Circadian Rhythms, Melatonin and Depression

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Abstract: The master biological clock situated in the suprachiasmatic nuclei of the anterior hypothalamus plays a vital role in orchestrating the circadian rhythms of multiple biological processes. Increasing evidence points to a role of the biological clock in the development of depression. In seasonal depression and in bipolar disorders it seems likely that the circadian system plays a vital role in the genesis of the disorder. For major unipolar depressive disorder (MDD) available data suggest a primary involvement of the circadian system but further and larger studies are necessary to conclude.

Melatonin and melatonin agonists have chronobiotic effects, which mean that they can readjust the circadian system. Seasonal affective disorders and mood disturbances caused by circadian malfunction are theoretically treatable by manipulating the circadian system using chronobiotic drugs, chronotherapy or bright light therapy. In MDD, melatonin alone has no antidepressant action but novel melatoninergic compounds demonstrate antidepressant properties. Of these, the most advanced is the novel melatonin agonist agomelatine, which combines joint MT1 and MT2 agonism with 5-HT$_{2C}$ receptor antagonism. Adding a chronobiotic effect to the inhibition of 5-HT$_{2C}$ receptors may explain the rapid impact of agomelatine on depression, since studies showed that agomelatine had an early impact on sleep quality and alertness at awakening. Further studies are necessary in order to better characterize the effect of agomelatine and other novel melatoninergic drugs on the circadian system of MDD patients.

In summary, antidepressants with intrinsic chronobiotic properties offer a novel approach to treatment of depression.

Keywords: Major depression disorder, circadian rhythms, melatonin, melatonin agonists.

INTRODUCTION

Until recently, most available antidepressants acted via mono-aminergic mechanisms. This review focuses on the possible circadian aspects of major depression, which have been highlighted by the effective antidepressant activity of a novel melatoninergic agonist, agomelatine. Agomelatine has a dual mechanism of action acting as both a melatonergic agonist and a 5-hydroxytryptamine 2C (5-HT$_{2C}$) antagonist.

THE CIRCADIAN RHYTHM

All biological processes are organized according to time-dependent cycles, the most basic one being the 24-hour cycle (the circadian rhythm). Many processes have circadian rhythmicity, and these are orchestrated by the suprachiasmatic nuclei (SCN) located in the anterior hypothalamus [3] which has been shown to have an intrinsic rhythm and acts as the master biological clock. The circadian clock, at the molecular level, involves genes such as Period (Per1/2/3), Cryptochrome (Cry1/2), Bmal1, Clock and some nuclear orphan receptors (Rev-erbα/β and Rorα/β/γ) that participate in the genesis of the observed rhythms [4-6].

Models of sleep regulation show that sleep is modulated by both the homeostatic process and the circadian process [7, 8]. The homeostatic process tracks sleep need, which increases during wakefulness and decreases while sleep. The higher the sleep need, the easier it is to fall asleep. However sleep timing and sleep structure depend on both the circadian and the sleep-homeostatic system which are intimately interrelated at the molecular level. Clock genes implicated in circadian rhythmicity are also involved in sleep homeostasis [9] (for review see Franken and Dijk [10]).

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MELATONIN AND THE CIRCADIAN SYSTEM

Melatonin (MEL, N-acetyl-5-methoxytryptamine) was discovered by the American dermatologist Aaron Lerner in 1958 [11] and is primarily synthesised by the pineal gland during darkness. The activity of the pineal gland is very sensitive to circadian and seasonal variations in the length of the photoperiod, i.e. the respective duration of light and dark exposure, and acts as a 'photoneuroendocrine transducer' – providing information about day length. The photoperiodic day/night message is transmitted from the retina to the pineal gland through a polysynaptic pathway via the SCN, the final link of which is a noradrenergic synapse from the superior cervical ganglion to the pineal gland [12]. The SCN clock thus drives most circadian biological rhythms including MEL secretion, the "rest/activity rhythm" and core body temperature [13,14]. The activity of the SCN is modulated by MEL via a regulatory feedback loop. MEL levels in the pineal are low during the day, begin to increase soon after darkness begins, reach peak levels at mid darkness and then decrease towards the end of the night to reach daytime levels shortly before light onset. MEL secretion is inhibited by light. The light signal from the retina is transmitted to the SCN via a photoreceptor system. Photoreception in mammalian retina is not restricted to rods and cons but extends to a subset of retinal ganglion cells expressing the photopigment melanopsine (mRGCs). In mammals, circadian photoentrainment is dependent on the light-evoked output from intrinsically photosensitive retinal ganglion cells (ipRGCs) to the SCN of the hypothalamus. mRGCs projections extend across the dorsolateral geniculate nucleus origin of the thalamo-cortical projection neurons and are known to drive such reflex responses as circadian photoentrainment for short-wavelength blue light and pupillomotor movements. Newer work in rodents suggests that rods photoreceptors drive circadian photo entrainment across a wide range of light intensities [15,16]. However, mRGCs survive even with complete rod and cone loss and could make a significant contribution to assessing brightness and

supporting vision even in people with advanced retinal degeneration [17-19].

Exposure to bright light thus acts as a signal to the circadian clock. The periodicity of the circadian clock has been shown, in controlled conditions, to be slightly longer than 24 hours [20], and the clock is reset every morning by exposure to daylight. In humans peak values of MEL concentration occur in the middle of the night and are associated with the lowest point in rhythms of core body temperature, alertness, mental performance and many metabolic functions, and with maximum sleep propensity. Studies have shown that MEL is able to regulate the vascular tone of the caudal artery in the rat [21], and this effect on the presence of peripheral melatonin receptors may explain melatonin's effects on the thermoregulatory system [22].

Recent studies have shown that the biological clock, like other physiological processes, is affected by aging, with reductions in melatonin secretion noted in many studies [23-25]. This may be in part due to changes in the cornea affecting the quantity of light stimulating ipRGCs, to behavioural changes which limit light exposure [26] and other zeitgebers (e.g. physical activity), and also to changes in the pineal gland [27]. The changes in circadian rhythms explain many of the sleep changes noted in the elderly such as increased sleep fragmentation, daytime sleepiness and phase advances [28-30].

MELATONIN AND RECEPTORS

MEL acts mainly through two G protein-coupled receptors with 7 transmembrane domains, named MT1 and MT2 [31]. These two receptors are present in the retina, SNC, adrenal glands, liver, arteries, heart, kidneys, gastrointestinal tract, macrophages, adipocytes and blood platelets [32,33]. When activated, according to the cells, melatonin frequently decreases cAMP, but may also activate phospholipase C and protein kinase C, acting via the MAP kinase or PI3 kinase. Both the chronobiotic and soporific actions of MEL are largely or, perhaps, exclusively mediated by MT1 and MT2 receptors (see Dubocovich *et al* for a comprehensive review on MT receptors) [34]. In the SCN, these two receptors seem to act in a concerted way, resetting the circadian clock via the MT2 receptor and suppressing neuronal firing via MT1 receptor. The third known binding site is named MT3. This MT3 binding site is a non-classical one since it is not a seven transmembrane domain receptor, but an enzyme, quinone reductase 2. It is widely distributed in mammals [35, 36]. The relationship between the multiple physiological functions of MEL and this protein remains unclear.

EXOGENOUS MELATONIN ADMINISTRATION

MEL has a short half live in the circulation, with a range of 20 to 45 minutes [37] which is largely caused by an extensive hepatic first-pass metabolism. Understanding the effects of MEL on circadian rhythms requires separating acute sedative effects from phase shifting (moving the timing of circadian rhythms) effects, also referred to as "chronobiotic" effects [38]. Exogenous MEL administration has both acute and phase-shifting effects on sleep and on more strongly endogenous circadian rhythms such as the core body temperature [13]. The phase shifting effects are determined by the time of administration, which is known as the MEL "phase response curve" [39]. Exogenous MEL given in the late afternoon or early evening will advance the circadian clock, while early morning treatment delays the circadian clock. Taken in the middle of the day, no phase shifting effect is seen. The phase response curve for exogenous MEL in man exhibits a shift of 12 hours in relation to the response curve for bright light treatment. In other words, exogenous MEL in the evening advances the circadian clock but this effect may also be obtained by phototherapy (bright light) treatment given in the morning. Phase shifts affect sleep wake rhythms, with phase advances leading to earlier falling asleep and waking times, while phase delay leads to later sleep onset and

waking times. However while MEL given in the early evening is an advancer of circadian rhythm, it is less potent as a delayer of circadian rhythm when given in the morning [40], and in clinical practice it is preferable to administer phototherapy in the evening since MEL can also produce unwanted drowsiness (an acute effect) when given in the morning [41]. Thus, exogenous MEL is particularly effective in circadian rhythm disorders with phase delay such as delayed sleep phase syndrome (where patients need to fall asleep and wake earlier than they are actually doing) [42] and in the more rare free-running or non 24-hour circadian rhythm which is due to a lack of synchronization of the SCN with social and environmental time cues, where exogenous melatonin acts as a signal of the photoperiod [43]. Free-running or non 24-hour circadian rhythm is seen in the totally blind patients, in patients with CNS lesions, and in a number of neurological diseases.

MELATONIN AND SLEEP

Although it is certain that exogenous MEL has an entrainment effect on circadian rhythms in humans [13,14], its mechanism of action as a sleep inducer is less clear. Thermoregulatory processes have long been implicated in the initiation of human sleep, as sleep occurs on the downward slope of the core temperature curve occurring in the evening. This distal heat loss, via vasodilatation and increased skin temperature, seems to be intimately coupled with increased sleepiness and sleep induction. Exogenous MEL administration during the day when MEL is absent mimics the endogenous thermophysiological processes occurring in the evening and the sleep facilitating effect of MEL may be related to a hypothermic response mediated by peripheral vasodilatation [22, 44].

SEROTONIN, 5-HT$_{2C}$ RECEPTORS, MOOD AND CIRCADIAN SYSTEM

Serotonin (5-HT) plays an important role in the regulation of the time-keeping system in nocturnal and diurnal rodents [45] with a modulation of light-induced phase shifts by the serotonergic system [45-47]. The implication of the serotonergic system may explain the potentiation of light induced phase delay by exercise which activates the serotonergic system [48] .

5-HT$_{2C}$ receptors are present in the SCN, where they modify the response of intrinsic neurons to photic input [45, 49, 50]. Interestingly, a polysynaptic circuit runs from the SCN to the ventrotegmental nucleus, the origin of mesocortical and mesolimbic dopaminergic pathways [51]. This neural link provides an anatomical substrate for an indirect influence of SCN-localized 5-HT$_{2C}$ receptors on ascending dopaminergic transmission. Moreover, 5-HT$_{2C}$ receptors are also present in the locus coeruleus which is the source of forebrain adrenergic pathways [52] . Adrenergic and dopaminergic pathways are therefore subject to indirect inhibition by 5-HT$_{2C}$ receptors, acting through the excitation of GABAergic neurons. So, their blockade disinhibits fronto-cortical dopaminergic and adrenergic transmission, the activity of which may be compromised in depression [52, 53]. Sleep deprivation seems to decrease activity of 5-HT$_{2C}$ receptors [52] and 5-HT$_{2C}$ receptors antagonists promote slow-wave sleep [54]. Overall, it appears that 5-HT$_{2C}$ receptor antagonism should favourably influence mood, circadian synchronisation and sleep quality.

IMPLICATION OF THE CIRCADIAN SYSTEM IN UNIPOLAR MAJOR DEPRESSION DISORDER (MDD)

Disturbance of sleep-wake cycles is one of the core symptoms of MDD [55, 56]. The most frequently reported sleep disturbance is insomnia, usually in the form of sleep maintenance insomnia following nocturnal awakenings or early morning wakening. It has been estimated that up to 80% of depressed patients experience some form of insomnia [57, 58]. However, insomnia is not the only sleep disturbance associated with MDD, as hypersomnia, fatigue, and daytime drowsiness are also highly prevalent [59]. Sleep dis-

turbances in MDD may be determined at a molecular level as a polymorphism in CLOCK protein with C alleles associated with a higher incidence of initial insomnia [60, 61], although more recent studies have shown that CLOCK protein polymorphism (CLOCK 3111T/C) is not specifically linked to MDD [62]. However, there are only few studies comparing the association of CLOCK variant in mood disorders and controls [63] and it is possible that the CLOCK genotype is associated with certain mood disorders, patient characteristics or ethnic differences. For example, a recent study in Korean patients compared to a control population found an association between CLOCK 3111T/C and bipolar disorder [64]. Further analysis of clock machinery may clarify the contribution of clock genes to mood disorders and the association of mood disorders and sleep disorders.

Several factors link the circadian system to depression:

1. A circadian variation in mood is present in both healthy and depressed patients, with the majority of depressed patients having lower mood in the morning [65] although a subset show reverse diurnal variation [66].

2. Difficulties falling asleep associated with early morning awakening are common in depression [67], and both advance and delay of circadian rhythms can be seen (see below). Poor sleep maintenance and diurnal sleepiness frequently seen in depression may represent blunting of circadian rhythms. Seasonal depression is typically associated with hypersomnia and delayed circadian phase measured by core temperature and melatonin secretion [68], although 24-hour cortisol secretion is variable [69].

3. Treatments targeting circadian rhythms such as bright light therapy, sleep deprivation, and behavioural therapies have been shown to be effective, suggesting that depression is associated with alterations in circadian rhythmicity (for reviews see Terman [70] and Wirtz Justice *et al.* [71]).

4. Patients with genetic circadian disorders such as familial advanced phase sleep syndrome [72] and delayed sleep phase syndrome [73] and acquired disorders such as shift-work sleep disorder [74,75] have an increased incidence of depression.

It seems likely that a bidirectional effect between depression and circadian changes exists [76] as not only does depression lead to circadian changes, but circadian changes are also associated with a higher incidence of depression.

A great deal of depression research over the last decade [77] [78] has focused on changes in processes linked to circadian rhythms in patients with seasonal and non-seasonal depression. Mood, sleep, core temperature, hormone secretion and circadian rhythms have been found to be phase shifted, diminished in amplitude or out of phase with each other. Sleep modifications in MDD are associated with changes in timing and amplitude of MEL secretion [79-82] (see Bunney and Potkin [83], for comprehensive review) or disorganised with circadian misalignment between MEL onset time and sleep mid point time [84]. In addition, most studies confirm an increased core temperature and decreased peak amplitude in MDD [85] , implying blunting of the circadian rhythm. Remission is associated with a normalization of temperature rhythm amplitude [86] . Cortisol and norepinephrine secretion have been found to be phase advanced [87], although 24-hour cortisol secretion is variable [69]. Recent published data suggest that the most common circadian phase disturbance in depression may actually be a phase delay and not advance [88].

In conclusion, as changes are noted in many of the rhythms orchestrated by the biological clock a central abnormality of circadian rhythms seems probable in MDD. Control of circadian rhythms is complex and whether the phase changes and blunting found in depression are caused by changes in the suprachiasmatic nucleus [52] [89], in the pineal gland leading to abnormal MEL secretion, or in behaviour affecting light exposure and social zeit-

gebers is unclear. From this perspective, it has been hypothesized that treatments with a chronobiotic effect such as MEL may exert a favourable effect on depression.

BIPOLAR DISORDER

Sleep in bipolar disorder is characterized by erratic sleep wake cycles associated with sleep disturbance or hyposomnia during manic episodes and mixed episodes of hyposomnia or hypersomnia during depressive episodes. Symptoms may fluctuate dramatically between the two extremes. As sleep disturbance is a core feature of bipolar disorder and because diurnal rhythm abnormalities occur in bodily functions other that sleep it has been hypothesized that sleep dysfunction and circadian rhythm instability may play a role in the illness [90]. Recognizing the primacy of biology, Goodwin and Jamison [91] hypothesized that the "the genetic defect in manic depressive illness involves the circadian pacemaker or systems that modulate it. They further postulated that psychological factors will interact with biology to create three probable pathways to recurrence in bipolar disorders: 1) stressful live events; 2) disruption in social rhythms and 3) no adherence to medications. Their model suggests that individuals with bipolar disorder are fundamentally vulnerable to disruptions in circadian rhythms. Psychological stressors then interact with this biological vulnerability to cause symptoms. For instance, stressful life events and disrupt social rhythms, which causes disturbances in circadian integrity, which in turn, may lead to recurrence. Alternately, problematic interpersonal relationships or disordered schedules contribute to a patient's difficulty adhering to a medication regime which, again may lead to recurrence. As a direct consequence of this model, one would assume that helping patients learn to take their medication regularly, lead more orderly lives, and resolve interpersonal problems more effectively would promote circadian integrity and minimize risk of recurrence. Mood stabilizers, and specifically lithium monotherapy, are considered the "gold standard" of pharmacotherapy for bipolar disorder. However, pharmacotherapy alone is frequently not sufficient to stop patients moving through the various phases of the disorder and patients are frequently treated with mood stabilizers in combination to sedative hypnotics, and antidepressants. Influenced by the instability model, interpersonal and social rhythm therapy (IPSRT) was developed [92] which when administered in concert with medication, helps patients regularize their daily routines, diminish interpersonal problems and adhere to medications regimes. The hypothesis that regular social routines and stable interpersonal relationships protect against recurrence has proven in a randomized controlled trial of patients treated by mood stabilisers with and without IPSRT [93].

In conclusion, erratic sleep/wake and social rhythm schedules may contribute both to the initial presentation of a bipolar disorder and to recurrence. IPSRT helps patients stabilise social rhythms leading to improved circadian stability and prevention of recurrence. It modulates both biological and psychosocial factors to mitigate patients' circadian and sleep-wake cycle vulnerabilities, improves overall functioning, and helps patients better manage the potential chaos of bipolar disorder. The success of IPSRT raises the potential of chronobiotic treatments in bipolar disorder, with the possibility that exogenous melatonine administration, in association with mood stabilisers and/or IPSRT may help synchronize erratic sleep wake schedules.

EFFECTS OF MELATONIN AND MELATONIN AGONISTS IN SLEEP AND DEPRESSION

The short half-life of MEL and the need to carefully synchronize MEL dosage with patients' circadian phase has led to a search for other products. Candidates to date include prolonged-release melatonin (PRM) and melatonin agonists such as ramelteon, agomelatine, TIK-301 and tasimelteon (see Table **1**).

Table 1. **Pharmacokinetic and Pharmacodynamic Characteristics of Approved Receptor Agonists and Agonists Under Development**

	Circadin (MEL)	Ramelteon	Agomelatine	Tasimelteon	TIK-301
Binding affinity	MT1: Ki = 0.080 nM MT2: Ki = 0.383 nM MT3: Ki = 24.1 nM	MT1: Ki = 0.014 nM MT2: Ki = 0.112 nM	MT1: Ki = 0.062 nM MT2: Ki = 0.268 nM 5-HT$_{2C}$*: IC50 = 270 nM	MT1: Ki = 0.350 nM MT2: Ki = 0.170 nM	MT1: Ki = 0.081nM MT2: Ki = 0.042 nM 5-HT$_{2C}$* , 5-HT$_{2B}$*
Bioavailability	15%	< 2%	< 5%	-	-
Half-life	40-50 min 3.5-4 h (terminal)	1-2 h	1-2 h	-	-
Protein binding	60%	82%	95%	-	-
Volume of distribution	-	73.6 L	35 L	-	-
Company	Neurim	Takeda	Servier	Vanda	Tikvah
*Serotonin antagonist nM: nanomol/l					

Comments: Compared to their affinities for the MT1 receptors, melatonin, ramelteon and agomelatine showed lower affinity for the MT2 receptors. Ramelteon is the most potent agonist, its affinities for MT1 and MT2 being 3-16 times higher than those of melatonin.

MELATONIN

Prolonged Release Melatonin (PRM, Circadin®)

The first commercially available MEL was a prolonged-release tablet (PRM 2 mg, Circadin®). Circadin® is developed by Neurim, Israel, and approved in Europe by the European Medicines Evaluation Agency (EMEA) for the treatment of insomnia in patients aged 55 years and over. This formulation releases MEL gradually in the gut when administered orally in order to introduce MEL into the circulation over the following 8-10 hour, and has proven to be effective and safe for the short-term treatment (3 weeks) of adults aged 55 years and older who have primary insomnia [94-97]. Most of the evaluation of PRM was performed using subjective measures of sleep latency, sleep quality and form at awakening. PRM has been shown to statistically improve some objective sleep parameters but its efficacy is below that of conventional hypnotics [98] with a low but statistically significant percentage of responders against placebo (26% versus 15%; p = 0.014) [99]. However, it has the advantage of being devoid of typical side effects of benzodiazepines, such as next-day hangover, withdrawal effects and dependence liability [96,97,99]. The indication of PRM as a short term treatment (21 days) for insomnia for adults aged 55 years or older was based on studies provided by Neurim [99]. The age cut-off for response to PRM and long term maintenance of efficacy and safety were investigated in a further study [100]. In this latest study, patients with primary insomnia aged 18–80 were randomized to receive PRM 2 mg two hours before bedtime or placebo. At 3 weeks, significant differences in sleep diary measuring sleep latency in the PRM group were found in the 55–80 year group (-15.4 versus - 5.5 min, p = 0.014) but not in younger patients, whereas long term treatment over a 6-month period demonstrated an improvement of subjective sleep latency, quality of sleep, daytime functioning, quality of life and clinical status improved with PRM in all age groups. Again no withdrawal symptoms or rebound insomnia were detected and most adverse events were mild with no significant differences between PRM and placebo groups in any safety outcome.

PRM has been used as replacement therapy in patients lacking basal melatonin secretion following pineal surgery [101]. Pineal region tumours or pineal resection may be associated with psychiatric manifestations [102], which have been reported to improve following replacement therapy [103] and further studies are planned to clarify the role of melatonin replacement therapy in management of patients following pineal resection.

Two studies have looked at the effects of PRM in depression. In Dolberg's double blind study [104], patients treated with fluoxetine 20 mg were randomized to receive PRM 5 mg or 10 mg or placebo. A second study [105] was an open study in patients with treatment-resistant depression. Patients were on antidepressant treatment, and received additional PRM 5 mg (for two weeks) and 10 mg (for the following two weeks). Both studies showed that PRM improved sleep in patients with major depressive disorder (MDD) but had no effect on depression.

MELATONIN ANALOGS

Ramelteon

Ramelteon is an indenofuran derivative that has high affinity for MT1/MT2 receptors (Rozerem; Takeda Pharmaceuticals Inc.), and approved in the United States for insomnia. In humans, ramelteon promotes sleep and is used for the treatment of primary insomnia as characterized by difficulty with sleep-onset [106] [107].

Ramelteon reduces sleep latency and increases total sleep time in chronic insomniacs and unlike benzodiazepine derived hypnotics, has no next day memory, cognitive or motor impairment, and no withdrawal symptoms or rebound insomnia when treatment is stopped [108,109] (see Neubauer 2008 for a complete review[110]). Nevertheless, the EMEA found the efficacy of ramelteon in improving sleep latency insufficient for a marketing authorization. The firm applied to the EMEA for the indication of treatment of only one aspect of sleep: "primary insomnia characterized by difficulty falling asleep in patients 18 years and older". The EMEA considered that "even if targeting of individual symptom within a syndrome would have been possible, the effect on sleep latency was not observed consistently in the development of ramelteon". Furthermore the EMEA considered that the significant reduction of sleep latency was of doubtful clinical relevance. An additional factor was the safety profile of ramelteon which showed an increased risk of depression adverse event in the elderly (aged 65 and more). As a result, marketing authorization was not granted.

Ramelteon has a half life of 1 to 2 hours which is longer that that of MEL (40 – 50 minutes), and like MEL is able to phase shift circadian rhythms [111]. Ramelteon has not yet been tested as a

possible antidepressant and does not have affinity for serotonin receptors [112]. However, a recent double blind, placebo-controlled, parallel-group study comparing ramelteon 8 mg to placebo in a small sample of 21 patients with bipolar disorder, receiving at least one mood stabilizing medication and experiencing mild-to-moderate manic symptoms and clinically significant sleep disturbance, showed that ramelteon and placebo had similar rates of reduction in ratings of symptoms of insomnia, mania or global severity of illness. However, ramelteon was associated with an improvement of global rating of depressive symptoms [113].

AGOMELATINE

Agomelatine (Valdoxan®; Servier, France), originally named S-20098, was approved by the EMEA in 2009. Agomelatine combines melatonergic actions (agonist of MT1 and MT2 receptors) with inhibition of the serotonergic receptor subtype 5-HT$_{2C}$ [114,115] and is licensed for treatment of MDD.

CIRCADIAN INFLUENCE OF AGOMELATINE

The phase shifting effects of agomelatine were originally investigated in rodents. In rats maintained in total darkness, drifting of circadian rhythms was reversed by agomelatine, demonstrating a chronobiotic effect similar to MEL [116]. This was further demonstrated by resynchronization of circadian rhythms in a phase advance model of jet lag [117] and in a phase delay model [118].

Two studies in healthy volunteers investigated the phase shifting effects of agomelatine. In the first study of 8 men [44], a single oral administration at 18: 00 of either melatonin 5 mg or agomelatine (5 or 100 mg) induced an earlier dim-light melatonin onset, an earlier increase in distal skin temperature, and an earlier decrease in core body temperature, heart rate, and proximal skin temperature. In a second double-blind, two-period, and cross-over study of 8 elderly men [119], the chronic phase shifting effects of agomelatine 50 mg or placebo at 18: 30 were tested over 15 days and showed phase advances averaging nearly two hours for core temperature and cortisol secretion.

Agomelatine has been shown to have an effect not only on phase but also on the amplitude of circadian rhythms, which are known to be blunted in MDD [85], in a recent 6 week randomized double-blind parallel study of agomelatine (25-50 mg in 154 patients) versus the selective serotonin reuptake inhibitor (SSRI) sertraline (50-100 mg in 159 patients) in MDD patients. In this study the main parameter was the relative amplitude (RA) of the rest activity cycle, which is an indirect measure of the influence of nocturnal sleep disturbance, with night-time restlessness, daytime retardation and napping on the rest activity rhythm. The study showed that agomelatine increased the mean RA on actigraphy from the first week (p = 0.01), whereas the effects with sertraline, while similar, did not occur until the second week of treatment. This was accompanied by an improvement in sleep (sleep latency and efficiency) in the agomelatine group as compared to sertraline from week 1 to week 6 [120].[105]. During the 6 weeks treatment, depressive symptoms (p<0.05) and anxiety symptoms (p<0.05) improved significantly in patients treated with agomelatine compared to those treated with sertraline. This implies that agomelatine normalizes the blunted circadian rhythms of MDD patients [85, 102, 106] more quickly than with the selective serotonin reuptake inhibitor (SSRI). However, there was no 1 to 1 correlation between the RA and depressive symptoms. Further studies investigating the effects of agomelatine in circadian rhythms of MDD patients using more sensitive indicators of the phase and amplitude of the circadian clock such as melatonin secretion or core body temperature are needed.

AGOMELATINE AND DEPRESSION

The antidepressant efficacy of agomelatine has been investigated in a series of randomized placebo controlled studies (see

Kennedy and Rizvi [121] and De Bodinat *et al* [54] 2010 for detailed reviews). Six of these studies investigated the short-term efficacy versus placebo (see Table **2**), and three with positive outcomes have been published [122-124]. Each of these studies used a randomized, double-blind, parallel, placebo controlled design, with agomelatine given in the evening. Four of these studies used an SSRI antidepressant as an active control. All studies included a 6-week treatment period, except for the dose finding trial that had an 8-week duration treatment [122]. The primary efficacy outcome measured for all of these studies was the 17-item Hamilton Depression Rating Scale (HAMD-17). Three short term efficacy randomized, double blind, parallel studies versus active comparators have been performed (see Table **3**); one versus venlafaxine [125], one versus sertraline [120] and the most recent versus fluoxetine [126]. Two studies showed that the clinical efficacy of agomelatine was superior to that of the comparator. The most recent of the three studies [126] with 515 patients found that agomelatine was significantly more effective than fluoxetine in improving depression in patients with severe MDD and a HAMD-17 > 24, although once sleep related items had been removed from the HAMD-17, the superiority of agomelatine versus fluoxetine was weaker (p = 0.055). Two further studies investigated relapse prevention in depressed patients with recurrent depression (see Table **4**), one was negative, largely due to a low rate of relapse in the placebo group [121] and the second was positive [127]. In this positive study following 8 or 10 weeks of open label, flexible dosing treatment with agomelatine 25 or 50 mg/day, patients achieving a HAMD-17 total score of ≤ 10 and a Clinical Global Impression-Improvement score ≤ 2, were randomized to receive placebo or continue with the same dose of agomelatine for 24 weeks further under double blind conditions, and then for another 20 weeks. After 6 months of treatment, patients on agomelatine showed a two fold lower relapse rate than patients on placebo, an improvement that continued at 10 months of treatment [128].

SLEEP ARCHITECTURE IN MDD PATIENTS TREATED WITH AGOMELATINE

The effect of agomelatine on objective measures of sleep has been explored in a preliminary open-label study in patients with MDD at a consulting sleep unit, with a baseline HAMD-17 score of ≥ 20 [129]. Fifteen patients with MDD (8 women and 7 men; mean age, 36.5 ± 11.3 years; mean total HAMD-17 score, 21.8 ± 1.5 at baseline) and sleep disturbance received agomelatine 25 mg in the evening for 6 weeks, and were assessed by polysomnography (PSG) at baseline and at weeks 1, 2, and 6. Sleep architecture was improved by agomelatine with normalization of slow wave sleep (SWS) distribution over the first four sleep cycles, a significant increase in the duration of SWS and an increase in the delta ratio (from 0.88 ± 0.35 at baseline to 1.16 ± 0.57 at 6 weeks, P=0.007)). No effects were seen on rapid eye movement (REM) sleep. Sleep efficiency increased due to a reduction in intra-sleep awakenings. The changes on electroencephalogram (EEG) were progressive, starting from as early as week 1, and continuing through to the end of the study. The overall changes in PSG parameters during treatment with agomelatine were associated with a simultaneous improvement in depressive symptoms and the early changes in sleep structure observed in this study are in line with reports of an early onset of antidepressant action with this agent [122,124] and with the results of the subjective sleep study [125]. A further study of cyclic alternating pattern (CAP), a measure of sleep fragmentation, in MDD patients found significant differences in CAP at baseline between patients and controls, with disturbed NREM sleep in the depressed group shown by a significantly higher CAP rate and CAP time. This further supports the hypothesis that NREM sleep disturbances play a primary role in mood impairment in MDD. During treatment with agomelatine, CAP rate in the MDD patients decreased from 61.5 ± 5.9% at baseline, to 32.9 ± 11.0% at week 1, to 30.1 ± 10.7% at week 6 (P<0.0001). As with changes in sleep

Table 2. Short-term Efficacy Studies of Agomelatine Versus Placebo in the Treatment of Major Depressive Disorder

	Objective	N°	Agomelatine	Comparator	Duration	HAMD-17 Score at Selection	Primary Endpoint	Result HAMD-17 Total Score
Lôo *et al.* [122] 2002	Dose finding: difference vs placebo Assay sensitivity	711	1, 5, 25mg	Placebo Paroxetine 20 mg as positive control	8 weeks	≥ 22	HAMD-17	Agomelatine 25 mg > to placebo (P=0.034) Paroxetine 20 mg > to placebo (P=0.030)
CL3-022	Superiority vs. placebo Assay sensitivity	419	25 mg	Placebo Fluoxetine 20 mg as positive control	6 weeks + 18 weeks extension	≥ 22	HAMD-17	Agomelatine 25 mg vs. placebo (no difference) Fluoxetine 20 mg > to placebo (P=0.030)
CL3-023	Superiority vs. placebo Assay sensitivity	417	25 mg	Placebo Paroxetine 20 mg as positive control	6 weeks + 18 weeks extension	≥ 22	HAMD-17	Agomelatine 25 mg vs. placebo (no difference) Paroxetine 20 mg vs placebo (no difference)
CL3-024	Superiority vs. placebo Assay Sensitivity	607	25, 50 mg	Placebo Fluoxetine 20 mg as positive control	6 weeks + 18 weeks extension	≥ 22	HAMD-17	Agomelatine 25 and 50 mg vs. placebo (no difference) Fluoxetine 20 mg vs. placebo (no difference)
Kennedy and Emsley 2006 [124]	Superiority vs. placebo	212	25 to 50 mg	Placebo	6 weeks + 46 weeks extension	≥ 22	HAMD-17	Agomelatine 25-50mg > to placebo (P=0.026)
Olié and Kasper 2007 [123]	Superiority vs. placebo	238	25 to 50 mg	Placebo	6 weeks + 46 weeks extension	≥ 22	HAMD-17	Agomelatine 25-50mg > to placebo (P<0.001)

All studies were randomized double blind in parallel groups. HAMD-17: 17- item Hamilton Depression Rating Scale; N°: number of randomized patients
References for studies: CL3-022 CL3-023, CL3-024
- European Medicines Evaluation Agency, CHMP assessment report for Valdoxan, EMEA/655251/2008, London 20 November 2008
- Haute Autorité de Santé, France, Transparency Committee, Valdoxan CT 6808, opinion 18 November 2009

Table 3. Short-term Efficacy Studies of Agomelatine Versus an Active Comparator in the Treatment of Major Depressive Disorder

	Objective	N°	Agomelatine	Comparator	Duration	HAMD-17 Score at Selection	Primary Endpoint	Result HAMD-17 Total Score
Lemoine *et al.* [125] 2007	Superiority vs. active comparator	332	25 to 50 mg	Venlafaxine 75 to 150 mg	6 weeks + 18 weeks extension	≥ 20	Leeds Sleep Evaluation Questionnaire	Agomelatine 25, 50 mg vs. venlafaxine 75, 150 mg (No difference)
Kasper *et al.* [120] 2010	Superiority vs. active comparator	313	25 to 50 mg	Sertraline 50 to 100 mg	6 weeks + 18 weeks extension	≥ 22	Circadian Rest Activity Cycle	Agomelatine > sertraline (P=0.031)
Hale *et al.* [126] 2010	Superiority vs. active comparator	515	25 to 50 mg	Fluoxetine 20 to 40 mg	8 weeks + 16 weeks extension	≥ 25	HAMD-17	Agomelatine > fluoxetine (P=0.024)

All studies were multicenter, randomized double blind in parallel groups
HAMD-17: 17- item Hamilton Depression Rating Scale; N°: number of randomized patients

Table 4.   **Studies of Relapse Prevention in Depressed Patients with Recurrent Depression**

	Objective	N°	Agomelatine	Comparator	Duration	HAMD-17 Score at Selection	Primary Endpoint	Result HAMD-17 Total Score
CL3-021	Superiority vs. placebo	367	25 mg	Placebo	Open 8 weeks + double blind 26 weeks	≥ 22	HAMD-17	Incidence of relapse: no difference between groups
Goodwin *et al.* [127] 2009	Superiority vs. placebo	339	25, 50 mg	Placebo	Open 8, 10 weeks + double blind 24 weeks	≥ 22	HAMD-17	Incidence of relapse lower with agomelatine compared to placebo (P<0.0001)

All studies were multicenter, randomized double blind in parallel groups
HAMD-17: 17- item Hamilton Depression Rating Scale; N°: number of randomized patients
References for study CL3-021:
- European Medicines Agency, CHMP assessment report for Valdoxan, EMEA/655251/2008, London 20 November 2008
- Haute Autorité de Santé, France, Transparency Committee, Valdoxan CT 6808, opinion 18 November 2009

architecture, the improvements started in the first week of treatment. These studies imply that in patients treated by agomelatine, the reduction in HAMD-17 and reorganization of SWS and NREM is simultaneous, with no change in REM sleep [130]. A not yet published randomized double blind long term (6 months) comparison study of agomelatine versus an SSRI (escitalopram), using polysomnography confirms the early and sustained improvement of sleep with agomelatine in comparison to the SRRI (Quera-Salva M.A- personal poster communication to the CINP meeting 2010). Agomelatine improved sleep latency and preserved sleep cycles throughout the study in comparison to the SSRI. In addition, patients felt better on awakening and less sleepy during the daytime, suggesting a chronobiotic action of agomelatine.

SUBJECTIVE SLEEP IN MDD PATIENTS TREATED WITH AGOMELATINE

A pooled analysis of three 6 to 8 week studies on the antidepressant efficacy of agomelatine versus placebo in MDD patients [122-124] has recently been performed [131]. The pooled population comprised 358 patients receiving agomelatine 25/50 mg/day and 363 patients receiving placebo. The results showed a significant effect of agomelatine versus placebo at the end of 6 to 8 weeks for sleep related items on the HAMD-17 (4, 5, and 6) which was evident from week 2 for items 4 (early insomnia, P=0.002) and 5 (late insomnia, P=0.026). To ensure that the positive effects of agomelatine were not simply due to an improvement in sleep, the total HAMD-17 score was analyzed without the sleep related items 4, 5, and 6 which showed a significant reduction of the HAMD-17 score from 22.7 ± 2.7 to 11.8 ± 6.7 in the agomelatine 25/50 mg/day group versus placebo after 6 or 8 weeks (P<0.001). This confirms that the antidepressant efficacy of agomelatine evaluated by the HAMD-17 scale is not solely due to its positive effects on sleep.

The improvement in subjective sleep with agomelatine has also been evaluated using the Leeds Sleep Evaluation Questionnaire in the clinical trial of agomelatine versus venlafaxine [125]. Patients treated with agomelatine had less difficulty falling asleep compared to patients treated by venlafaxine, with improvements starting at week 1 (p=0.007). At the end of 6 weeks treatment, patients rated their ease of falling asleep as significantly better for agomelatine than for venlafaxine (p=0.001). There were also significant differences in favour of agomelatine at the end of the treatment on quality of sleep, awakening from sleep and behaviour following awakening, indicating a global difference in the impact of the two antidepressants on sleep. Daytime functioning, measured using visual-analog-scales for "daytime sleepiness" and "feeling well" showed a significant advantage of agomelatine for daytime sleepiness compared to venlafaxine after 1 week of treatment, and for feeling well after weeks 1 and 2. Although values in the agomelatine group remained low thereafter, the patients treated with venlafaxine slowly improved and the differences became non-significant. In agreement with the evaluations for sleep, the Clinical Global Impression-Improvement rating-scale assessments were significantly in favour of agomelatine at week 1, and at the last observation. Subjective sleep improvements start early on in treatment and are maintained throughout the course of treatment.

AGOMELATINE AND SIDE EFFECTS

Overall, agomelatine has been well tolerated in all clinical studies presented. Based in the complete database of double blind six months studies, the only emerging adverse event significantly associated with agomelatine (1120 patients) compared to placebo (998 patients) was dizziness: 5.9% versus 3.5% respectively (p<0.01). Agomelatine has a good gastrointestinal tolerability, has no influence on weight and has minimal effect on sexual function compared to SSRIs such as venlafaxine [132] and paroxetine [133]. Some isolated and reversible increases in serum alanine and/or aspartate transaminases were observed within the first months of treatment across all patients: 1.1% for all doses of agomelatine compared to 0.7% for placebo. They were principally observed at a dose of 50 mg per day with a crude incidence rate of 1.39% which is similar to that documented in comparative studies with venlafaxine of 75–150 mg [54]. This led to a recommendation by the EMEA to monitor liver function tests as a precautionary measure at the onset of treatment, at 6 weeks, 12 weeks and 6 months, and then periodically if clinically indicated.

Finally, there has been a recent article describing a single case with fully reversible QTc prolongation after treatment with agomelatine [134]. QTc prolongation during antidepressant treatment has been reported both with tricyclic antidepressants [135] and with serotonin reuptake inhibitors in overdose [136-138], indicating that is not unknown, particularly in the elderly. In the case of

agomelatine it seems probable that the effect may be related to the 5-HT$_{2C}$ antagonistic properties [139,140]. However this finding has not been reported in trials to date or by ongoing pharmaco-vigilance, and its clinical relevance is unclear.

MELATONIN ANALOGS UNDER DEVELOPMENT

TIK-301

TIK-301, also known as beta-methyl-6-chloromelatonin or LY 156735 is an indole compound developed originally by Eli Llily. Tikvah Pharmaceutical took over the development in August 2007. The pharmacokinetics of TK-301 has been extensively studied and the compound has reached Phase II trials. Statistically significant reduction of sleep latency has been shown in patients with primary insomnia [141]. TIK-301 is effective in phase shifting the circadian clock at much lower doses (5 mg) [142]. TIK-301 has been studied for over a decade as a MT1 and MT2 melatonin agonist in primary insomnia, but due to its recently discovered antagonist properties at 5-HT$_{2B}$ and 5-HT$_{2C}$ serotonin receptors it should no longer be regarded as only a melatonergic drug, and this may affect the future development of TIK-301.

Tasimelteon

Tasimelteon (VEC-162) is a novel MT1 and MT2 agonist developed by Vanda Pharmaceuticals inc. (Rockville, MD, USA), under licencing from Bristol Myers. Tasimelteon was effective in reducing sleep-onset latency in phase II and III clinical trials and in resetting the circadian melatonin rhythm in phase II trials [143] in comparison to placebo in healthy individuals imposed to a 5-hour advance in the sleep–wake schedule. This indicates that tasimelteon is potentially suitable as treatment for jet-lag, shift-work and circadian rhythm sleep disorders such as free-running sleep wake patterns of blind individuals with no light perception. Tasimelteon was well tolerated in this short term study however long term safety studies are needed.

Neu-P11

Neu-P11 is a novel pyrone-indole melatonin agonist developed by Neurim Pharmaceuticals Ltd, with lower affinity to serotonin receptors (5HT$_{1A}$ and 5HT$_{1B}$ and 5HT$_{2B}$) but without interaction with GABA-A receptors (information from Neurim pharmaceuticals). Studies in rodents suggested that Neu-P11 has sleep promoting effects, anxiolytic and antidepressant activity [144]. The sleep inducing properties of NEU-P11 were also found in a Phase I clinical study [145]. To date, the exact structure of NEU-P11 and details of its binding to specific melatonin receptors has not been released by Neurim Pharmaceuticals.

CONCLUSION

The biological clock plays a vital role in orchestrating the circadian rhythms of multiple biological processes, and increasing evidence points to a role of the biological clock in the development of depression. Depression is a complex and heterogeneous disorder with multiple forms and the link between abnormal circadian rhythms and depression seems to be bidirectional. Whether circadian abnormalities are a cause or a consequence of depression may well depend on the subtype of depression. In seasonal depression where changes in circadian rhythms are followed by the development of symptoms or recurrence, it seems likely that the circadian system plays a vital role in the genesis of the disorder [146]. In bipolar disorder, erratic sleep/wake and social rhythm schedules may contribute both to the disorder and to recurrence, as shown by the positive effects of IPSRT in preventing recurrence. In MDD, available data suggest a primary involvement of the circadian system but further and larger studies comparing different circadian parameters in healthy volunteers and patients with MDD are necessary to conclude. Ideally, exploring the role of the circadian system in depression should be done in studies under constant routine.

Despite the difficulties of performing such studies in patients with a moderate to severe MDD episode they should be encouraged.

Melatonin, PRM, ramelteon, agomelatine, tasimelteon and TIK-301 all have chronobiotic effects: that is they can induce phase shifts to readjust the circadian oscillator system, but simple phase shifting seems to be inadequate to treat all forms of depression. Anxiolytic and antidepressant effects of melatonin have been described, but a clear distinction is necessary between those forms of depression which are related or unrelated to chronobiological phenomena. Seasonal affective disorders and mood disturbances caused by circadian malfunction are theoretically treatable by manipulating the circadian system using chronobiotic drugs such as MEL [147]. However, the efficacy of melatonin or selective melatonergic agonists in MDD is rather limited. In the case of agomelatine, the antidepressant properties are mainly explained by the joint MT1 and MT2 antagonism and the inhibition of 5-HT$_{2C}$ receptors. Thus, in MDD, melatonergic drugs may only be suitable if the compounds possess additional properties, such as actions as 5-HT$_{2C}$ antagonists, as found with agomelatine. The inhibition of this serotonergic receptor subtype seems to be sufficient for the antidepressant effects observed and is also found with non-melatonergic drugs such as amitriptyline, trazodone and mirtazapine. However, these other antidepressants with 5-HT$_{2C}$ receptor antagonist actions improve sleep but also induce daytime sleepiness. In trials to date, agomelatine does not induce hangover effects, is associated with reduced daytime sleepiness and a feeling of clear thinking [125,132].

Agomelatine seems to be at least as effective as SSRIs and two previous randomized, double blind, parallel efficacy studies versus an SSRI comparator showed a comparable between group difference in favor of agomelatine [120,126]. In Hale's [126] study the superiority of agomelatine versus fluoxetine was confirmed even if weaker (p = 0.055) when the sleep items of the HAMD-17 scale were removed. It is likely that the superiority of agomelatine versus the SRRI comparator is due to both MT1 and MT2 agonist effects and the inhibition of 5-HT$_{2C}$ receptors, since agomelatine not only improves sleep but also patient alertness on waking and during the day in comparison to an SSRI. However, further studies are necessary in order to better characterize the effects of agomelatine, using more sensitive indicators of circadian rhythms, such as melatonin secretion or core body temperature in addition to actigraphy.

In conclusion, circadian rhythms are closely linked with depression. Manipulating circadian rhythms via melatonin or bright light as an adjunct to classical antidepressant treatment or using antidepressants with intrinsic chronobiotic properties offers a new approach to treatment.

ABBREVIATIONS

5-HT	=	Serotonin or 5-hydroxytryptamine
5-HT$_{2C}$	=	5-Hydroxytryptamine 2C receptors
CAP	=	Cyclic alternating pattern
EEG	=	Electroencephalogram
EMEA	=	European Medicines Evaluation Agency
HAMD-17	=	17-Item Hamilton depression Rating Scale
IPSRT	=	Interpersonal and social rhythm therapy
ipRGCs	=	Intrinsically photosensitive retinal ganglion cells
MDD	=	Major depressive disorder
MEL	=	Melatonin or N-acetyl-5-methoxytryptamine
mRGCs	=	Retinal ganglion cells expressing the photopigment melanopsine
PRM	=	Prolonged-release melatonin
PSG	=	Polysomnography

RA	=	Relative amplitude
REM	=	Rapid eye movement sleep
SCN	=	Suprachiasmatic nuclei
SSRI	=	Selective serotonin reuptake inhibitor
SWS	=	Slow wave sleep

CONFLICTS OF INTEREST

Dr. Quera Salva is a scientific advisor of Servier.

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