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What is This?

Addressing circadian rhythm disturbances in depressed patients

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Abstract

Desynchronisation of normal circadian rhythms, including the sleep–wake rhythm, is common in major depressive disorder (MDD). The association between sleep disturbances and depression has long been recognised. Disturbed sleep is a diagnostic criterion for MDD, and insomnia commonly precedes the onset of symptomatic mood disorders. Disruptions of the sleep–wake cycle (sleep architecture and timing) are residual symptoms that may prevent the attainment of high-quality remission and delay recovery from MDD. Therefore, early recognition and treatment of sleep disturbances may be important for the treatment and prevention of recurrent depression. Evidence suggests that melatonergic (MT_1 and MT_2) and the $5-HT_{2C}$ serotonergic receptor subtypes are important modulators of circadian rhythmicity. Agomelatine is the first melatonergic antidepressant; an agonist of melatonin MT_1 and MT_2 receptors, with additional antagonist properties at the $5-HT_{2C}$ receptors. Agomelatine combines antidepressant efficacy including quality and efficiency of sleep, with a more favourable side-effect profile than current antidepressant treatments, including neutral effects on sexual function, bodyweight and the absence of discontinuation symptoms. These positive features provide a novel approach to the treatment of depression and the attainment of high-quality remission in MDD.

Key words

Introduction

There is increasing attention to the role of biological rhythms in the pathophysiology of major depressive disorder (MDD) (McClung, 2007). Disturbances of normal circadian rhythms including variations in the sleep–wake cycle are known to powerfully influence mood, and it is well established that sleep disturbances and circadian rhythm abnormalities are linked (Van Cauter and Turek, 1986; van Bemmel, 1997). The association between sleep disturbances and depression is recognised by the inclusion of disturbed sleep as one of the nine diagnostic criteria for major depressive episodes of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association, 2000). Additionally, insomnia commonly precedes the onset of mood disorder symptoms (Ohayon and Roth, 2003), and sleep disturbance and other symptoms are strong predictors of future depression (Ford and Kamerow, 1989; Breslau, *et al.*, 1996; Lustberg and Reynolds, 2000; Roberts, *et al.*, 2000; Riemann and Voderholzer, 2003). Thus, early recognition and treatment of disturbances of the sleep–wake cycle may be important for treatment and prevention of recurrent depression. In this article, we will examine the interlinked relationship of circadian rhythm disorders and depression, address the issues of remission, relapse and recurrence in MDD and consider how high-quality remission may be achieved in patients with MDD.

Circadian rhythm dysfunction in depressed patients

A core biological clock mechanism, residing in the suprachiasmatic nucleus (SCN) within the anterior hypothalamus, regulates circadian rhythms in the brain and body of mammals. The periodicity of these endogenous rhythms is continuously synchronised or entrained by environmental signals, primarily the light–dark cycle. A major non-photic regulatory pathway for the SCN is the hormone melatonin, originating from the pineal gland. Melatonergic receptors and $5-HT_{2C}$ receptors, located in the SCN are modulators of SCN function and rhythmicity. The stability of internal and external phase relationships is hypothesised to be essential for a stable 'normal' mood state. Consequently, desynchronisation of internal circadian rhythms with the external world may result in mood fluctuation and contribute to a chronobiological susceptibility to depression. Many diverse rhythms are disrupted in depressed

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patients, including the 24-h profiles of cortisol, prolactin, melatonin, growth hormone, norepinephrine, 3-methoxy-4-hydroxyphenylglycol (MHPG), thyrotropin and body temperature (Linkowski, *et al*., 1985; Mendlewicz, *et al*., 1985; Van Cauter and Turek, 2000; Koenigsberg, *et al*., 2004). There are also characteristic disturbances of sleep architecture and timing, including early emergence of rapid eye movement (REM) sleep and lower slow wave activity during non-REM (NREM) sleep (Van Cauter and Turek, 2000; Staner, *et al*., 2003; Lopes, *et al*., 2008). Clinical findings such as these suggest that desynchronisation of internal rhythms plays an important role in the pathophysiology of depressive disorders, and, as a corollary, that resetting circadian rhythms may have an antidepressant effect. Resynchronisation of disturbed circadian rhythms and normalisation of disrupted sleep–wake cycles would be highly desirable features in addition to primary antidepressant activity in the clinical management of depression.

Pharmacology of agomelatine and circadian function

Agomelatine is a new antidepressant with an innovative pharmacological profile. It is the first melatonergic antidepressant, and is an agonist of melatonin MT_1 and MT_2 receptors and, in addition, has antagonist properties at the $5\text{-}HT_{2C}$ receptors (Millan, *et al*., 2003; Audinot, *et al*., 2003). A high concentration of melatonergic and serotonergic receptors, responsible for the modulation of biological rhythms via melatonin and 5-HT, respectively, has been identified in the SCN (Pickard and Rea, 1997; von Gall, *et al*., 2002). The expression of MT_1 receptors has been shown to have diurnal rhythmicity, regulated by light and the internal clock (Masana, *et al*., 2000), whereas the expression for mRNA of $5\text{-}HT_{2C}$, but not 5-HT1a or 5-HT2a receptors, has a circadian rhythm pattern (Holmes, *et al*., 1995). Circadian rhythmicity also has been reported for MT_1 and $5\text{-}HT_{2C}$ receptors in mammals (Holmes, *et al*., 1995; Masana, *et al*., 2000). Agomelatine has a high affinity at human MT_1 and MT_2 and $5\text{-}HT_{2C}$ receptors (Audinot, *et al*., 2003; Millan, *et al*., 2003). Preclinical investigation has shown agomelatine to have notable dose-related chronobiotic activity, resynchronising disrupted circadian rhythms in animal models (Armstrong, *et al*., 1993; Martinet, *et al*., 1996).

Remission, relapse and recurrence in MDD

Remission, defined as minimal depressive symptoms (typically a score within the normal range on a depression rating scale), has become the accepted goal of acute and maintenance treatment for MDD (Rush, *et al*., 2006). This definition has increasingly replaced response, a clinically meaningful degree of symptom reduction (typically a ≥50% reduction in baseline severity as measured by rating scales), as a primary outcome measure in clinical trials. High-quality remission implies that patients are asymptomatic, with no or only minimal residual

symptoms, and a full restoration of day-to-day functioning and quality of life. If the period of remission continues for at least 4 months without a relapse of symptoms, the American College of Neuropsychopharmacology (ACNP) Task Force considers that recovery has been achieved (Rush, *et al*., 2006).

Epidemiological and clinical evidence showing treatment to full remission is a strong predictor of prolonged time to relapse or recurrence of MDD suggests that preventing repeat depressive episodes from occurring in the first place may be a more effective strategy than delaying treatment until relapse or recurrence occurs (Nierenberg, *et al*., 2003). The presence of residual symptoms strongly predicts subsequent early relapse (the return of symptoms before recovery has been achieved) (Paykel, *et al*., 1995; Judd, *et al*., 1998), and up to 85% of recovered patients will have a recurrence (the development of a new major depressive episode following recovery) within 15 years (Mueller, *et al*., 1999). Residual symptoms were associated with early relapse of 76% over 10 months in one study (Paykel, *et al*., 1995), compared with 25% in those with full remission. In another prospective study with 10 years of follow-up, patients with residual symptoms relapsed over threefold faster than those with asymptomatic recovery (Judd, *et al*., 1998). The importance of achieving full remission is highlighted by several other studies that show residual symptoms are associated with early relapse (Faravelli, *et al*., 1986; Cornwall and Scott, 1997; Van Londen, *et al*., 1998; Pintor, *et al*., 2003).

However, although remission is the first step to achieve full recovery, maintenance therapy is generally necessary because, without long-term treatment, most patients will eventually experience relapse or recurrence (Judd, *et al*., 1998; Mueller, *et al*., 1999; Solomon, *et al*., 2000; Geddes, *et al*., 2003). Systematic review of pooled data from 31 randomised trials (4410 participants) found that continuing antidepressant treatment reduced the risk of relapse by over 50% (Geddes, *et al*., 2003). The benefits of continued treatment persisted for up to 3 years; the mean rate of relapse with active treatment was 18% compared with 41% with placebo (Geddes, *et al*., 2003).

An ideal antidepressant should combine high short-term clinical efficacy for acute phase treatment with good long-term efficacy and tolerability for the maintenance phase. However, despite the widespread use of newer antidepressants such as the SSRIs and serotonin–norepinephrine reuptake inhibitors (SNRIs), the management of MDD remains suboptimal, and there are continuing concerns about side effects of treatment. The STAR*D trial in a large, representative group of outpatients with MDD showed that one-third of patients do not achieve remission, despite up to four sequential treatment steps including SSRIs, SNRIs and combination therapy (Rush, *et al*., 2006). In STAR*D, 16–30% of patients at each treatment level experienced intolerable side effects leading to treatment withdrawal. Gastrointestinal disturbances, nausea and vomiting, weight gain, sexual dysfunction and discontinuation effects are well-established side effects of SSRIs and SNRIs (Vanderkooy, *et al*., 2002). Furthermore, many antidepressants, including SSRIs and SNRIs, can interfere with sleep (Mayers and Baldwin, 2005). This is of clinical concern because

sleep disturbances and fatigue, the most common residual symptom remaining after remission, can reduce the quality of remission and impair recovery (Nierenberg, *et al.*, 1999). In particular, tricyclic antidepressants, although improving sleep continuity, can markedly reduce REM sleep and may cause sedation and daytime sleepiness (Mayers and Baldwin, 2005). SSRIs and SNRIs also suppress REM sleep and can impair sleep continuity, and are often reported to cause insomnia and/or reduced daytime alertness (Mayers and Baldwin, 2005). Clearly, there is an unmet need for an effective antidepressant with a favourable tolerability profile, to facilitate short-term and long-term adherence important to the attainment of remission and recovery.

In placebo-controlled clinical studies, agomelatine at a dose of 25–50 mg/day has been shown to be effective in treating MDD (Lôo, *et al.*, 2002; Kennedy and Emsley, 2006; Olié and Kasper, 2007). Agomelatine also is very well tolerated, with an adverse events profile similar to placebo (Zupancic and Guilleminault, 2006). The novel mechanism of antidepressant activity of agomelatine and the potential for regulation of the sleep–wake cycle through synergy of action at melatonergic MT_1 and MT_2 receptors and $5-HT_{2C}$ serotonergic receptors in the SCN may result in better quality of remission and improved adherence to antidepressant treatment to maximise the achievement of recovery.

Quality of remission with the melatonergic antidepressant agomelatine

The efficacy of agomelatine in MDD was proven in three short-term, placebo-controlled trials (Lôo, *et al.*, 2002; Kennedy and Emsley, 2006; Olié and Kasper, 2007). The standard dose of agomelatine 25 mg/day was shown to be significantly more effective than placebo in reducing Hamilton Depression Rating Scale (HAMD) scores during 6–8 weeks of treatment. Additional clinical benefits were observed in cases of insufficient improvement when the dose was increased to 50 mg/day (Lôo, *et al.*, 2002; Kennedy and Emsley, 2006). In one trial that used a stringent definition of remission (HAMD ≤6), 30.4% of patients achieved remission with agomelatine 25 mg compared with 15.4% with placebo (*P* < 0.01) (Lôo, *et al.*, 2002), suggesting that agomelatine has good potential for providing high-quality remission. Of interest, the remission rate with the comparator in this study, the SSRI paroxetine 20 mg/day, was 25.7%. Agomelatine has similar antidepressant efficacy to the SNRI venlafaxine (Kennedy and Guilleminault, 2006; Lemoine, *et al.*, 2007), and one study reports percentages of patients with remission after 12 weeks of 73% and 66.9%, respectively, in the agomelatine and venlafaxine groups (Kennedy, 2007).

Severe depression is associated with greater suffering and a higher level of social and occupational impairment, and achieving high-quality remission can be especially difficult in patients with severe depression (Nemeroff, 2007). Pooled analysis of the three pivotal placebo-controlled trials in MDD show that ago-
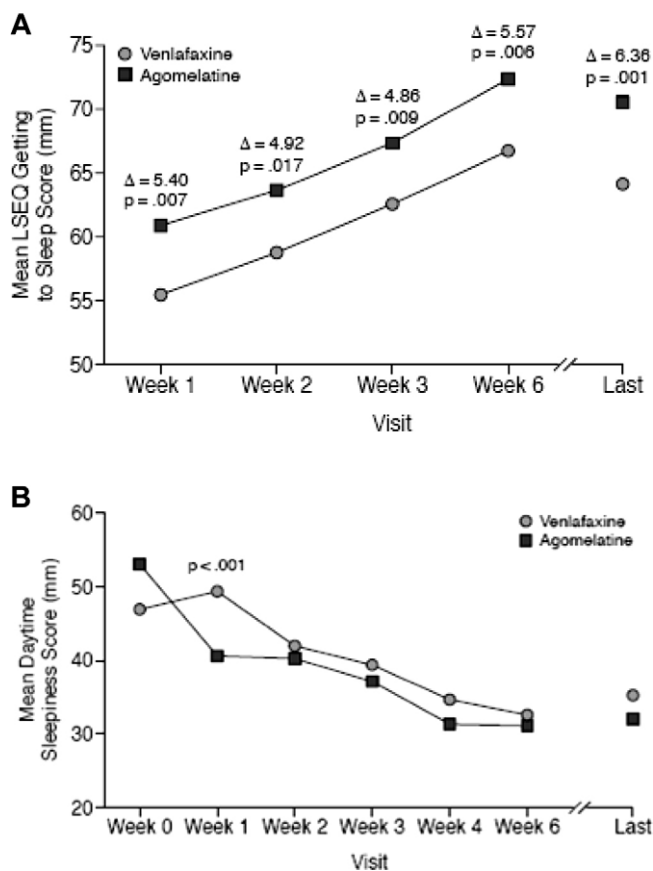
melatine at a dose of 25–50 mg is particularly effective in comparison with placebo, for treating severe depression (HAMD ≥ 25) (Montgomery and Kasper, 2007). There was an increasing magnitude of difference from placebo with increasing severity of baseline depression, rising from 2.06 points on the HAMD for the subgroup with baseline HAMD 22–25 to 4.45 points for patients with baseline HAMD >30. This severity-related treatment effect has also been reported for the SSRI escitalopram (but not citalopram) (Lam and Andersen, 2006) and for the SNRI venlafaxine given at high doses (Guelfi, *et al.*, 1995) and duloxetine (Shelton, *et al.*, 2007).

Other positive features of agomelatine may contribute to high-quality remission. As a melatonergic agonist and $5-HT_{2C}$ antagonist, agomelatine could be expected to have a beneficial regulatory effect on the sleep–wake cycle. Indeed, treatment with agomelatine improved sleep continuity and quality in an open polysomnographic study of agomelatine 25 mg/day in patients with MDD (Quera Salva, *et al.*, 2007). Treatment with agomelatine normalised the distribution of slow-wave sleep activity while preserving REM sleep. The regulation of sleep architecture occurred very early during treatment; with sleep efficiency increasing and the duration of stages 3–4 decreasing progressively throughout the first four sleep cycles from day 7 (Figure 1) (Quera Salva, *et al.*, 2007). The improvements in sleep were accompanied by improvements in daytime alertness. These results were in line with those of a large double-blind study that used the Leeds Sleep Evaluation Questionnaire (LSEQ) to assess the subjective quality of sleep of patients receiving agomelatine or venlafaxine and visual analogue scales to evaluate alertness during the day (Lemoine,
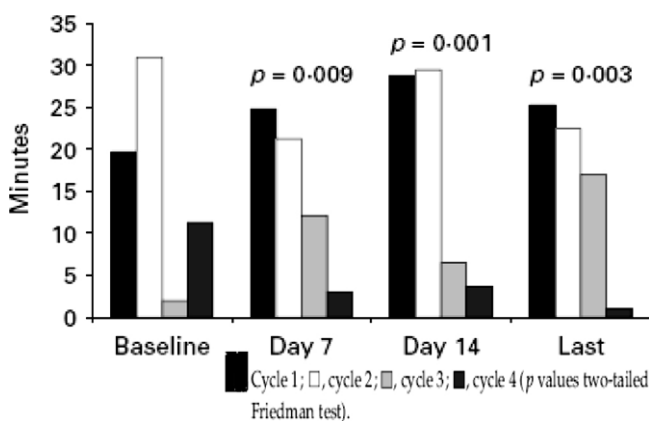
Figure 1 Distribution of slow-wave sleep (median duration of stages 3–4) during the first four sleep cycles of each visit in patients with MDD receiving agomelatine 25 mg/day. Reproduced from Maria-Antonia Quera Salva, Bernard Vanier, Judith Laredo, Sarah Hartley, Florian Chapotot *et al.* Major depressive disorder, sleep EEG and agomelatine: an open label study. 2007 *The International Journal of Neuropsychopharmacology* with permission from Cambridge University Press.

et al., 2007). Subjective sleep and daytime condition improved earlier (as soon as the first week of treatment) and to a greater extent with agomelatine than with venlafaxine. The improvement in sleep was rapidly apparent with agomelatine, and the difference in LSEQ score between treatments was significant after 1 week and continued throughout the 6-week treatment period (Lemoine, *et al.*, 2007). Scores for 'getting to sleep easier', 'getting to sleep quicker', quality of sleep and ease of awakening were all significantly better with agomelatine, suggesting that agomelatine improves the symptoms of depression and regulates sleep without sedative effects, contributing to improved quality of life and contributing to an improved quality of remission (Figure 2). Agomelatine's clinical benefits compared with SSRIs relating to the early regulation of the sleep–wake cycle and daytime alertness are currently under investigation.

Further investigation of the impact of agomelatine on the sleep of patients with MDD has been undertaken using polysomnography to analyse the cyclic alternating pattern (CAP) in NREM sleep (Lopes, *et al.*, 2008). The CAP is a visual scoring pattern that allows for an analysis of the electrocortical events distinguishable from background electroencephalographic (EEG) rhythms, allowing a more in-depth analysis of NREM sleep than conventional sleep staging methods. A significant decrease from baseline in CAP rate, time and cycle after 7 and 42 nights of treatment was observed. Changes in NREM sleep paralleled subjective reports of better sleep and better mood. When CAP rate, CAP time and distribution of CAP phases A at day 42 were analysed, there were no significant differences between controls and patients with MDD, suggesting that agomelatine normalises NREM sleep in depressed patients.

Conclusion

Agomelatine is the first melatonergic antidepressant, with a mechanism of action comprising agonistic activity at melatonin MT_1 and MT_2 receptors and antagonistic properties at the $5\text{-}HT_{2C}$ receptors. It has a reported efficacy in MDD and has also been shown to be effective in treating severe depression. Early indications of resynchronisation of disrupted circadian rhythms, including the sleep–wake cycle by agomelatine may contribute to high-quality remission in patients with MDD. Combined with an excellent tolerability and safety profile, agomelatine may offer a valuable option for the short-term and long-term management of MDD.

Figure 2 Time course of Leeds Sleep Evaluation Questionnaire (LSEQ) 'Getting to Sleep' Scores (A) and Daytime Sleepiness Visual Analogue Scale Scores (B), in patients with MDD treated with agomelatine or venlafaxine. Modified from Lemoine P, Guilleminault C and Alvarez E. Improvement in subjective sleep in major depressive disorder with a novel antidepressant, agomelatine: randomized, double-blind comparison with venlafaxine. 2007 *The Journal of Clinical Psychiatry* with permission from Physicians Postgraduate Press, Inc.

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