patients with depression is due to disturbances in the organization of pathways active in regulation of the sleep/wake cycle (Armitage, 2007).

4. Physiology of sleep regulatory mechanisms: role of the melatonergic system

Two different processes participate in sleep regulation, namely, a homeostatic mechanism depending on sleep debt and the circadian system that regulates sleep induction and wakefulness (Borbely, 1982). NREM sleep and, in particular, slow wave sleep, are controlled by the homeostatic processes. In healthy young individuals, sleep progresses through four non-REM stages (stage 1 through stage 4), which take nearly 70 to 90 min (Fig. 1). Stage 1 sleep represents the transition from drowsy wakefulness to deep sleep stages and accounts for less than 5% of the total sleep at night. Stage 2 sleep is characterized by the appearance of K-complexes and sleep spindles. Stage 3 and stage 4 are deep stages of sleep (i.e. slow wave sleep) and display desynchronized delta waves. Thereafter, the individual enters into a REM sleep episode followed by reentry into NREM. The elapsed time from sleep onset to the beginning of the first REM period is called REMOL.

Periods of NREM sleep constitute nearly 80% of the total sleep time while REM sleep accounts for 20% of the sleep time. REM sleep grows longer with each successive ultradian cycle. During each night, individuals experience approximately five cycles of NREM sleep and REM sleep that last 70 to 90 min each. This entire sequence of sleep stages throughout the night constitutes the "sleep architecture" of an individual (Fuller et al., 2006).

As mentioned above, physiological regulation of sleep involves a homeostatic process (referred to as "S", for sleep) that depends upon sleep and wakefulness period and a circadian process ("C") that is independent of sleep and waking behaviors (Borbely, 1982; Daan et al., 1984). The S component controls NREM sleep and the C component controls REM sleep and the ratio of NREM/REM sleep.

The SCN interacts with both sleep regulatory mechanisms, S and C. Indeed, it has been suggested that a functional disruption of the master clock plays a role in disorders of sleep and wakefulness (Zee and Manthena, 2007). Isolation of the SCN from other regions of the brain abolished circadian electrical activity in these brain structures without affecting the circadian electrical activity of SCN neurons (Inouye and Kawamura, 1979).

Melatonin is a major neurohormone influencing the activity of SCN neurons. The effect of melatonin is

exerted via two distinct melatonin receptors, MT_1 and MT_2 (Reppert et al., 1996; Dubocovich and Markowska, 2005). Melatonin inhibits (via MT_1 receptors) as well as phase-shifts (via MT_2 receptors) the electrical activity of SCN neurons (Mason and Brooks, 1988). In transgenic mice lacking MT_1 receptors, melatonin does not elicit acute inhibitory responses but can still shift the phase of circadian rhythmicity in SCN firing rate (Liu et al., 1997). Therefore, MT_2 receptors in the SCN are considered responsible for the phase-shifting and entrainment effects of melatonin. The firing rate of the SCN decreases in the transition from NREM to REM sleep, as shown by the simultaneous recording of electroencephalographic activity and SCN electrical activity in male Wistar rats (Deboer et al., 2003). These observations however require further confirmation in primates, since the relative amount of REM sleep in rodents is quite limited.

The role of the SCN in the regulation of sleep was first studied in squirrel monkeys. In this primate species SCN lesions, on the one hand, resulted in the loss of consolidated sleep/wake periods and, on the other hand, caused a prolonged sleep compared to animals with an intact SCN (Edgar et al., 1993). The evidence supported the conclusion that the circadian signal arising from the SCN promotes wakefulness during the day and facilitates consolidation of sleep during the subjective night. Indeed, the mechanisms by which the SCN regulates sleep appear to be complex. The primary projections from the SCN involve hypothalamic and extrahypothalamic structures (e.g., the basal forebrain or midline thalamic nuclei) that are involved in the regulation of sleep/wake cycle, autonomic regulation, psychomotor performance and melatonin secretion (Abrahamson et al., 2001; Aston-Jones, 2005; Saper et al., 2005). The main purpose of the SCN output system is to integrate environmental cues with the circadian system, thus conferring maximum flexibility to the response (Saper et al., 2005). Hence, the neural pathways from the SCN, which promote wakefulness are complemented by those involved in SCN promotion of sleep (Zee and Manthena, 2007). The sleep-promoting action of the SCN also depends upon melatonin whose circadian secretion is regulated by the SCN. Signals from the SCN have been shown to influence physiology and behavior including melatonin synthesis, temperature and sleep (Bunney and Bunney, 2000).

5. Regulation of melatonin secretion by the SCN

Melatonin secretion from the pineal gland is greater at night than during the day in all animal species, irrespective of whether they are diurnal, nocturnal or crepuscular (Cardinali and Pevet, 1998; Reiter, 2003; Claustrat et al., 2005). The circadian pattern of melatonin synthesis and secretion is abolished by SCN lesions (Klein and Moore, 1979). The circadian activity of the SCN is synchronized to the environmental light/dark cycle by light perceived in the retina. The signal from the retina is mainly transmitted to the SCN through a monosynaptic retinohypothalamic tract that originates from particular light-perceptive, melanopsin-containing retinal ganglion cells (Berson et al., 2002), plus a minor contribution given by mid-wavelength cones (Panda, 2007). Projections from the SCN pass through the paraventricular nucleus, medial forebrain bundle and reticular formation to reach the intermediolateral horn cells of the spinal cord. Fibers from these cells synapse with neurons of the sympathetic superior cervical ganglia, the source of the postganglionic sympathetic innervation of the pineal gland (Klein et al., 1971). NE released from the sympathetic nerve endings interacts with β-adrenoceptors in the pinealocyes and activates adenylate cyclase, thereby enhancing pineal melatonin synthesis and secretion. During the light phase of the daily photoperiod, when the SCN electrical activity is high, NE release is low, while during scotophase, when the SCN electrical activity is low, the increase in pineal NE release stimulates melatonin synthesis and secretion (Gerdin et al., 2004).

6. Melatonin's role in the regulation of sleep

The fact that the nocturnal increase of melatonin secretion occurs approximately 2 h in advance to the individual's habitual bedtime (Tzischinsky et al., 1993; Shochat et al., 1997) and that this correlates well with the onset of evening sleepiness have prompted many investigators to suggest that melatonin is involved in the physiological regulation of sleep (Zhdanova and Tucci, 2003). The period of wakefulness immediately prior to the increase of sleep propensity ('*opening of sleep gate*') is known as the '*forbidden zone*' for sleep (Strogatz et al., 1986; Lavie, 1986). During this time, the sleep propensity is lowest and SCN neuronal activity is very high (Buysse et al., 2004; Long et al., 2005). The transition from wakefulness/arousal to high sleep propensity coincides with the nocturnal rise of melatonin secretion (Dijk and Cajochen, 1997). Melatonin promotes sleep by inhibiting the firing of SCN neurons through activation of GABAergic mechanisms in the SCN (Niles, 1991; Golombek et al., 1996). From the studies on the effects of melatonin administration on sleep, it has been concluded that melatonin exerts both

direct hypnotic effects and circadian rhythm regulating effects on sleep (Rajaratnam et al., 2004).

As discussed above, PSG studies of adults with major depression have consistently shown that they suffer from various sleep abnormalities such as prolonged sleep onset latency, decreased slow wave sleep and increased REM sleep and sleep fragmentation. Taken together, this evidence suggests that melatonin, a major hormone involved in the regulation of sleep, merits consideration as one of the triggering factors underlying the pathogenesis of MDD and bipolar depressive disorder (Srinivasan et al., 2006).

7. Melatonin in MDD

The nature of disruption of melatonin secretion in MDD has been under intensive study ever since Wetterberg and his co-workers proposed MDD as a "*low melatonin syndrome*", a concept that focuses on low melatonin secretion as a biological marker for depression (Wetterberg, 1979). A number of studies have reported low nocturnal melatonin secretion in depressives (Venkoba rao et al., 1983; Claustrat et al., 1984; Nair et al., 1984; Brown et al., 1985; Beck-Friis et al., 1985; Sack and Lewy, 1988). However, increases in melatonin secretion in depressives has also been reported (Rubin et al., 1992; Shafii et al., 1996; Sekula et al., 1997; Crasson et al., 2004). The differences could be ascribed to changes in depressive symptomatology or to the pattern of melatonin secretion, inasmuch as there are studies showing that daytime melatonin secretion in depressives is increased (Crasson et al., 2004).

In a large scale study involving 382 postmenopausal women, the participants were asked to collect, measure and record every fractional urine voiding volume over two 24-h intervals in the course of the week, approximately 3 days apart (an average of ten specimens per 24 h) to measure urinary 6-sulfatoxymelatonin excretion (Tuunainen et al., 2002). 6-Sulfatoxymelatonin is the major melatonin metabolite in urine and is regarded as an index of melatonin secretion rate (Bojkowski and Arendt, 1990). A positive family history of depression was associated with a longer duration of urinary 6-sulfatoxymelatonin excretion (Tuunainen et al., 2002).

The association of depression and sleep disturbances was evaluated in 459 postmenopausal women, in which lower levels of illumination were found to be associated with more complaints of sleep and depressive symptoms (Kripke et al., 2004). Bright light treatment of women suffering from antepartum depression not only advanced the rhythm of melatonin secretion, but also mitigated depressive symptoms (Epperson et al., 2004).

Studies of sleep in recurrent depressive and bipolar disorders have been useful for constructing hypotheses about the etiology and pathophysiology of the disease. A marked reduction in sleep during the night immediately before switching from depression to mania was noted in bipolar depressive patients (Bunney et al., 1970; Sitaram et al., 1978; Wehr and Goodwin, 1979). Measurements of melatonin levels have shown significantly lower levels in unipolar and bipolar depressive patients (Beck-Friis et al., 1985; Souetre et al., 1989). Phase advances in melatonin secretion have also been noted in bipolar depressive patients (Lewy et al., 1979; Kennedy et al., 1989). The significance of the association of sleep disturbances and melatonin levels in bipolar depressive patients remains to be fully elucidated.

Exogenous melatonin administration affects the phase of the circadian oscillator regulating sleep/wakefulness (Arendt and Skene, 2005; Cardinali et al., 2006). Kayumov et al. (2001) studied eight depressed patients with an established diagnosis of delayed sleep phase syndrome, and whose sleep onset time and wake time were very much delayed. Melatonin treatment not only improved the total sleep time but also decreased the depressive symptoms (Kayumov et al., 2001), thus showing a relationship between sleep disturbance and the depressive symptomatology.

8. Antidepressants and sleep: role of the novel melatonergic antidepressant agomelatine

As noted above, sleep disturbances are key features of depressive symptomatology with more than 80% of depressed patients complaining of sleep disturbances (Reynolds and Kupler, 1988). Persistent insomnia is also one of the main causes for increased risk of relapse and recurrence of depression and also for increased risk of suicide in adults (Wingard and Berkman, 1983; Ford and Kamerow, 1989; Breslau et al., 1996). It is well known that most depression severity rating scales focus on insomnia or reduced total sleep time (Armitage, 2007). Disturbed sleep is one of the diagnostic criteria in the DSM-IV for major depressive disorder. Decreases in sleep efficiency, slow wave sleep and total sleep time, and increases in awakenings and in sleep onset latency time, have all been documented in patients with MDD (Lam, 2006). Although some studies show persistence of sleep architecture abnormalities even during remission phase (Rush et al., 1986) the improvement in the clinical state (Kupfer et al., 1981) or relapse (Cairns

et al., 1980) are preceded by sleep changes. Hence the administration of an appropriate antidepressant that improves sleep efficiency as well as reducing depressive symptomatology is very important for correcting the underlying neurochemical or neurophysiological abnormalities in MDD.

Classical antidepressants can influence sleep. However, the effects are diverse and vary among compounds. Some of them that are in clinical use improve the sleep of depressed patients after about 3 to 4 weeks of treatment, but their greatest effects are on REM sleep, with less consistent changes seen in NREM sleep (Lam, 2006). Compounds such as mianserin, nefazodone, and trazodone (5-HT antagonists) may promote sleep and improve its continuity (Argyropoulos and Wilson, 2005). However, the majority of available drugs generally produce unwanted negative effects on sleep (Lam, 2006). Antidepressants such as TCAs or selective serotonin reuptake inhibitors (SSRIs) suppress REM sleep and increase REMOL (Sonntag et al., 1996; Trivedi et al., 1999; Armitage et al., 2000).

Detailed analyses have revealed that drugs such as SSRIs (which are the most widely prescribed antidepressants) have adverse effects on sleep, and the depression associated insomnia is often worsened by the use of these drugs (Lam, 2006; Moltzen and Bang-Andersen, 2006). Hence, caution should be exercised in choosing an antidepressant. An ideal agent should not only mitigate symptoms of depression, but should also decrease sleep onset difficulties, reduce wakefulness after sleep onset, improve sleep quality and promote a feeling of freshness on the day after (Kupfer, 2006).

Prolonged treatment with antidepressants such as desipramine, clomipramine and fluoxetine has been shown to affect the distribution of melatonin receptor mRNAs in the brain. Most of the drugs increase the amount of MT_1 receptor mRNA in hippocampal regions (Imbesi et al., 2006). The extent to which the antidepressant response to a particular drug depends upon the distribution of melatonin receptors in the brain merits further detailed investigation (Hirsch-Rodriguez et al., 2006).

Agomelatine is a naphthalenic compound chemically designated as *N*-[2-(7-methoxynaphth-1-yl) ethyl]acetamide. It has been found to be effective as an antidepressant not only in animal models of depression, but also in patients with MDD. Agomelatine is a novel antidepressant drug which acts simultaneously as a melatonin MT_1 and MT_2 receptor agonist and as a 5-HT_{2C} antagonist (Yous et al., 1992; Millan et al., 2003). This dual mechanism of action is unique and is the basis of both its antidepressant efficacy and its capacity to mitigate sleep–wakefulness rhythm disorders (Krauchi et al., 1997). Agomelatine has been found to be effective in several animal models of depression such as learned helplessness (Bertaina-Anglade et al., 2002), chronic mild stress (Papp et al., 2003), forced swimming (Bourin et al., 2004), psychosocial stress in tree shrews (Fuchs et al., 2006) and transgenic mice with decreased glucocorticoid receptor (GR) expression (Barden et al., 2005). The latter model is based on evidence indicating that a malfunction of the GR system can be instrumental in depression (Pepin et al., 1992). The antidepressant activity of agomelatine was assessed in this transgenic mouse model by using a forced swimming test (Barden et al., 2005). In the same model, agomelatine was investigated for anxiolytic properties in the elevated plus maze. The effects of agomelatine were compared to those of desipramine or melatonin. Drugs were injected daily to mice i.p. at a 10 mg/kg dose for 21 to 42 days, 2 h before the onset of the dark period. Treatment with agomelatine reversed the decreased mobility seen in the transgenic mice in the forced swimming test, the effect being comparable to that of melatonin or desipramine. Both the number of open arm entries and the total time spent in open arms of the elevated plus maze were greatly increased in transgenic mice, and agomelatine was effective in reversing the transgenic mouse behavioral changes noted in the elevated plus maze (Barden et al., 2005). In the same study, agomelatine accelerated readjustment of circadian cycles of temperature and activity of transgenic mice following an induced phase-shift, the effect of agomelatine being more potent than that of melatonin (Barden et al., 2005). This resynchronizing effect of agomelatine is of considerable therapeutic value since an internal desynchronization of circadian rhythms (i.e., loss of synchronization between two or more rhythms so that they free-run with different periods within the same organism) is presumably implicated in the pathophysiology of depressive disorders (Wehr and Wirz-Justice, 1982; Lader, in press). Therefore, the antidepressant action of agomelatine could depend partially on its chronobiotic properties.

In a multicenter, multinational placebo-controlled study involving 711 patients from different European countries, agomelatine at doses of 25 mg/day was found to be very effective for improving depressive symptoms (Loo et al., 2002). Its antagonism of 5-HT_{2C} receptors coupled with its action on melatonergic receptors in the SCN, which can reset the disturbed circadian rhythms, accounts for agomelatine's therapeutic efficacy in more complex cases of depression (Rouillon, 2006). Because of its rapid promotion of symptom relief, agomelatine is

an ideal choice for clinical cases of depression in which sleep disturbance is a prominent feature (Pandi-Perumal et al., 2006).

Effects on sleep require a distinction between chronobiological aspects and those related to sleep stages. Concerning sleep architecture, different findings have been reported. In an earlier study (Cajochen et al., 1997), the acute administration of agomelatine for a single night resulted in increases in REM sleep without modifications of NREM sleep. In a more recent PSG study of depressive patients, agomelatine treatment in doses of 25 mg/day for 6 weeks improved both sleep quality and continuity. It also increased the duration of NREM sleep without modifying REM sleep (Salva et al., 2007). These findings demonstrate that while agomelatine's chronic and acute actions appear to be different, its sleep-promoting benefits remain constant.

The chronobiotic potential of agomelatine, which is not surprising in view of its melatonergic agonist effects, also extends to the synchronization of various body functions, a phenomenon which has been documented in at least one study (Leproult et al., 2005). The available evidence thus suggests that agomelatine is involved not only in sleep regulation but also promotes wakefulness (Dubocovich, 2006).

An ideal sleep-promoting compound should not cause hangover effects nor impair daytime activity. Agomelatine appears to approach this ideal inasmuch as in two studies it only occasionally caused mild fatigue (Pjrek et al., 2007), while improvements in daytime alertness were observed in other cases (Kupfer, 2006). The advantageous property of melatonergic agonists is that they promote sleep, at reasonable doses, only in the appropriate circadian phase, a characteristic also found with another MT_1/MT_2 agonist, ramelteon, which is, however, devoid of the 5-HT_{2C} receptor antagonism (Pandi-Perumal et al., 2007).

On the other hand, any antidepressant efficacy of agomelatine requires a continual action during daytime. On a solely chronobiological basis, agomelatine should not behave differently from an agent like ramelteon, which does not exhibit antidepressive properties (Pandi-Perumal et al., 2007). Therefore, agomelatine may continually modulate the serotonergic system during the day, without inducing sleepiness. Agomelatine's effects appear to be mediated physiologically inasmuch as this single compound, which also antagonizes 5-HT_{2C} receptors at night, acts differently in different circadian phases. These effects are in contrast to the mechanism of more traditional antidepressants which elevate the daytime mood of patients by activating the CNS. Consequently, if these drug effects are sustained into the night their mode of action can impair sleep quality (Ruhe et al., 2007). By contrast, agomelatine thus has a dually phased mechanism of action. At night, its sleep-promoting melatonergic effects prevail over its potentially antihypnotic 5-HT_{2C} antagonism, whereas during the day, its antidepressant action via 5-HT_{2C} inhibition is uncoupled from melatonin's nocturnal actions. This sequential mode could be regarded as a major advantage of agomelatine over other antidepressants (Millan, 2006). An enhanced level of sleep quality elevates the patient's mood in the morning and thus, while the antidepressant effect via 5-HT_{2C} inhibition prevails during the daytime hours, he experiences an improved quality of life. Another, perhaps substantial, advantage of agomelatine is that it has concomitant, neurogenic action in the hippocampus. This effect may underlie its antidepressant and anxiolytic properties (Banasr et al., 2006) and can have value for long-term antidepressant therapy.

The effectiveness of agomelatine's melatonergic and selective antiserotonergic action has been confirmed in a number of clinical trials. In a double-blind multicenter trial involving a large population of MDD patients ($n=165$), the efficacy of agomelatine (25 mg/day) was compared to that of venlafaxine (75 mg/day) ($n=167$) in terms of subjective sleep onset and sleep quality. At the end of one week, agomelatine treatment significantly improved subjective assessments of sleep onset and quality when compared to venlafaxine. The improvement in sleep quality with preserved daytime alertness as noted in this study was significant. A reduction in depressive symptoms was shown by decreases in scores on the Hamilton depression rating scale, which dropped from 20.0 to 11.±9.9 following agomelatine treatment (Guilleminault, 2005). Moreover, agomelatine improved sleep even before it elevated the mood thus suggesting that the improvement of sleep in depressed patients can be a prerequisite for improving their clinical status (Lam, 2006).

The superior efficacy of agomelatine over other antidepressants has been consistently supported by many investigations (Norman and Burrows, 2007). The drug was also found to display excellent tolerability at a daily dose of 25 mg and did not exhibit significant side effects to the extent and severity observed with other antidepressants such as SSRIs (Zupancic and Guilleminault, 2006; Pjrek et al., 2007). In particular, it did not produce sexual side effects (Montgomery, 2006), constipation, body weight gain, orthostatic hypotension or memory disorders (Hamon and Bourgoin, 2006). Moreover, agomelatine did not induce habituation nor addiction; for instance, in preclinical tests it was not self-administered

by rhesus monkeys (Wiley et al., 1998) and accordingly, did not cause discontinuation symptoms (Montgomery et al., 2004).

Although there has been no evidence of mental side effects associated with agomelatine an issue which remains to be explored is its potential toxicity (e.g. hepatotoxicity) following long-term use. Inasmuch as agomelatine is a naphthalenic compound, it should act on the P_{450} system and therefore its effects should be monitored closely.

9. Agomelatine in sleep disturbances of SAD

Seasonal affective disorder (SAD) or winter depression has been defined as a seasonal pattern of recurrent major depressive episodes that occur during winter/fall in the absence of seasonal psychosocial stressors, and with a full remission of symptoms in the spring/summer (American Psychiatric Association, 1994). A seasonal pattern can also occur in MDD and bipolar depressive disorder (Sohn and Lam, 2005; Lader, in press). Epidemiological studies show that the incidence of SAD in the general population is 15 to 25% (Axelsson et al., 2002; Magnusson and Boivin, 2003). Patients with SAD manifest atypical depressive symptoms such as carbohydrate craving, hypersomnia, hyperphagia or weight gain (Rosenthal et al., 1984).

Sleep disturbances are the hallmark of SAD and include hypersomnia, difficulty in waking up in the morning and daytime sleepiness during the winter season. These abnormal features disappear or are even reversed throughout the summer remission with the opposite symptoms of hyposomnia or insomnia (Rosenthal et al., 1984). Hypersomnia and late awakening are regarded as signs of both a phase delay and prolongation of melatonin secretion (Putilov and Danilenko, 2005). The phase delay of circadian rhythms relative to sleep that is documented in patients with SAD has been given as possible explanation for hypersomnia (Avery et al., 1997).

It is well known that in human chronobiological studies both core body temperature and melatonin secretion are used as "markers" for assessing circadian phase position. The phase delay of the circadian pacemaker relative to timing of the habitual sleep–wake cycle has been postulated to be a major contributing factor in the pathophysiology of SAD (Koorengevel et al., 2002). In some studies (Lewy et al., 1987, 1998; Sack et al., 1990) the dim light melatonin onset (DLMO) test has revealed that in patients with SAD the melatonin secretory pattern is phase delayed. Other studies (Checkley et al., 1993; Eastman et al., 1993; Wirz-Justice et al., 1996; Thompson et al., 1997) however have not confirmed this finding. SAD patients have been shown to exhibit longer periods of melatonin synthesis at night during winter as compared to summer (Wehr et al., 2001) thus suggesting that patients with SAD generate a "biological signal" with change in season in a manner similar to that of photoperiodic mammals.

Bright light treatment has been shown effective in correcting not only the phase abnormality of SAD patients but also their depressive symptoms as well. In a 4-week long study it was found that application of bright light (2500 lx) for 2 h in the morning (0600–0800 h) normalized circadian rhythmicity in core body temperature, cortisol and mood (Avery et al., 1997). Similarly, application of bright light for 7 days in the morning (0600–0800 h) improved scores in the Structured Interview Guide for the Hamilton Depression Rating Scale, SAD version (SIGH-SAD) in SAD patients (Rice et al., 1995). A significant correlation between the magnitude of phase advances of melatonin secretion after morning light and the improvement in the depression scores was observed (Terman et al., 2001). Bright light of high intensity (10 000 lx) was applied in that study for about 30 min. Terman et al. (2001) suggested that the best treatment for winter depression was to expose the patients to bright light 8.5 h after DLMO.

Following the identification of agomelatine as a MT_1/MT_2 melatonergic agonist with antidepressant properties, its efficacy was tested in 37 acutely depressed SAD patients (Pjrek et al., 2007). In an open study with agomelatine (25 mg/day in the evening) over 14 weeks, treatment outcome was assessed by the SIGH-SAD scale and Circscreen, a self-rating scale for the assessment of sleep and circadian rhythm disorders (Laredo et al., 2002). Agomelatine led to a progressive and statistically significant decrease of SAD symptoms from week 2 onward. Overall, treatment with agomelatine yielded a response rate of 75.7% and a remission rate of 70.3%. Throughout the study only one adverse event (mild fatigue) was related to the drug (Pjrek et al., 2007). These results indicate that SAD can be effectively and safely treated with agomelatine.

10. Conclusions

Epidemiological and electroencephalographic studies implicate serious sleep disturbances as one of the major underlying causes in MDD and bipolar disorder. Physiological sleep regulatory mechanisms include the active role of the SCN and modulatory effects of melatonin on the electrical activity of the SCN. Disturbances in the rhythm and the amplitude of melatonin secretion could account for symptomatic disturbances to

both sleep and mood. Antidepressants that are in use today have both beneficial and adverse effects on sleep. The recently introduced melatonergic antidepressant agomelatine with its melatonin agonist property and 5-HT_{2C} antagonist property has shown effectiveness for reducing symptoms. Additionally it has a demonstrated superiority over other antidepressants for improving sleep quality. It also has been found effective in alleviating sleep problems of patients with SAD. Analysis of factors involved in the disturbances of sleep and melatonin secretion suggest that disturbances of both these parameters may be contributing causal factors in the pathophysiology of depression.

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References

Abrahamson, E.E., Leak, R.K., Moore, R.Y., 2001. The suprachiasmatic nucleus projects to posterior hypothalamic arousal systems. Neuroreport 12, 435–440.

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders. 4th Ed (DSM-IV). American Psychiatric Press, Washington, DC.

Anderson, J.L., Rosen, L.N., Mendelson, W.B., Jacobsen, F.M., Skwerer, R.G., Joseph-Vanderpool, J.R., Duncan, C.C., Wehr, T.A., Rosenthal, N.E., 1994. Sleep in fall/winter seasonal affective disorder: effects of light and changing seasons. Journal of Psychosomatic Research 38, 323–337.

Arendt, J., Skene, D.J., 2005. Melatonin as a chronobiotic. Sleep Medicine Reviews 9, 25–39.

Argyropoulos, S.V., Wilson, S.J., 2005. Sleep disturbances in depression and the effects of antidepressants. International Review of Psychiatry 17, 237–245.

Armitage, R., 2007. Sleep and circadian rhythms in mood disorders. Acta Psychiatrica Scandinavica 104–115 Suppl.

Armitage, R., Hoffmann, R.F., 2001. Sleep EEG, depression and gender. Sleep Medicine Reviews 5, 237–246.

Armitage, R., Hoffmann, R., Fitch, T., Trivedi, M., Rush, A.J., 2000. Temporal characteristics of delta activity during NREM sleep in depressed outpatients and healthy adults: group and sex effects. Sleep 23, 607–617.

Aston-Jones, G., 2005. Brain structures and receptors involved in alertness. Sleep Medicine 6 (Suppl 1), S3–S7.

Avery, D.H., Dahl, K., Savage, M.V., Brengelmann, G.L., Larsen, L.H., Kenny, M.A., Eder, D.N., Vitiello, M.V., Prinz, P.N., 1997. Circadian temperature and cortisol rhythms during a constant routine are phase-delayed in hypersomnic winter depression. Biological Psychiatry 41, 1109–1123.

Axelsson, J., Karadottir, R., Karlsson, M.M., 2002. Differences in prevalence of seasonal affective disorder that are not explained by either genetic or latitude differences. International Journal of Circumpolar Health 61, 17–20.

Banasr, M., Soumier, A., Hery, M., Mocaer, E., Daszuta, A., 2006. Agomelatine, a new antidepressant, induces regional changes in hippocampal neurogenesis. Biological Psychiatry 59, 1087–1096.

Barden, N., Shink, E., Labbe, M., Vacher, R., Rochford, J., Mocaer, E., 2005. Antidepressant action of agomelatine (S 20098) in a transgenic mouse model. Progress in Neuropsychopharmacology and Biological Psychiatry 29, 908–916.

Beck-Friis, J., Kjellman, B.F., Aperia, B., Unden, F., von Rosen, D., Ljunggren, J.G., Wetterberg, L., 1985. Serum melatonin in relation to clinical variables in patients with major depressive disorder and a hypothesis of a low melatonin syndrome. Acta Psychiatrica Scandinavica 71, 319–330.

Berger, M., Doerr, P., Lund, R., Bronisch, T., von Zerssen, D., 1982. Neuroendocrinological and neurophysiological studies in major depressive disorders: are there biological markers for the endogenous subtype? Biological Psychiatry 17, 1217–1242.

Berson, D.M., Dunn, F.A., Takao, M., 2002. Phototransduction by retinal ganglion cells that set the circadian clock. Science 295, 1070–1073.

Bertaina-Anglade, V., Mocaer, E., Drieu La Rochelle, C., 2002. Antidepressant-like action of S20098 (agomelatine) in the learned helplessness test. International Journal of Neuropsychopharmacology 5 (suppl 1), S65.

Berton, O., Nestler, E.J., 2006. New approaches to antidepressant drug discovery: beyond monoamines. Nature Reviews Neuroscience 7, 137–151.

Bojkowski, C.J., Arendt, J., 1990. Factors influencing urinary 6-sulphatoxymelatonin, a major melatonin metabolite, in normal human subjects. Clinical Endocrinology (Oxford) 33, 435–444.

Borbely, A.A., 1982. A two process model of sleep regulation. Human Neurobiology 1, 195–204.

Bourin, M., Mocaer, E., Porsolt, R., 2004. Antidepressant-like activity of S 20098 (agomelatine) in the forced swimming test in rodents: involvement of melatonin and serotonin receptors. Journal of Psychiatry and Neuroscience 29, 126–133.

Breslau, N., Roth, T., Rosenthal, L., Andreski, P., 1996. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. Biological Psychiatry 39, 411–418.

Brown, R., Kocsis, J.H., Caroff, S., Amsterdam, J., Winokur, A., Stokes, P.E., Frazer, A., 1985. Differences in nocturnal melatonin secretion between melancholic depressed patients and control subjects. American Journal of Psychiatry 142, 811–816.

Bunney, W.E., Bunney, B.G., 2000. Molecular clock genes in man and lower animals: possible implications for circadian abnormalities in depression. Neuropsychopharmacology 22, 335–345.

Bunney Jr., W.E., Murphy, D.L., Goodwin, F.K., Borge, G.F., 1970. The switch process from depression to mania: relationship to drugs which alter brain amines. Lancet 1, 1022–1027.

Buysse, D.J., Frank, E., Lowe, K.K., Cherry, C.R., Kupfer, D.J., 1997. Electroencephalographic sleep correlates of episode and vulnerability to recurrence in depression. Biological Psychiatry 41, 406–418.

Buysse, D.J., Nofzinger, E.A., Germain, A., Meltzer, C.C., Wood, A., Ombao, H., Kupfer, D.J., Moore, R.Y., 2004. Regional brain glucose metabolism during morning and evening wakefulness in humans: preliminary findings. Sleep 27, 1245–1254.

Cairns, J., Waldron, J., MacLean, A.W., Knowles, J.B., 1980. Sleep and depression: a case study of EEG sleep prior to relapse. Canadian Journal of Psychiatry 25, 259–263.

Cajochen, C., Krauchi, K., Mori, D., Graw, P., Wirz-Justice, A., 1997. Melatonin and S-20098 increase REM sleep and wake-up propensity without modifying NREM sleep homeostasis. American Journal of Physiology 272, R1189–R1196.

Cardinali, D.P., Pevet, P., 1998. Basic aspects of melatonin action. Sleep Medicine Reviews 2, 175–190.

Cardinali, D.P., Furio, A.M., Reyes, M.P., Brusco, L.I., 2006. The use of chronobiotics in the resynchronization of the sleep/wake cycle. Cancer Causes & Control 17 (4), 601–609.

Checkley, S.A., Murphy, D.G., Abbas, M., Marks, M., Winton, F., Palazidou, E., Murphy, D.M., Franey, C., Arendt, J., 1993. Melatonin rhythms in seasonal affective disorder. British Journal of Psychiatry 163, 332–337.

Claustrat, B., Chazot, G., Brun, J., Jordan, D., Sassolas, G., 1984. A chronobiological study of melatonin and cortisol secretion in depressed subjects: plasma melatonin, a biochemical marker in major depression. Biological Psychiatry 19, 1215–1228.

Claustrat, B., Brun, J., Chazot, G., 2005. The basic physiology and pathophysiology of melatonin. Sleep Medicine Reviews 9, 11–24.

Crasson, M., Kjiri, S., Colin, A., Kjiri, K., L'hermite-Baleriaux, M., Ansseau, M., Legros, J.J., 2004. Serum melatonin and urinary 6-sulfatoxymelatonin in major depression. Psychoneuroendocrinology 29, 1–12.

Daan, S., Beersma, D.G., Borbely, A.A., 1984. Timing of human sleep: recovery process gated by a circadian pacemaker. American Journal of Physiology 246, R161–R183.

Deboer, T., Vansteensel, M.J., Detari, L., Meijer, J.H., 2003. Sleep states alter activity of suprachiasmatic nucleus neurons. Nature Neuroscience 6, 1086–1090.

Dijk, D.J., Cajochen, C., 1997. Melatonin and the circadian regulation of sleep initiation, consolidation, structure, and the sleep EEG. Journal of Biological Rhythms 12, 627–635.

Drevets, W.C., 2001. Neuroimaging and neuropathological studies of depression: implications for the cognitive–emotional features of mood disorders. Current Opinions in Neurobiology 11, 240–249.

Dubocovich, M.L., 2006. Agomelatine targets a range of major depressive disorder symptoms. Current Opinion in Investigational Drugs 7, 670–680.

Dubocovich, M.L., Markowska, M., 2005. Functional MT_1 and MT_2 melatonin receptors in mammals. Endocrine 27, 101–110.

Duncan Jr., W.C., Pettigrew, K.D., Gillin, J.C., 1979. REM architecture changes in bipolar and unipolar depression. American Journal of Psychiatry 136, 1424–1427.

Eastman, C.I., Gallo, L.C., Lahmeyer, H.W., Fogg, L.F., 1993. The circadian rhythm of temperature during light treatment for winter depression. Biological Psychiatry 34, 210–220.

Edgar, D.M., Dement, W.C., Fuller, C.A., 1993. Effect of SCN lesions on sleep in squirrel monkeys: evidence for opponent processes in sleep–wake regulation. Journal of Neuroscience 13, 1065–1079.

Epperson, C.N., Terman, M., Terman, J.S., Hanusa, B.H., Oren, D.A., Peindl, K.S., Wisner, K.L., 2004. Randomized clinical trial of bright light therapy for antepartum depression: preliminary findings. Journal of Clinical Psychiatry 65, 421–425.

Feinberg, M., Gillin, J.C., Carroll, B.J., Greden, J.F., Zis, A.P., 1982. EEG studies of sleep in the diagnosis of depression. Biological Psychiatry 17, 305–316.

Ford, D.E., Kamerow, D.B., 1989. Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? Journal of the American Medical Association 262, 1479–1484.

Fuchs, E., Simon, M., Schmelting, B., 2006. Pharmacology of a new antidepressant: benefit of the implication of the melatonergic system. International Clinical Psychopharmacology 21 Suppl 1, S17–S20.

Fuller, P.M., Gooley, J.J., Saper, C.B., 2006. Neurobiology of the sleep–wake cycle: sleep architecture, circadian regulation, and regulatory feedback. Journal of Biological Rhythms 21, 482–493.

Gerdin, M.J., Masana, M.I., Rivera-Bermudez, M.A., Hudson, R.L., Earnest, D.J., Gillette, M.U., Dubocovich, M.L., 2004. Melatonin desensitizes endogenous MT_2 melatonin receptors in the rat suprachiasmatic nucleus: relevance for defining the periods of sensitivity of the mammalian circadian clock to melatonin. FASEB Journal 18, 1646–1656.

Giles, D.E., Etzel, B.A., Biggs, M.M., 1990. Risk factors in unipolar depression: II. Relation between proband REM latency and cognitions of relatives. Psychiatry Research 33, 39–49.

Gillin, J.C., Buchsbaum, M.S., Valladares-Neto, D.C., Hong, C.C., Hazlett, E., Langer, S.Z., Wu, J., 1996. Effects of zolpidem on local cerebral glucose metabolism during non-REM sleep in normal volunteers: a positron emission tomography study. Neuropsychopharmacology 15, 302–313.

Golombek, D.A., Pevet, P., Cardinali, D.P., 1996. Melatonin effect on behavior: possible mediation by the central GABAergic system. Neuroscience Biobehavioral Reviews 20, 403–412.

Guilleminault, C., 2005. Efficacy of agomelatine versus venlafaxine on subjective sleep of patients with major depressive disorder. European Neuropsychopharmacology 15 Suppl 3, S419.

Hamon, M., Bourgoin, S., 2006. Pharmacological profile of antidepressants: a likely basis for their efficacy and side effects? European Neuropsychopharmacology 16 (Suppl 5), S625–S632.

Hirsch-Rodriguez, E., Imbesi, M., Manev, R., Uz, T., Manev, H., 2006. The pattern of melatonin receptor expression in the brain may influence antidepressant treatment. Medical Hypotheses 69, 120–124.

Hubain, P., Le Bon, O., Vandenhende, F., Van Wijnendaele, R., Linkowski, P., 2006. Major depression in males: effects of age, severity and adaptation on sleep variables. Psychiatry Research 145, 169–177.

Hudson, J.I., Lipinski, J.F., Keck Jr., P.E., Aizley, H.G., Lukas, S.E., Rothschild, A.J., Waternaux, C.M., Kupfer, D.J., 1992. Polysomnographic characteristics of young manic patients. Comparison with unipolar depressed patients and normal control subjects. Archives of General Psychiatry 49, 378–383.

Imbesi, M., Uz, T., Yildiz, S., Arslan, A.D., Manev, H., 2006. Drug and region-specific effects of protracted antidepressant and cocaine treatment on the content of melatonin MT1 and MT2 receptor mRNA in the mouse brain. International Journal of Neuroprotection and Neurogenetics 2, 185–189.

Inouye, S.T., Kawamura, H., 1979. Persistence of circadian rhythmicity in a mammalian hypothalamic "island" containing the suprachiasmatic nucleus. Proceedings of the National Academy of Sciences U. S. A. 76, 5962–5966.

Kayumov, L., Brown, G., Jindal, R., Buttoo, K., Shapiro, C.M., 2001. A randomized, double-blind, placebo-controlled crossover study of the effect of exogenous melatonin on delayed sleep phase syndrome. Psychosomatic Medicine 63, 40–48.

Kennedy, S.H., Tighe, S., McVey, G., Brown, G.M., 1989. Melatonin and cortisol "switches" during mania, depression, and euthymia in a drug-free bipolar patient. Journal of Nervous and Mental Disorders 177, 300–303.

Klein, D.C., Moore, R.Y., 1979. Pineal *N*-acetyltransferase and hydroxyindole-*O*-methyltransferase: control by the retinohypothalamic tract and the suprachiasmatic nucleus. Brain Research 174, 245–262.

Klein, D.C., Weller, J.L., Moore, R.Y., 1971. Melatonin metabolism: neural regulation of pineal serotonin: acetyl coenzyme A *N*-acetyltransferase activity. Proceedings of the National Academy of Sciences U. S. A. 68, 3107–3110.

Klerman, E.B., Boulos, Z., Edgar, D.M., Mistlberger, R.E., Moore-Ede, M.C., 1999. Circadian and homeostatic influences on sleep in the squirrel monkey: sleep after sleep deprivation. Sleep 22, 45–59.

Koorengevel, K.M., Beersma, D.G., den Boer, J.A., van den Hoofdakker, R.H., 2002. A forced desynchrony study of circadian pacemaker characteristics in seasonal affective disorder. Journal of Biological Rhythms 17, 463–475.

Krauchi, K., Cajochen, C., Mori, D., Graw, P., Wirz-Justice, A., 1997. Early evening melatonin and S-20098 advance circadian phase and nocturnal regulation of core body temperature. American Journal of Physiology 272, R1178–R1188.

Kripke, D.F., Jean-Louis, G., Elliott, J.A., Klauber, M.R., Rex, K.M., Tuunainen, A., Langer, R.D., 2004. Ethnicity, sleep, mood, and illumination in postmenopausal women. BMC Psychiatry 4, 8.

Kupfer, D.J., 2006. Depression and associated sleep disturbances: patient benefits with agomelatine. European Neuropsychopharmacology 16 (Suppl 5), S639–S643.

Kupfer, D.J., Ehlers, C.L., 1989. Two roads to rapid eye movement latency. Archives of General Psychiatry 46, 945–948.

Kupfer, D.J., Spiker, D.G., Coble, P.A., Neil, J.F., Ulrich, R., Shaw, D.H., 1981. Sleep and treatment prediction in endogenous depression. American Journal of Psychiatry 138, 429–434.

Lader, M., in press. Limitations of current medical treatments for depression: Disturbed circadian rhythms as a possible therapeutic target. European Neuropsychopharmacology in press.

Lam, R.W., 2006. Sleep disturbances and depression: a challenge for antidepressants. International Clinical Psychopharmacology 21 (Suppl 1), S25–S29.

Laredo, J., Quera-Salva, M.A., Flissard, B., de Bodinat, C., 2002. Screening of sleep and circadian rhythms in major depression. Journal of Sleep Research 11 (suppl. 1), 132–133.

Lauer, C.J., Wiegand, M., Krieg, J.C., 1992. All-night electroencephalographic sleep and cranial computed tomography in depression. A study of unipolar and bipolar patients. European Archives of Psychiatry and Clinical Neuroscience 242, 59–68.

Lavie, P., 1986. Ultrashort sleep–waking schedule. III. 'Gates' and 'forbidden zones' for sleep. Electroencephalography and Clinical Neurophysiology 63, 414–425.

Leproult, R., Van Onderbergen, A., L'hermite-Baleriaux, M., Van Cauter, E., Copinschi, G., 2005. Phase-shifts of 24-h rhythms of hormonal release and body temperature following early evening administration of the melatonin agonist agomelatine in healthy older men. Clinical Endocrinology (Oxford) 63, 298–304.

Lewy, A.J., Wehr, T., Gold, P.W., Goodwin, F.K., 1979. Plasma melatonin in manic depressive illness. In: Usdin, E., Kopin, I.J., Barchas, J.D. (Eds.), Catecholamines: Basic and Clinical Frontiers, vol II. Pergamon Press, Oxford, pp. 1173–1175.

Lewy, A.J., Sack, R.L., Singer, C.M., White, D.M., 1987. The phase shift hypothesis for bright light's therapeutic mechanism of action: theoretical considerations and experimental evidence. Psychopharmacological Bulletin 23, 349–353.

Lewy, A.J., Bauer, V.K., Cutler, N.L., Sack, R.L., Ahmed, S., Thomas, K.H., Blood, M.L., Jackson, J.M., 1998. Morning vs evening light treatment of patients with winter depression. Archives of General Psychiatry 55, 890–896.

Liu, C., Weaver, D.R., Jin, X., Shearman, L.P., Pieschl, R.L., Gribkoff, V.K., Reppert, S.M., 1997. Molecular dissection of two distinct actions of melatonin on the suprachiasmatic circadian clock. Neuron 19, 91–102.

Long, M.A., Jutras, M.J., Connors, B.W., Burwell, R.D., 2005. Electrical synapses coordinate activity in the suprachiasmatic nucleus. Nature Neuroscience 8, 61–66.

Loo, H., Hale, A., D'haenen, H., 2002. Determination of the dose of agomelatine, a melatoninergic agonist and selective 5-HT(2C) antagonist, in the treatment of major depressive disorder: a placebo-controlled dose range study. International Clinical Psychopharmacology 17, 239–247.

Lustberg, L., Reynolds, C.F., 2000. Depression and insomnia: questions of cause and effect. Sleep Medicine Reviews 4, 253–262.

Magnusson, A., Boivin, D., 2003. Seasonal affective disorder: an overview. Chronobiology International 20, 189–207.

Mason, R., Brooks, A., 1988. The electrophysiological effects of melatonin and a putative melatonin antagonist (*N*-acetyltryptamine) on rat suprachiasmatic neurones in vitro. Neuroscience Letters 95, 296–301.

Mayberg, H.S., 2003. Positron emission tomography imaging in depression: a neural systems perspective. Neuroimaging Clinics of North America 13, 805–815.

McArthur, A.J., Hunt, A.E., Gillette, M.U., 1997. Melatonin action and signal transduction in the rat suprachiasmatic circadian clock: activation of protein kinase C at dusk and dawn. Endocrinology 138, 627–634.

Mendelson, W.B., Sack, D.A., James, S.P., Martin, J.V., Wagner, R., Garnett, D., Milton, J., Wehr, T.A., 1987. Frequency analysis of the sleep EEG in depression. Psychiatry Research 21, 89–94.

Millan, M.J., 2006. Multi-target strategies for the improved treatment of depressive states: conceptual foundations and neuronal substrates, drug discovery and therapeutic application. Pharmacology and Therapeutics 110, 135–370.

Millan, M.J., Gobert, A., Lejeune, F., Dekeyne, A., Newman-Tancredi, A., Pasteau, V., Rivet, J.M., Cussac, D., 2003. The novel melatonin agonist agomelatine (S20098) is an antagonist at 5-hydroxytryptamine$_{2C}$ receptors, blockade of which enhances the activity of frontocortical dopaminergic and adrenergic pathways. Journal of Pharmacology and Experimental Therapeutics 306, 954–964.

Moltzen, E.K., Bang-Andersen, B., 2006. Serotonin reuptake inhibitors: the corner stone in treatment of depression for half a century—a medicinal chemistry survey. Current Topics in Medicinal Chemistry 6, 1801–1823.

Montgomery, S.A., 2006. Major depressive disorders: clinical efficacy and tolerability of agomelatine, a new melatonergic agonist. European Neuropsychopharmacology 16 (Suppl 5), S633–S638.

Montgomery, S.A., Kennedy, S.H., Burrows, G.D., Lejoyeux, M., Hindmarch, I., 2004. Absence of discontinuation symptoms with agomelatine and occurrence of discontinuation symptoms with paroxetine: a randomized, double-blind, placebo-controlled discontinuation study. International Clinical Psychopharmacology 19, 271–280.

Nair, N.P., Hariharasubramanian, N., Pilapil, C., 1984. Circadian rhythm of plasma melatonin in endogenous depression. Progress in Neuropsychopharmacology and Biological Psychiatry 8, 715–718.

Nestler, E.J., Barrot, M., DiLeone, R.J., Eisch, A.J., Gold, S.J., Monteggia, L.M., 2002. Neurobiology of depression. Neuron 34, 13–25.

Niles, L., 1991. Melatonin interaction with the benzodiazepine–GABA receptor complex in the CNS. Advances in Experimental Medical Biology 294, 267–277.

Norman, T.R., Burrows, G.D., 2007. Emerging treatments for major depression. Expert Reviews in Neurotherapeutics 7, 203–213.

Panda, S., 2007. Multiple photopigments entrain the Mammalian circadian oscillator. Neuron 53, 619–621.

Pandi-Perumal, S.R., Srinivasan, V., Cardinali, D.P., Monti, J.M., 2006. Could agomelatine be the ideal antidepressant? Expert Review Neurotherapeutics 6, 1595–1608.

Pandi-Perumal, S.R., Srinivasan, V., Poeggeler, B., Hardeland, R., Cardinali, D.P., 2007. Drug insight: the use of melatonergic agonists for the treatment of insomnia — focus on ramelteon. Nature Clinical Practice Neurology 3 (4), 221–228.

Papp, M., Gruca, P., Boyer, P.A., Mocaer, E., 2003. Effect of agomelatine in the chronic mild stress model of depression in the rat. Neuropsychopharmacology 28, 694–703.

Pepin, M.C., Pothier, F., Barden, N., 1992. Antidepressant drug action in a transgenic mouse model of the endocrine changes seen in depression. Molecular Pharmacology 42, 991–995.

Perlis, M.L., Giles, D.E., Buysse, D.J., Tu, X., Kupfer, D.J., 1997. Self-reported sleep disturbance as a prodromal symptom in recurrent depression. Journal of Affective Disorders 42, 209–212.

Pjrek, E., Winkler, D., Konstantinidis, A., Willeit, M., Praschak-Rieder, N., Kasper, S., 2007. Agomelatine in the treatment of seasonal affective disorder. Psychopharmacology (Berlin) 190, 575–579.

Putilov, A.A., Danilenko, K.V., 2005. Antidepressant effects of light therapy and "natural" treatments for winter depression. Biological Rhythm Research 36, 423–437.

Rajaratnam, S.M., Middleton, B., Stone, B.M., Arendt, J., Dijk, D.J., 2004. Melatonin advances the circadian timing of EEG sleep and directly facilitates sleep without altering its duration in extended sleep opportunities in humans. Journal of Physiology 561, 339–351.

Reiter, R.J., 2003. Melatonin: clinical relevance. Best Practice & Research. Clinical Endocrinology & Metabolism 17, 273–285.

Reppert, S.M., Weaver, D.R., Godson, C., 1996. Melatonin receptors step into the light: cloning and classification of subtypes. Trends in Pharmacological Sciences 17, 100–102.

Reynolds, C.F., Kupler, D., 1988. Sleep in depression. In: Williams, R.Z., Karacan, I., Moore, C.A. (Eds.), Sleep disorders, diagnosis and treatment. John Wiley, New York, pp. 147–164.

Rice, J., Mayor, J., Tucker, H.A., Bielski, R.J., 1995. Effect of light therapy on salivary melatonin in seasonal affective disorder. Psychiatry Research 56, 221–228.

Riemann, D., Berger, M., Voderholzer, U., 2001. Sleep and depression—results from psychobiological studies: an overview. Biological Psychology 57, 67–103.

Rosenthal, N.E., Sack, D.A., Gillin, J.C., Lewy, A.J., Goodwin, F.K., Davenport, Y., Mueller, P.S., Newsome, D.A., Wehr, T.A., 1984. Seasonal affective disorder. A description of the syndrome and preliminary findings with light therapy. Archives of General Psychiatry 41, 72–80.

Rosenzweig-Lipson, S., Beyer, C.E., Hughes, Z.A., Khawaja, X., Rajarao, S.J., Malberg, J.E., Rahman, Z., Ring, R.H., Schechter, L.E., 2007. Differentiating antidepressants of the future: efficacy and safety. Pharmacology and Therapeutics 113, 134–153.

Rouillon, F., 2006. Efficacy and tolerance profile of agomelatine and practical use in depressed patients. International Clinical Psychopharmacology 21 Suppl 1, S31–S35.

Rubin, R.T., Heist, E.K., McGeoy, S.S., Hanada, K., Lesser, I.M., 1992. Neuroendocrine aspects of primary endogenous depression. XI. Serum melatonin measures in patients and matched control subjects. Archives of General Psychiatry 49, 558–567.

Ruhe, H.G., Mason, N.S., Schene, A.H., 2007. Mood is indirectly related to serotonin, norepinephrine and dopamine levels in humans: a meta-analysis of monoamine depletion studies. Molecular Psychiatry 12, 331–359.

Rush, A.J., Erman, M.K., Giles, D.E., Schlesser, M.A., Carpenter, G., Vasavada, N., Roffwarg, H.P., 1986. Polysomnographic findings in recently drug-free and clinically remitted depressed patients. Archives of General Psychiatry 43, 878–884.

Rush, A.J., Giles, D.E., Jarrett, R.B., Feldman-Koffler, F., Debus, J.R., Weissenburger, J., Orsulak, P.J., Roffwarg, H.P., 1989. Reduced REM latency predicts response to tricyclic medication in depressed outpatients. Biological Psychiatry 26, 61–72.

Sack, R.L., Lewy, A.J., 1988. Melatonin and major affective disorders. In: Miles, A., Philbrich, D., Thompson, C. (Eds.), Melatonin: Clinical Perspectives. Oxford Medical Publications, New York, pp. 205–227.

Sack, R.L., Lewy, A.J., White, D.M., Singer, C.M., Fireman, M.J., Vandiver, R., 1990. Morning vs evening light treatment for winter depression. Evidence that the therapeutic effects of light are mediated by circadian phase shifts. Archives of General Psychiatry 47, 343–351.

Salva, M.A., Vanier, B., Laredo, J., Hartley, S., Chapotot, F., Moulin, C., Lofaso, F., Guilleminault, C., 2007. Major depressive disorder, sleep EEG and agomelatine: an open-label study. International Journal of Neuropsychopharmacology 1–6.

Saper, C.B., Scammell, T.E., Lu, J., 2005. Hypothalamic regulation of sleep and circadian rhythms. Nature 437, 1257–1263.

Sekula, L.K., Lucke, J.F., Heist, E.K., Czambel, R.K., Rubin, R.T., 1997. Neuroendocrine aspects of primary endogenous depression. XV: Mathematical modeling of nocturnal melatonin secretion in major depressives and normal controls. Psychiatry Research 69, 143–153.

Shafii, M., MacMillan, D.R., Key, M.P., Derrick, A.M., Kaufman, N., Nahinsky, I.D., 1996. Nocturnal serum melatonin profile in major depression in children and adolescents. Archives of General Psychiatry 53, 1009–1013.

Shochat, T., Luboshitzky, R., Lavie, P., 1997. Nocturnal melatonin onset is phase locked to the primary sleep gate. American Journal of Physiology 273, R364–R370.

Sitaram, N., Gillin, J.C., Bunney Jr., W.E., 1978. The switch process in manic-depressive illness. Circadian variation in time of switch and sleep and manic ratings before and after switch. Acta Psychiatrica Scandinavica 58, 267–278.

Sohn, C.H., Lam, R.W., 2005. Update on the biology of seasonal affective disorder. CNS Spectrums 10, 635–646.

Sonntag, A., Rothe, B., Guldner, J., Yassouridis, A., Holsboer, F., Steiger, A., 1996. Trimipramine and imipramine exert different effects on the sleep EEG and on nocturnal hormone secretion during treatment of major depression. Depression 4, 1–13.

Souetre, E., Salvati, E., Belugou, J.L., Pringuey, D., Candito, M., Krebs, B., Ardisson, J.L., Darcourt, G., 1989. Circadian rhythms in depression and recovery: evidence for blunted amplitude as the main chronobiological abnormality. Psychiatry Research 28, 263–278.

Srinivasan, V., Smits, M., Spence, W., Lowe, A.D., Kayumov, L., Pandi-Perumal, S.R., Parry, B., Cardinali, D.P., 2006. Melatonin in mood disorders. World Journal of Biological Psychiatry 7, 138–151.

Strogatz, S.H., Kronauer, R.E., Czeisler, C.A., 1986. Circadian regulation dominates homeostatic control of sleep length and prior wake length in humans. Sleep 9, 353–364.

Terman, J.S., Terman, M., Lo, E.S., Cooper, T.B., 2001. Circadian time of morning light administration and therapeutic response in winter depression. Archives of General Psychiatry 58, 69–75.

Thompson, C., Childs, P.A., Martin, N.J., Rodin, I., Smythe, P.J., 1997. Effects of morning phototherapy on circadian markers in seasonal affective disorder. British Journal of Psychiatry 170, 431–435.

Trivedi, M.H., Rush, A.J., Armitage, R., Gullion, C.M., Grannemann, B.D., Orsulak, P.J., Roffwarg, H.P., 1999. Effects of fluoxetine on the polysomnogram in outpatients with major depression. Neuropsychopharmacology 20, 447–459.

Tuunainen, A., Kripke, D.F., Elliott, J.A., Assmus, J.D., Rex, K.M., Klauber, M.R., Langer, R.D., 2002. Depression and endogenous melatonin in postmenopausal women. Journal of Affective Disorders 69, 149–158.

Tzischinsky, O., Shlitner, A., Lavie, P., 1993. The association between the nocturnal sleep gate and nocturnal onset of urinary 6-sulfatoxymelatonin. Journal of Biological Rhythms 8, 199–209.

Venkoba rao, A., Parvathi Devi, S., Srinivasan, V., 1983. Urinary melatonin in depression. Indian Journal of Psychiatry 25, 167–172.

Wehr, T., Goodwin, F.K., 1979. Tricyclics modulate frequency of mood cycles. Chronobiologia 6, 377–385.

Wehr, T.A., Wirz-Justice, A., 1982. Circadian rhythm mechanisms in affective illness and in antidepressant drug action. Pharmacopsychiatria. 15, 31–39.

Wehr, T.A., Duncan Jr., W.C., Sher, L., Aeschbach, D., Schwartz, P.J., Turner, E.H., Postolache, T.T., Rosenthal, N.E., 2001. A circadian signal of change of season in patients with seasonal affective disorder. Archives of General Psychiatry 58, 1108–1114.

Wetterberg, L., 1979. Clinical importance of melatonin. Progress in Brain Research 52, 539–547.

Wiley, J.L., Dance, M.E., Balster, R.L., 1998. Preclinical evaluation of the reinforcing and discriminative stimulus effects of agomelatine (S-20098), a melatonin agonist. Psychopharmacology (Berlin) 140, 503–509.

Wingard, D.L., Berkman, L.F., 1983. Mortality risk associated with sleeping patterns among adults. Sleep 6, 102–107.

Wirz-Justice, A., Graw, P., Krauchi, K., Sarrafzadeh, A., English, J., Arendt, J., Sand, L., 1996. 'Natural' light treatment of seasonal affective disorder. Journal of Affective Disorders 37, 109–120.

Yous, S., Andrieux, J., Howell, H.E., Morgan, P.J., Renard, P., Pfeiffer, B., Lesieur, D., Guardiola-Lemaitre, B., 1992. Novel naphthalenic ligands with high affinity for the melatonin receptor. Journal of Medical Chemistry 35, 1484–1486.

Zee, P.C., Manthena, P., 2007. The brain's master circadian clock: implications and opportunities for therapy of sleep disorders. Sleep Medicine Reviews 11, 59–70.

Zhdanova, I.V., Tucci, V., 2003. Melatonin circadian rhythms and sleep. Current Treatments and Options in Neurology 5, 225–229.

Zupancic, M., Guilleminault, C., 2006. Agomelatine: a preliminary review of a new antidepressant. CNS Drugs 20, 981–992.