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EXPERT REVIEW

Mood Disorders, Circadian Rhythms, Melatonin and Melatonin Agonists

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Abstract: Recent advances in the understanding of circadian rhythms have led to an interest in the treatment of major depressive disorder with chronobiotic agents. Many tissues have autonomous circadian rhythms, which are orchestrated by the master clock, situated in the suprachiasmatic nucleus (SNC). Melatonin (N-acetyl-5-hydroxytryptamine) is secreted from the pineal gland during darkness. Melatonin acts mainly on MT1 and MT2 receptors, which are present in the SNC, regulating physiological and neuroendocrine functions, including circadian entrainment, referred to as the chronobiotic effet. Circadian rhythms has been shown to be either misaligned or phase shifted or decreased in amplitude in both acute episodes and relapse of major depressive disorder (MDD) and bipolar disorder. Manipulation of circadian rhythms either using physical treatments (such as high intensity light) or behavioral therapy has shown promise in improving symptoms. Pharmacotherapy using melatonin and pure melatonin receptor agonists, while improving sleep, has not been shown to improve symptoms of depression. A novel antidepressant, agomelatine, combines 5HT2c antagonist and melatonin agonist action, and has shown promise in both acute treatment of MDD and in preventing relapse.

Keywords: major depression disorder, circadian rhythms, melatonin, melatonin agonists, agomelatine

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Introduction

Many physiological systems have underlying circadian rhythms. These rhythms are orchestrated by a central biological clock, situated in the suprachiasmatic nucleus (SCN). The mechanisms behind the innate rhythm of the biological clock and its adjustments to the photoperiod are being elucidated and it is becoming clear that abnormalities of circadian rhythms are linked to several common diseases.

Major depressive disorder (MDD) is a frequent disorder that poses a major handicap to patients. Understanding MDD is essential in order not only to treat acute episodes, but also to prevent recurrence. Several disorders are closely linked to MDD, and it is probable that several subtypes of MDD exist.[1] Bipolar disorder is sometimes hard to distinguish from MDD due to infrequent episodes of elevated mood, and seasonal depression[2] may rest undiagnosed as neither patients nor physicians have linked the onset of recurrence to changes in day length.[2]

Links between depression and circadian rhythms have long been suspected due to the existence of seasonal depression, where the onset of low mood correlates with a reduction in daylength (also called the photoperiod).[3] More recently, attention has focused on chaotic sleep wake cycles in patients suffering from bipolar disorder, where degradation in regular rhythms is associated with worsening of functional status and relapse of symptoms.[4–6] Recent psychological and pharmacological treatments developed for depression target circadian rhythms and have been shown to be effective. What are circadian rhythms and why are they important in depression?

Circadian Rhythms

A biological clock is present in nearly all organisms, and regulates biological processes with circadian periodicity (circa = around, dies = one day). Many processes have their own intrinsic rhythmicity controlled by molecular oscillators which rely on transcriptional feedback loops.[7] These autonomous processes continue to function in vitro, but in vivo they require synchronization to function harmoniously, and this is provided by the master biological clock. The mammalian biological clock is situated in the suprachiasmatic nucleus (SCN), which is located in the anterior hypothalamus.[8] The intrinsic rhythm of the SCN orchestrates the rhythm of the other biological processes. The circadian clock at the molecular level involves genes that participate in the genesis of the circadian rhythms such as Period (PER 1/2/3), Cryptochrome (Cry ½), Bmal1, Clock and some nuclear orphan receptors (Rev-erbα/β and Rorα/β/γ).[7] Studies focused on the periodicity of the biological clock, in healthy volunteers under constant routine conditions and isolated from external stimuli, found that the biological clock has a periodicity slightly longer than 24 hours.[9] Under experimental conditions using constant routine, due to this >24 hour periodicity[9] the biological clock becomes progressively delayed. Initial delay of sleep onset and wake times terminates in total desynchronisation, where the different biological rhythms no longer correspond to each other. This slippage of sleep and wake times is occasionally seen in patients and is termed a free running rhythm: free running because it is not entrained by the usual time given signals or zeitgebers, which reset the clock. The most potent zeitgeber is light, which explains why free running rhythms are most often seen in practice in patients without light perception. Other zeitgebers include social and professional stimuli[10] and free running rhythms may be found where these are weakened or absent.

The light signal from the retina is detected by rods, cones and retinal ganglion cells expressing the photopigment melanopsin. The signal from these photosensitive cells is transmitted to the SCN.[11] Both rods and melanopsin containing cells are important in photoentrainment.[12,13] Melanopsin containing cells are particularly sensitive to short wavelength blue light, and may survive after total rod and cone loss in certain blind patients, explaining why circadian rhythms may be preserved despite loss of vision.[14] Resetting of the biological clock occurs every morning on exposure to daylight, but artificial light also entrains the clock,[9] and bright light therapy can be effective in non-blind patients with free running rhythms.[10] While bright light acts as a zeitgeber it also increases vigilance.[15] Exposure to bright light in the morning resets the clock and shortens the intrinsic rhythm, triggering an earlier sleep onset in the evening, and exposure to bright light in the evening tends to delay sleep onset.[9]

Circadian Rhythms and Sleep

Sleep onset is controlled by two processes: the circadian process and the accumulated need for sleep or

the homeostatic process.[16] As wake time increases, sleep pressure increases, and so does the propensity to fall asleep. This is called the homeostatic process. Processes involved in the homeostatic process and the circadian rhythm share several clock genes,[17] and it is thus not surprising that optimal sleep quality depends on synchronization between circadian rhythms and the homeostatic process.

Disorders of the biological clock are relatively frequent. Delayed sleep phase syndrome is particularly common in adolescents,[18] with late sleep and wake times, whilst advanced sleep phase syndrome (where sleep and wake times are earlier than usual) is more common in the elderly and may be familial.[10] In congenital advanced sleep phase syndrome, genetic studies have identified mutations in Per and Clock genes.[19]

Melatonin

Melatonin (MEL, N-acetyl-5-methoxytryptamine) plays a key role in the circadian system, and is a neurohormone primarily synthesized by the pineal gland during darkness. Synthesis in the pineal gland from the precursor tryptophan occurs via conversion to serotonin which is subsequently acetylated by the enzyme arylalkylamine N-acetyltransferase (AANAT) and then converted into MEL by acetyl serotonin methyl transferase (ASMT also called hydroxyindole O-methyltransferase or HIOMT) MEL levels are low during the day, increase at night and then decrease before the end of darkness to daytime levels. This reactivity to light is regulated by the SCN via multisynaptic pathways projecting through the sub-paraventricular zone (SPZ), median forebrain bundle and reticular formation to the intermediolateral horn cells in the spinal cord. Preganglionic fibres from the spinal cord then project to the superior cervical ganglion from where postganglioic fibres project to the pineal gland[20] and release norepinephrine. Studies in rodents have shown that activation of B adrenergic receptors in the pineal leads to AANAT expression, phosphorylation and stabilization via protein kinase A (see Ho et al for a detailed review),[21] but the exact molecular mechanism in humans is still debated.[22] The formation of stabilized AANAT leads to MEL synthesis, which is abolished by SCN lesions.[8] Exposure to bright light during the night causes degradation of pineal AANAT and a reduction in melatonin synthesis.[23] MEL is released into capillaries and into the cerebrospinal fluid and is then rapidly distributed peripherally.[24] When administered intravenously, MEL has a metabolic half life of 20 minutes. MEL modulates the activity of the SCN via a feedback loop.[25] Melatonin production decreases with age, and this decrease has been linked not only to increased insomnia, but also leads to earlier sleep and wake times (advances sleep phase syndrome).[26,27]

Three receptors have been identified for melatonin, MT1, MT2 and MT3. MEL acts mainly through MT1 and MT2, two G protein-coupled receptors with 7 transmembrane domains.[28] For a thorough review of recent work on melatonin recpetors see Pandi-Perumal.[29] Melatonin binding sites have also been demonstrated in the rat in the preoptic area of the hypothalamus and the medulla pons, and seem able to inhibit dopamine (DA) release. Other interactions with calodulin calreticulin and tubulin are under investigation. MT3 has recently been identified as an enzyme, quinone oxidoreductase 2[30] which is one of a group of reductases which are active against oxidative stress.

MT1 & MT2 are found either singly or together in the retina, SNC, adrenal glands, arteries, heart, gastrointestinal tract, liver, kidneys, adipocytes, macrophages and blood platelets.[28,31,32] The distribution of MT2 is more limited, being mainly sited in the brain. The expression of melatonin receptors follows a circadian rhythm and is modulated by light during the night and by the presence of melatonin, which seems to downregulate its own receptors. The protein cascade activated by melatonin depends on the cell but actions on camp signal transduction cascade, MAP kinase and P13 kinase are seen.

Exogenous melatonin treatment has a phase shifting effect on circadian rhythms. The influence of an external agent on the biological clock is referred to as the chronobiotic effect. The chronobiotic effect of melatonin is due to the presence of MT1 and MT2 receptors in the SCN. MT1 receptors inhibit multiunit activity, while MT2 receptors are responsible for phase shifting reponses.[33] It seems likely from in vivo studies that the chronobiotic effet of exogenous melatonin is due to the concerted actions of MT2 resetting the circadian clock and MT1 suppressing neuronal firing at the SCN.[34]

MT1 and MT2 are expressed in the hippocampus, where they play a role in cognitive function, and

in other areas of the brain where their functions are currently under investigation. They are also expressed in peripheral tissues. They are found in coronary arteries and peripheral vessels where their vasodilatory effects lead to reduction in blood pressure. In the eye, MT receptors play a role in photo-transduction, aqueous secretion and are involved in maintaining circadian variations in intraocular pressure. In the immune system they play an immunomodulatory role, and in the skin they have a protective function and modulate hair growth. Expression in cancer cells leads to an oncostatic effect by melatonin in certain cancers but their role in other peripheral tissues is less well-known.[29]

Polymorphisms have been identified in melatonin MT1 and MT2 receptors, although their contribution to human sleep disorders remains to be clarified.[35,36] Like many G-protein couples receptors, MT1 and MT2 receptors are desensitized by physiological concentrations of melatonin,[37,38] but despite concerns that the administration of supraphysiological doses of melatonin for certain circadian rhythms disorders would lead to progressive desensitization,[37] this has not been shown to be the case, perhaps due to the underlying circadian variation in MEL receptors.

Serotonin

Serotonin (5-HT) plays a vital role in modulating the effects of light on the SCN via 5-HT2$_C$ receptors.[39–41] Exercise, which activates the serotoninergic system potentiates light induced delays of circadian rhythms.[42]

A polysynaptic circuit between the SCN and the ventro-tegmental nucleus provides a means for inhibiting input from SCN 5-HT2$_C$ receptors to indirectly affect ascending dopaminergic pathways,[43] and 5-HT2$_C$ receptors in the locus coeruleus may provide similar inhibiting input to adrenergic forebrain pathways.[44] This indirect effect by 5-HT2$_C$ receptors may play an important role in depression. Blockade of 5-HT2$_C$ receptors thus disinhibits fronto-cortical dopaminergic and adrenergic transmission. Interestingly 5-HT2$_C$ receptor blockade mimics the effects of sleep deprivation, which seems to decrease the activity of 5-HT2$_C$,[44] and increase slow wave sleep.[45] Overall, 5-HT2$_C$ receptors play an important role in circadian rhythms, sleep and depression and modulating their activity may be therapeutically useful.

Depression and Circadian Rhythms

A possible neuronal link thus exists between the circadian system and pathways known to be compromised in depression. Are depression and circadian rhythms linked in practice? If they are and the relationship is bidirectional, one would expect circadian rhythm disorders to trigger depression, and depression to trigger circadian disorders.[46] Ideally treatment of either of the underlying disorders should lead to an improvement in the other.

Looking initially at the links between circadian disorders and depression, it has been known for many years that in certain patients, seasonal variations in photoperiod lead to relapse of episodes of depression.[2,3] Polymorphisms on certain clock related genes have been shown to be linked to circadian rhythms such as familial advanced sleep phase syndrome[47] and delayed sleep phase syndrome[48] which both present a higher risk for depression.[19,49,50] However depression is also more frequent in patients with acquired circadian disorders such as shift work sleep disorder.[51] Finally in patients with bipolar disorder, the links between chaotic sleep-wake cycles and relapse are clear.[4–6] It seems likely that at least for a minority of patients, abnormalities in circadian rhythms can lead to depression.

Disturbance of sleep-wake cycles is so characteristic of MDD that it is considered one of the core symptoms.[1] Sleep maintenance insomnia and early morning wakenings are typically associated with MDD,[52,53] but other sleep wake disturbances such as hypersomnia, fatigue and daytime sleepiness are also seen.[54] Studies have shown multiple dysfunctions in circadian rhythms in patients with MDD. Rhythms can be blunted, leading to poor sleep maintenance,[55] advanced, with early morning waking, delayed, with sleep onset difficulties and morning sleepiness, or disorganised with circadian misalignment between melatonin secretion onset time and sleep mid point time.[56–58] Recent studies looking at the molecular basis of sleep disturbances in MDD have emphasised the role of CLOCK protein polymorphism, but results are not conclusive. It is possible that polymorphisms are relevant in certain subtypes of depression or in certain ethnic groups, and further studies are needed.[59–62,63]

Non pharmacological treatment targeting circadian rhythms have been shown to be effective in improving

depression. Bright light therapy effectively prevents relapse of seasonal depression, and has been used alone in seasonal and non seasonal MDD.[64,65] Psychological approaches such as interpersonal and social rhythm therapy (IPSRT)[5] and other methods of manipulating circadian rhythms have been shown to be effective in treating and in preventing relapse of bipolar disorder.[66] Equally pharmacological treatment of depression results in gradual normalization of sleep wake cycles and normalization of blunted circadian rhythms,[55] both in MDD and in bipolar disorder.

If circadian dysfunction is linked to MDD is this a consequence of central clock (ie, SCN) dysfunction, or a failure of peripheral clocks? Clock genes are expressed in structures known to be involved in MDD: the hippocampus, prefrontal cortex and ventral tegmental area (VTA) implying that these areas also have clocks called peripheral clocks. As treatments that reinforce peripheral rather than the central clock (such as IPSRT) are effective in MDD, this suggests a role for peripheral clocks in MDD.[67]

In summary a bidirectional relationship between circadian rhythms and depression seems likely.

Pharmacological Manipulation of Circadian Rhythms and MDD

Products active on circadian rhythms are considered to have chronobiotic effects. Several chronobiotic molecules are available, of which the best known is exogenous melatonin. Recently commercialised molecules include prolonged release melatonin PRM (Circadin®), melatonin agonists such as ramelteon (Rozarem®) and melatonin agonists with 5-HT2$_C$ antagonism such as agomelatine (Valdoxan®).

Exogenous Melatonin

Exogenous melatonin (MEL) has a short half life of 20–45 minutes due to a hepatic first pass metabolism.[25] Administration of MEL in the evening has the opposite effect to bright light: it advances the clock, and thus causes earlier sleep onset.[68] Given in the morning it theoretically should delay the clock and cause later sleep onset, but is not very effective[69] and has the side effect of drowsiness.[70] Bright light therapy in the evening is more effective to delay sleep onset. Exogenous melatonin is used in circadian disorders, particularly in delayed sleep phase syndrome where an earlier sleep time is required and in free running rhythms where a signal to the biological clock is required to reset the clock daily.[10,71] No studies in MDD have been performed.

Prolonged Release Melatonin (PRM)

Several different formulations of prolonged release melatonin have been developed and tested of which only one, Circadin, is currently marketed. It is difficult to draw conclusions from studies using heterogenous products. Detailed pharmacokinetic data and comparative studies are lacking. Circadin is released over an 8–10 hour period, mimicking the natural release of melatonin during the night. It has been shown to improve sleep latency, sleep quality and form on wake and is approved for medium-term use (3 months) by the European Medicines Agency in adults >55 years,[72–75] as studies were initially conducted in patients aged over 55. Circadin improves some subjective and objective sleep outcomes, is less powerful than conventional hypnotics, but has a better side effect profile.[74–77]

Melatonin and Circadin have been used as replacement therapy in patients post resection of pineal tumours in whom melatonin secretion is absent.[78,79] Lack of melatonin contributes to chaotic sleep wake cycles in these patients and may trigger psychiatric manifestations.[79] Case reports of improvement in both sleep wake patterns and in psychiatric symptoms following melatonin replacement therapy have been published, but further studies are needed.[80]

As prolonged release melatonin affects circadian rhythms is it active in MDD? Three small studies (one open[81] and two double blind[82, 83]) have attempted to address the issue, using heterogenous preparations of slow release melatonin 5 or 10 mg on top of antidepressant treatment. These studies showed an improvement in sleep, but no effect on depression.

Ramelteon

Ramelteon is a melatonin agonist, with affinity for MT1 and MT2 receptors. Its half-life of 1 to 2 hours is longer than that of MEL. It is licensed in the United States (but not in Europe) for adult insomnia, as studies have shown that it reduces sleep latency and increases total sleep time. Unlike benzodiazepines, Ramelteon does not have deleterious effects on memory, cognition

or motor function the day following treatment.[84–86] Interestingly, it has been shown to be associated with an increased risk of depression in the elderly (>65).

Ramelteon, like MEL and PRM has chronobiotic effects,[87] and as such could possibly affect depression. To date no studies have been performed in MDD, but a very small double blind placebo controlled trial in patients suffering from bipolar disorder and treated by mood stabilizing medication (21 patients) showed that the effect of ramelteon was similar to that of placebo on insomnia, mania and illness severity, although associated with an improvement in the global rating of depressive symptoms.[88]

Overall it seems likely that treatments acting purely on MT1 and MT2 do not have an effect on depressive symptoms in MDD, although they can improve sleep in patients with MDD treated by other antidepressants. A product active on both MT1/MT2 receptors and on other receptors known to be affected in depression could thus be an effective antidepressant and might (via stabilizing effects on circadian rhythms) reduce relapse. Studies performed to date are small and results are not conclusive. Larger studies are needed.

Agomelatine

The only currently available product which combines melatoninergic and serotoninergic actions is agomelatine, currently approved in Europe for use in MDD. Agomelatine is an MT1/MT2 agonist and a 5-$HT2_C$ antagonist.[89] With dual receptor action, Agomelatine could be expected to have chronobiotic effects (like Mel, PRM and ramelteon) and antidepressant effects like other 5-$HT2_C$ antagonists (such as mirtazapine).

Agomelatine and Circadian Rhythms

Agomelatine is known to have chronobiotic properties. In animal studies, rats deprived of light and thus with free running circadian rhythms or with circadian rhythms advanced or delayed have their rhythms entrained by both agomelatine and MEL.[90–92] This effect has been confirmed in humans, where a single dose of agomelatine at 18:00 led to early onset of melatonin secretion, core body temperature and heart rate decrease, markers of an advance in circadian rhythms.[93] In elderly men, treatment over 15 days led to a phase advance of nearly two hours in both core temperature and cortisol secretion.[94]

In the presence of depression Agomelatine has been shown to affect the amplitude of circadian rhythms, which are blunted in MDD.[55] Circadian rhythm amplitude can be indirectly measured via the rest activity cycle using actimetry which is sensitive to nocturnal restlessness, daytime napping and reduced activity. Flattening of the rest activity cycle is frequent in depressed patients. A 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 showed that treatment by agomelatine rapidly increased the rest activity cycle relative amplitude, whereas sertraline did not affect the rest activity cycle until the second week of treatment.[95]

Sleep is rapidly improved in patients with MDD treated by agomelatine, probably reflecting the action on MT1 and MT2 receptors. In the study cited above, sleep latency and efficiency was significantly improved in patients treated by agomelatine.

Further studies of circadian rhythms in depressed patients using sensitive measures of circadian rhythms such as core body temperature or melatonin secretion are needed to examine the chronobiotic effects of agomelatine in MDD in detail.

Agomelatine and Depression

Due to its dual 5$HT2_C$ receptor antagonist and MT1 MT2 agonist action, agomelatine is anticipated to have an effect on depression. A series of randomized controlled studies (see Table 1) have looked at the efficiency of agomeltine both as a treatment of depressive episodes and in preventing relapse. Detailed reviews by Kennedy and Rizvi[96] and de Bodinat et al[45] are available. A total of nine randomized double blind studies have been performed: six of agomelatine vs. placebo (three published)[97,98] and three of agomelatine vs. an active comparator using venlafaxine 25–50 mg,[99] sertraline 50–100 mg[95,100] and fluoxetine 20–40 mg.[101] Outcomes were measured with the 17 item Hamilton Depression Rating Scale (HAMD-17). Agomelatine was shown to be as effective as venlafaxine, but significantly more effective than sertraline and fluoxetine. However, this increased effectiveness in comparison to fluoxetine was in part due to the effect of sleep related items on the HAMD-17: once they

Table 1. Studies of agomelatine in the treatment of major depressive disorder.

	Objective	N°	Agomelatine	Comparator	Duration
Short-term efficacy studies of Agomelatine vs. placebo					
Lôo et al[97]	Dose finding: difference vs. placebo assay sensitivity	711	1, 5, 25 mg	Placebo Paroxetine 20 mg as positive control	8 weeks
CL3-022	Superiority vs. placebo assay sensitivity	419	25 mg	Placebo Fluoxetine 20 mg as positive control	6 weeks + 18 weeks extension
CL3-023	Superiority vs. placebo assay sensitivity	417	25 mg	Placebo Paroxetine 20 mg as positive control	6 weeks + 18 weeks extension
CL3-024	Superiority vs. placebo assay sensitivity	607	25, 50 mg	Placebo Fluoxetine 20 mg as positive control	6 weeks + 18 weeks extension
Kennedy and Emsley[98]	Superiority vs. placebo	212	25 to 50 mg	Placebo	6 weeks + 46 weeks extension
Olié and Kasper[100]	Superiority vs. placebo	238	25 to 50 mg	Placebo	6 weeks + 46 weeks extension
Short-term efficacy studies of Agomelatine vs. an active comparator					
Lemoine et al[99]	Superiority vs. active comparator	332	25 to 50 mg	Venlafaxine 75 to 150 mg	6 weeks + 18 weeks extension
Kasper et al[95]	Superiority vs. active comparator	313	25 to 50 mg	Sertraline 50 to 100 mg	6 weeks + 18 weeks extension
Hale et al[101]	Superiority vs. active comparator	515	25 to 50 mg	Fluoxetine 20 to 40 mg	8 weeks + 16 weeks extension
Studies of relapse prevention					
CL3-021	Superiority vs. placebo	367	25 mg	Placebo	Open 8 weeks double blind 26 weeks
Goodwin et al[102,103]	Superiority vs. placebo	339	25, 50 mg	Placebo	Open 8–10 weeks double blind 24 weeks

Notes: All studies were multicenter, and except for relapse studies, randomized double blind in parallel groups.
References for studies: CL3-021 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.

had been removed, the effect, although still present, was weaker.

Does agomelatine have an effect on relapse in patients with recurrent depression? Two studies randomized patients to either agomelatine or placebo and followed them up for up to 10 months (only one trial published).[102,103] The unpublished study found no effect of agomelatine, probably due to a low rate of relapse in the placebo group. The second study randomized patients who had successfully responded to agomelatine treatment for 8–10 weeks to either agomelatine or placebo for a further 24 weeks. Relapse rates were twice as low in the group randomized to agomelatine at 6 months, an improvement that continued at 10 months.

Subtypes of depression known to be associated with circadian disturbance such as seasonal affective disorder might be expected to respond well to agomelatonine but to date no studies have been performed. Data is also lacking on whether agomelatine has specific actions in certain populations such as women or the elderly.

Sleep and Agomelatine

The subjective effect of agomelatine on sleep has been shown in a recent pooled analysis of published studies of agomelatine vs. placebo with 358 patients treated by agomelatine (25–50 mg) and 363 patients on placebo. Treatment with agomelatine significantly decreased the CAP rate, with changes starting from the first week of treatment. A further polysomnographic study of agomelatine vs escitalopram confirms the sustained improvement of sleep and daytime vigilance.[107]

Agomelatine is also more effective than the active comparator venlafaxine on the Leeds sleep questionnaire, and effects start in the first week of treatment. At 6 weeks patients fall asleep more easily with agomelatine and have significant differences in the quality of sleep, and ease of waking. Patients also recorded a significant early improvement in daytime vigilance and feeling of well being with agomelatine compared with venlafaxine in the early stages of treatment although patients on venlafaxine gradually caught up with the patients in the agomelatine group after the second week and differences thereafter were insignificant.[99] Agomelatine thus is significantly more effective than active comparators and placebo on subjective sleep and changes start earlier. These early improvements in sleep are mirrored by early improvements in daytime functioning, and patients treated by conventional antidepressants improve to the same extent but more slowly.

Are changes in subjective sleep mirrored by changes in objective sleep? A preliminary open label study in patients with MDD showed sleep architecture progressively improved on polysomnography from the first week of treatment with normalization of distribution of slow wave sleep SWS over the first four sleep cycles allied with a increase of the delta ratio (delta first non REM episode/delta second non REM episode). No effects on rapid eye movement (REM) sleep were seen.[105] The changes in sleep parallel the improvements in symptoms of depression. A study of cyclic alternating pattern (CAP), which is a measure of sleep fragmentation showed that CAP rates and CAP time are significantly higher in depressed patients compared to controls, implying disturbed non REM sleep.[106] Treatment with agomelatine significantly decreased the CAP rate, with changes starting from the first week of treatment. A further polysomnographic study of agomelatine vs escitalopram confirms the sustained improvement of sleep and daytime vigilance.[107]

Agomelatine and Longterm Use

For the moment studies on the use of agomelatine have focused on short and medium term follow-up (see Table 1), with the addition of an open label period at the end of each study, prolonging study periods to 24 or 48 weeks. Several studies have demonstrated that the antidepressant efficiency of agomelatine is maintained during the period of the study and during the open label period with no difference between agomelatine and active comparators at the end of the open label study periods. Over a 24 week period, patients who responded initially to treatment by agomelatine and continued treatment were significantly less likely to relapse than patients randomised to placebo[103] and this was maintained over a ten month period.[102,107]

Safety of Agomelatine

Agomelatine has been shown in all studies to be well tolerated.[96–100,103] The most commonly reported events in the latest study by Quera-Salva et al[107] including 138 patients were headache (14.1%), nasopharyngitis (11.3%), nausea (9.9%), diarrhoea (5.6%), bronchitis (5.6%), hyperhidrosis (2.8%), fatigue (1.4%), and dizziness (1.4%). 66% of patients taking agomelatine reported at least one adverse event as compared with patients taking escitalopram, 82% of whom reported at least one adverse event. Of note, somnolence, a frequent complaint of patients taking $5HT2_C$ receptor agonists (mianserine and mirtazapine) is not seen in patients treated with agomelatine, who report a feeling of clear thinking on awakening and do not complain of daytime sleepiness.[99,107] Agomelatine has not shown adverse events related to sexual function, unlike active comparators (venlafaxine and escitalopram).[108,109] One case of reversible QTc

prolongation has been reported.[110] This is a known side effect of other antidepressants, having been reported with both tricyclics and serotonin reuptake inhibitors in overdose,[111–113] particularly in the elderly.[114] QTc prolongation with ketanserin has been reported[115,116] and thus the effect is probably due to agomelatine's 5HT2c antagonism. No further cases have been reported to date and the clinical significance of the finding remains unclear.

Conclusion

It is likely that a bidirectional link between circadian rhythms and MDD exists. Circadian dysfunction can trigger MDD and cause relapses, and MDD can cause circadian rhythm abnormalities. Classical antidepressant treatments normalize mood and abnormal sleep gradually over several weeks of treatment, while treatments directly active on circadian rhythms (bright light therapy and behavioural therapy) are active on depression. Innovative treatments combining chronobiotic and antidepressant effects have promise as they may stabilize circadian rhythms while acting as effective antidepressants, thus treating acute episodes of MDD and preventing relapse. Studies on agomelatine are encouraging, showing that agomelatine is as effective as active comparators in trials both in treatment of acute episodes of MDD and in relapse prevention. Agomelatine rapidly improves sleep and daytime functioning, is well tolerated and offers an exciting new approach to the treatment of MDD, especially in patients where sleep is disturbed.

Further work is needed to clarify the role of altered circadian rhythms in depression and the role of chronobiotic antidepressants in different subtypes of MDD such as seasonal affective and bipolar disorders.

Disclosure

Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

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