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REVIEW

Beyond the monoaminergic hypothesis: Agomelatine, a new antidepressant with an innovative mechanism of action

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Abstract

There are many potentials for the development of more effective, better tolerated, and more rapidly acting antidepressants. As there is large prevalence of circadian dysfunction in various affective disorders, including depression, one of the approaches is the development of antidepressant drugs with melatonergic agonist properties. Agomelatine, with its melatonergic agonistic (at both MT_1 an MT_2 receptors) and 5-HT_{2C} antagonistic properties, represents a new concept for the treatment of depression. The antidepressant action of agomelatine has been initially demonstrated in animal models of depression, such as the forced swim – the learned helplessness – and the chronic mild stress paradigms. Subsequent studies demonstrated that the antidepressant activity of agomelatine does not solely depend on its agonistic action at melatonergic receptors, but also on its antagonistic activity at 5-HT_{2C} receptors. Agomelatine also exhibits anxiolytic properties that bear a striking resemblance to those of selective 5-HT_{2C} receptor antagonists. In patients with major depressive disorder, agomelatine had efficacy at least comparable to that seen with available antidepressants. Interestingly, agomelatine demonstrated antidepressant efficacy not only in patients with a moderate depressive episode but also in a more severe depressed subpopulation of patients. The treatment effect increased with the severity of the disease. Agomelatine also rapidly regulates the sleep–wake cycle without causing sedation and improves daytime condition. Agomelatine has an excellent safety profile, is weight neutral, does not affect sexual functioning and does not cause discontinuation syndrome. Collectively, its efficacy, together with its excellent tolerability, makes agomelatine an especially promising antidepressant for the near future.

Key words: *Agomelatine, major depressive disorder, melatonergic receptors, 5-HT_{2C} receptors*

Introduction

Treatments for depression, that affects up to 20% and causes an enormous burden for the society (Kasper 1995), are far from ideal, and often inadequate. Fewer than 50% of patients with depression achieve full remission with optimized treatment. Despite the increase in the available therapeutic armamentarium (Kasper et al. 1994), in particular selective serotonin (5-HT) reuptake inhibitors (SSRIs) and serotonin-noradrenaline (NA) reuptake inhibitors (SNRIs), 50% of depressed patients remain untreated. In addition to the need to administer the drugs for weeks or months before seeing clinical benefit, side effects are still a serious problem even with the newer medications. A substantial number of patients discontinue antidepressant treatment during the first weeks of treatment, and poor compliance remains one of the most common obstacle of antidepressant treatment (Zajecka 2000). The SSRIs are relatively well tolerated compared with tricyclic, imipramine-type, antidepressants, but they also cause some adverse effects linked to their actions on gastrointestinal tract, sexual functioning and sleep patterns (Vida and Looper 1999). A withdrawal syndrome on stopping treatment has also been reported with the use of some SSRIs (Montgomery et al. 2004).

There is still a great need for faster acting, safer and better tolerated and more effective treatments for depression, as such treatments could lead to more complete remission in more patients (Möller 2008). To this aim, the field has to move beyond today's mechanisms of antidepressant medications, as it is now well recognized that synaptic facilitation

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and augmentation of the levels and effects of NA and 5-HT only partially explain the action of current antidepressants. There is now an accumulation of knowledge derived from animal studies about non-monoamine systems that might contribute to the pathophysiology of depression and human evidence in support of this concept is increasingly available (Baghai et al. 2006). Among the various strategies to help patients with new, more effective and better tolerated treatments, the re-synchronization of biological rhythms appears to be particularly attractive given that a disruption of circadian rhythms is characteristic of a large number of mood disorders (Kasper and Wehr 1992;Winkler et al. 2005).

The present review briefly describes some of the non-monoamine drugs for the treatment of depression, and also provides an overview on the available preclinical and clinical data on agomelatine, a new antidepressant with a novel mechanism of action.

Beyond the monoaminergic hypothesis

The "monoamine hypothesis" of depression, which involves imbalances in serotonergic, noradrenergic and possibly dopaminergic functions, has dominated notions and explanations of the pathophysiology of depression since the empirical discovery of the antidepressant properties of monoamine oxidase inhibitors (MAOIs) and tricyclics 50 years ago. Although the monoaminergic neurotransmitters (5-HT, NA and dopamine, DA) are undoubtedly involved, it is now recognized that changes in the levels of monoamines produced by antidepressants and subsequent adaptive processes, in particular a change in the sensitivity of some of their receptors, are not sufficient on their own to explain the mechanism of action of antidepressants. Indeed, it is difficult to correlate the time of the delayed clinical onset of antidepressant action (i.e., 3–6 weeks) with the increase in synaptic levels of monoamines, as this change occurs already after the initial dose of the drug.

Over almost 50 years, the number of hypotheses for the mechanism of action of antidepressants has grown steadily. For example, high concentrations of glucocorticoids are generally associated with a negative effect on mood, as well as with structural changes in the hippocampus, perhaps via a reduction in the synthesis of brain-derived neurotrophic factor (BDNF), by excessive release of glutamic acid and/or a reduction in the uptake of neuronal glucose (Manji et al. 2003); in agreement with these observations, inhibitors of glucocorticoid synthesis and antagonists of glucocorticoid receptors exhibit antidepressant-type effects (Reus and Wolkowitz 2001).

There is also interest in treating depression and anxiety disorders by modulating neuropeptide-actions. Indeed, antagonists at NK1 receptors of substance P have been claimed to exert antidepressant effects in both relevant animal paradigms and in clinical trials (Kramer et al. 1998). However, this approach has not resulted in a clinically effective antidepressant drug since subsequent studies have not been as straightforward to interpret (Krishnan 2002).

In agreement with the idea that functional abnormalities in the HPA stress axis are causally associated with affective disorders (Kasper et al. 1988), studies have demonstrated elevated levels of corticotropin releasing factor (CRF) in the cerebrospinal fluid of patients with moderate to severe depression. Indeed, treatment with antagonists at CRF-1 receptors have been shown to counteract behavioural deficits in animal models of depression (Griebel et al. 2002a,b) and to improve mood in depressed subjects (Zobel et al. 2000). However, at least for both CRF1- and NK1-receptor antagonists, one can speculate that they also act, although indirectly, through monoaminergic mechanisms. Indeed, tachykinin NK_1 receptor antagonists activate noradrenergic and dopaminergic pathways innervating the hippocampus and the frontal cortex, and long-term treatments with these antagonists produce adaptive changes in 5-HT neurotransmission (notably a functional desensitization of 5-HT_{1A} autoreceptors, responsible for an increased 5-HT tone) comparable to those observed after chronic treatment with MAOIs or SSRIs (Froger et al. 2001). In addition, CRF-1 antagonists indirectly enhance the activity of serotonergic pathways (Reul and Holsboer 2002; Manji et al. 2003) although they do not, in contrast to tachykinin NK_1 receptor antagonists, activate dopaminergic input to the cortex and may inhibit the activity of noradrenergic neurones (Millan et al. 2001; Lejeune et al. 2002).

Stress causes a cyclic-adenosine monophosphate response element binding protein (CREB)-mediated induction of the opioid peptide dynorphin in the nucleus accumbens, which, in turn, can cause certain depression-like behaviours, such as anhedonia, for example. Accordingly, administration of dynorphin antagonists, either systemically or locally into the nucleus accumbens, has been shown to decrease depression-like behaviours in rodents. Manipulation of the cannabinoid CB1 receptor, the main target for cannabinoids in the brain, through CB1 receptor agonists or antagonists also exert effects on anxiety and stress-related behaviours in rodents although the results obtained so far are inconsistent. It is also known that antidepressants alter the expression of different factors involved in the survival and growth of cells, such as CREB, bcl-2 and mitogen-activated protein-kinases. A number

of recent studies in animal models of depression have led to the idea that some deficit in hippocampal neurogenesis is implicated in the aetiology of major depressive disorders (Kempermann and Kronenberg 2003; Malberg and Schechter 2005), but the exact functional importance of this phenomenon in the pathophysiology of mood disorders remains controversial (Henn and Vollmayr 2004). Drugs that affect chromatin structure (e.g., histone deacetylase inhibitors) are now in early stages of development and will merit further consideration in depression research (Tsankova et al. 2006).

One promising hypothesis for the mechanism of action of antidepressants is based on the extensive list of physiological variables showing circadian rhythms abnormalities in depressed patients. The vast majority of the physiological, metabolic and behavioral functions are under the control of the circadian pacemaker, or biological clock, located in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus, which generates and entrains circadian rhythms. It is now clearly recognized that disorganized internal rhythmicity is characteristic of a large variety of affective disorders, including unipolar and bipolar depression, mania, seasonal affective disorder, premenstrual dysphoric disorder (Wehr and Wirz-Justice 1982; Claustrat et al. 1984; Brown et al. 1985; Thompson et al. 1988; Souetre et al. 1989; Wirz-Justice 1995). Many rhythms are phase advanced or delayed with respect to the sleep–wake cycle, diminished in amplitude and/or with day-to-day variability in entrainment (Souetre et al. 1989; Wirz-Justice 1995).

The relationship between the daily variation of mood, the endogenous circadian pacemaker and the appearance of depressive symptoms is complex. Physiological variables for which circadian abnormalities in depressed patients have been described include sleep timing and structure, body temperature and hormonal rhythms. Therefore, any re-synchronisation of deteriorated biological rhythms of a depressive individual could have a beneficial effect on depressive episodes. Available antidepressant treatments do not directly impact on depression-associated circadian disorders, and treatments aimed at correcting rhythm abnormalities would represent a new approach to the treatment of depression.

Development of agomelatine, a novel antidepressant

Preclinical (animal) studies

The exciting potential in the treatment of depression for a drug which would easily cross the blood brain barrier and synchronise circadian rhythms led to the synthesis of agomelatine (Yous et al. 1992). Agomelatine is a potent agonist at melatonergic MT_1 ($K_i = 0.10 \pm 0.01$ nM) and MT_2 ($K_i = 0.12 \pm 0.02$ nM) receptors (Yous et al. 1992; Audinot et al. 2003), which has also been shown to have affinity for 5-HT_{2C} receptors ($pK_i = 6.15 \pm 0.04$) (Millan et al. 2003). Supplementary pharmacological studies indicated that agomelatine acts as an antagonist at 5-HT_{2C} receptors as the drug inhibits the binding of [^{35}S]GTP-γ-S to Gq protein and the activation of phospholipase C normally evoked by selective 5-HT_{2C} receptor agonists (Millan et al. 2003). Such data clearly demonstrated that agomelatine is a 5-HT_{2C} receptor antagonist in the dose range corresponding to its antidepressant- and anxiolytic-like effects in rodents (see below). Due to these 5-HT_{2C} receptor antagonist properties, administration of agomelatine (10–40 mg/kg i.p.) produced concomitant DA and NA overflows in the frontal cortex (Millan et al. 2003), while 5-HT outflow remained unchanged. In addition, chronic treatment with agomelatine does not cause any adaptive changes in the activity of pre- and post-synaptic 5-HT_{1A} receptors (Hanoun et al. 2004). This is notable because the absence of any effect on 5-HT outflow as well as the absence of functional changes of 5-HT_{1A} receptors allow inference that agomelatine's antidepressant action is not mediated through those mechanisms known for tricyclics, SSRIs and MAOIs. Clinical agomelatine's data consistently show the low incidence of side effects classically associated with serotonin reuptake inhibition (see below) which further supports the argument that the mechanism of action of agomelatine differentiates from that of other antidepressants.

Improvement in the synchronisation of circadian rhythms. Studies carried out in vivo have shown that agomelatine accelerates resynchronization of circadian rhythms of locomotor activity and relevant biological parameters (i.e., body temperature, hormone secretions) in various animal models of abrupt shifts and disorganization of the light–dark cycle, in free-running conditions (Pitrosky et al. 1999) as well as in animal models of delayed sleep-phase syndrome. The re-synchronising activity of agomelatine has been shown in both nocturnal (rats, mice, hamsters) and diurnal (*Arvicanthis mordax*) animals (Redman et al. 1995; Van Reeth et al. 1998; Weibel et al. 2000). Re-synchronisation of circadian rhythms can be obtained by a phase advance (Van Reeth et al. 1997) when agomelatine is administered in the evening, as well as through a restoration of the rhythm profile, as shown in a model of fragmented

waking–sleeping rhythm (Grassi-Zucconi et al. 1996).

The ability of agomelatine to synchronize rest–activity rhythms in free-running animals requires the integrity of the suprachiasmatic nucleus and it would seem obvious that the agonistic effects of agomelatine at MT_1 and MT_2 receptors located in this hypothalamic nucleus contribute to the phase-advancing and resynchronizing actions of the drug (Armstrong et al. 1993; Redman et al. 1995; Redman and Francis 1998; Sack et al. 1998; Van Reeth et al. 2001). Nevertheless, the respective contribution of 5-HT_{2C} and melatonergic receptors to the influence of agomelatine on diurnal and other chronobiotic rhythms should justify additional studies.

Activity in models sensitive to antidepressant compounds (Table I). There are a number of validated and widely used paradigms available with proven sensitivity to various classes of antidepressants (Mitchell and Redfern 2005). The majority of these behavioural models are based on the reversal of the deleterious effects caused by stress situations, be it acute (forced swim test, tail suspension test), sub-chronic (learned helplessness) or chronic (chronic mild stress, prenatal stress). Other behavioural paradigms sensitive to antidepressants are based on the hierarchic position within social groups, i.e. dominant and subordinate animals under imposed environmental peculiarities such as post-weaning individual housing or social defeat. Finally, genomic models (i.e., deletion of CRH receptor-, tachykinin receptor- or serotonin transporter-encoding genes, transgenic expression of antisense mRNA of glucocorticoid receptor) and genetic models (Fawn Hooded rats, Flinders Sensitive line rats) as well as those using lesioning (olfactory bulbectomy) have also to be mentioned here.

Acute or repeated oral administration of agomelatine significantly reduced the duration of immobility of mice or rats in the forced swim test (Bourin et al. 2004). Agomelatine is also effective in the learned helplessness paradigm in rats (Bertaina-Anglade et al. 2006) and exhibited a clear-cut antidepressant-like effect in the olfactory bulbectomized rat model (Norman et al. 2004). In sharp contrast, melatonin has no antidepressant-like effects in either of these three models when applying identical experimental conditions.

Today, the chronic mild stress paradigm (Willner et al. 1992) is considered the most relevant animal model for providing evidence of antidepressant properties of a drug because it focuses on anhedonia, one of the key symptoms of depression (Mitchell and Redfern 2005). Rodents subjected to this chronic stress procedure also show many other symptoms of

Table I. Demonstration of the antidepressant-like activity of agomelatine in preclinical models

	Agomelatine (dose)	Positive control(s)	Main findings
Despair test (1)	2, 10, 50 mg/kg p.o.	Imipramine (64 mg/kg p.o.)	Acute or repeated (for 13 days) oral administration of agomelatine significantly reduced the duration of immobility of Wistar rats in the forced swim test, like that found with imipramine. In mice, agomelatine produced the same effect as fluoxetine.
Learned helplessness (2)	10 and 50 mg/kg p.o.	Imipramine (64 mg/kg p.o.)	Agomelatine is effective in the learned helplessness paradigm in rats, and its antidepressant-like activity in this model is comparable to that of imipramine.
Chronic mild stress (3)	10 and 50 mg/kg, i.p	Imipramine (10 mg/kg, i.p.) Fluoxetine (10 mg/kg, i.p.)	After a 2–3-week treatment, agomelatine reverses the anhedonia seen in this model, irrespective of the time of day of its administration. There is no withdrawal relapse one week after cessation of treatment.
Transgenic model (4)	10 mg/kg, i.p	Desipramine (10 mg/kg, i.p.)	In transgenic mice with low glucocorticoid receptor (GR) function, agomelatine was effective in reversing the transgenic mouse behavioural changes noted in the Porsolt forced swim test as well as in the elevated plus maze. Agomelatine also markedly accelerated readjustment of circadian cycles of temperature and activity following an induced phase shift. Desipramine was without effect.
Genetically helpless mice (5)	50 mg/kg, i.p	Fluoxetine (10 mg/kg, i.p.)	The helpless line (H/Rouen), which is much more immobile in the tail suspension test (TST) than the so-called non-helpless (NH/Rouen) line, corresponds to a new genetic model of depression. Chronic agomelatine and fluoxetine treatment (3 weeks) were devoid of any effects in the TST in NH/Rouen mice at all tested days, whereas both treatments significantly reduced the immobility time of H/Rouen mice at D8, D15 and D22.
Bulbectomized rat model (6)	10 and 50 mg/kg i.p.	Imipramine (10 mg/kg i.p.)	Agomelatine exhibited a clear-cut antidepressant-like effect in the olfactory bulbectomized rat model. Like imipramine (14 days), agomelatine (14 days) re-normalized the locomotor hyperactivity characteristic of bulbectomized rats to the level displayed by sham-operated control animals.

(1) Bourin et al. (2004); (2) Bertaina-Anglade et al. (2006); (3) Papp et al. (2003); (4) Barden et al. (2005); (5) El Yacoubi et al. (2006); (6) Norman et al. (2004).

depression, including a reduction in sexual activity, aggression and locomotor activity, the fragmentation of sleep and an increase in the number of episodes of rapid eye movements (REM).

Agomelatine reverses the anhedonia seen in this model and, once installed, the effect of agomelatine remains robust, with no withdrawal relapse 1 week after cessation of treatment (Papp et al. 2003). It should also be noted that the effect of evening agomelatine treatment can be related to the agonistic action on melatonergic receptors, which in consequence leads to normalization of the general impairment of circadian rhythms previously observed in animals undergoing the chronic mild stress procedure. This possibility is strongly supported by the finding that a melatonergic antagonist given acutely to stressed animals successfully treated with agomelatine, fully reversed the effectiveness of the antidepressant. These data indicate that the mechanism of therapeutic action of evening administration of agomelatine differs from that of traditional antidepressants, and provides further evidence that the antidepressant-like effect of agomelatine depends in part of its interaction with melatonergic receptors. On the other hand, opposed to melatonin, agomelatine remains effective in this model irrespective of the time of day of its administration indicating that its antidepressant activity is not only due to its action at melatonergic receptors. An additional support to this non-melatonergic-mediated effect is the observation that an MT_1/MT_2 receptor antagonist does not suppress the antidepressant effect of agomelatine given in the morning. These data thus support the idea that the agomelatine's antagonistic activity at 5-HT_{2C} receptors also contributes to the antidepressant action of this drug. In fact, although their respective – possibly synergistic – contributions remains to be further elucidated, both melatonergic agonistic and 5-HT_{2C} antagonistic actions seem to underly the antidepressant activity of agomelatine.

Activity in predictive models of an anxiolytic effect. Agomelatine, in addition to its antidepressant activity, exerts a clear-cut anxiolytic action in various animal models, and mechanistic studies in rats provided compelling evidence for a role of 5-HT_{2C} receptor blockade in this anxiolytic action. Indeed, agomelatine's anxiolytic properties bear a striking resemblance to those of selective 5-HT_{2C} receptor antagonists. An anxiolytic effect of acute administration of agomelatine (10–40 mg/kg i.p.), associated with its antagonist action at 5-HT_{2C} receptors, has been shown in rats in the elevated plus maze, in the social interaction test and in two conflict tests (Geller Seifert, Vogel). This anxiolytic activity is not additive with that of the selective 5-HT_{2C} receptor antagonist SB243,213. On the other hand, the melatonergic receptor antagonist S-22153 did not counteract the anxiolytic effect of agomelatine (Millan et al. 2005; Papp et al. 2006). Altogether, these data strongly support, though indirectly, a major role of the antagonism at 5-HT_{2C} receptors for agomelatine's anxiolytic activity.

Clinical studies with agomelatine

Proof of antidepressant efficacy. A dose-ranging multinational study, double blind and randomised (Loo et al. 2002), examined the antidepressant efficacy of three different doses of agomelatine (1, 5 or 25 mg) in more than 700 MDD (major depression disorder) patients; agomelatine was administered for 8 weeks. The antidepressant efficacy of 25 mg agomelatine was demonstrated in both the mean efficacy criterion (decrease in the HAMD-17 total score, Δ vs. placebo: 2.57, $P=0.034$) and in secondary outcome measures (MADRS, CGI-S, number of responders). The assay sensitivity in this study was established by the demonstration of the efficacy of 20 mg paroxetine vs. placebo on the primary outcome variable.

While this study provided evidence for the 25-mg dose to be the lowest effective dose, it has been subsequently demonstrated that a dose increase to 50 mg/day could improve the efficacy in certain patients. To date, the antidepressant efficacy of agomelatine 25 mg has been confirmed in two additional multinational trials of identical design, double blind, randomised, parallel groups with a 6-week placebo-controlled treatment period (Kennedy and Emsley 2006; Olié and Kasper 2007). A total of 238 and 212 patients were randomised in these trials, respectively. After an initial 2-week treatment with agomelatine 25 mg, patients with insufficient response to treatment received agomelatine 50 mg respecting blinded conditions for both investigators and patients. In these two flexible dose design studies, agomelatine showed an antidepressant efficacy significantly superior to placebo for the mean HAMD score in the total population ($\Delta=3.44$, $P<0.001$ (Figure 1), and $\Delta=2.30$, $P=0.026$, respectively) as well as in the dose-adjusted population ($\Delta=3.71$, $P=0.018$ and $\Delta=3.13$, $P=0.045$, respectively). Secondary outcome measures showed improvement with agomelatine in CGI severity scales, number of responders, as well as in the survival analysis of time to first response.

All these studies demonstrated that agomelatine, at 25- and 50-mg once daily doses, is effective in the treatment of MDD with consistent efficacy shown by improvements in both primary and secondary measures.

These three studies showed clinically relevant effect in terms of responder rate (14.8–19.0% versus

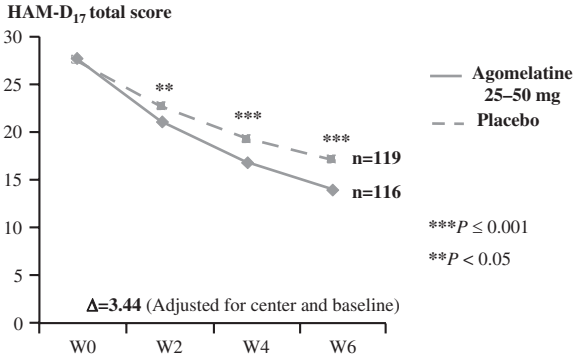

Figure 1. Agomelatine improves depressive symptoms. A clearly significant difference from placebo was shown at the end of treatment in both short-term studies, with a significant improvement seen as early as from W2. The treatment size effect was clinically relevant in both studies, with a 3.44-point difference from placebo in the final rates of the HAM-D17 scale. ** $P<0.05$; *** $P<0.001$. Reprinted from Olié and Kasper (2007).

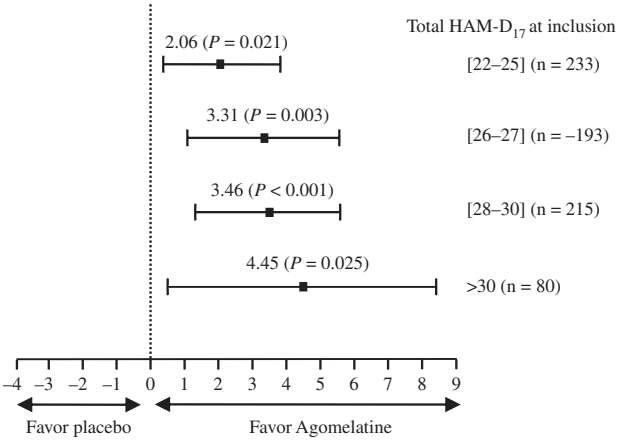

Figure 2. In the pool of pivotal placebo-controlled studies, using non-overlapping cut-offs of the HAM-D17 scale at inclusion, the meta-analytic estimation of the difference with placebo (6–8 weeks, LOCF) demonstrated that the treatment effect of agomelatine increases with the severity of the depression. Even in the most severe depression with a HAM-D above 30, agomelatine provides a highly significant improvement for depressed patients. Reprinted from Montgomery and Kasper (2007).

placebo), and are quantitatively comparable with what is usually observed with SSRIs (Thase 2002).

Many psychiatrists consider clearly demonstrated efficacy in severely depressed patients as the key criterion in establishing the effectiveness of any antidepressant (Montgomery and Lecrubier 1999). Severe depression is recognized as being associated with greater suffering and mortality, as well as with greater disability when compared to moderate depression (Kasper 1993; Murray and Lopez 1997). In all three placebo-controlled studies, agomelatine showed efficacy in severe depression, irrespective of the severity criteria used (baseline HAMD $\geq$25 or HAMD $\geq$25 and CGI $\geq$5, baseline HAMD $\geq$30). Furthermore, the difference in the mean HAMD scores between agomelatine and placebo for the severe subpopulation exceeded the difference observed in the overall population, which reinforces the demonstration of the clinically relevant effect of agomelatine (den Boer et al. 2006; Montgomery 2006a,b). A meta-analysis of the severe depressed subpopulations in these studies, using increasing cut offs of the HAMD scale at inclusion, showed that the treatment effect of agomelatine increased with the severity of depression (Figure 2) (Montgomery and Kasper 2007). The consistent efficacy of agomelatine whatever the severity of depression is highly satisfying as it means that all patients should profit from this antidepressant treatment.

Two double-blind randomised studies versus venlafaxine provided additional supportive information for clinically relevant efficacy of agomelatine: in one study, both antidepressants were given as a flexible dose design (agomelatine 25–50 mg and venlafaxine 75–150 mg for 6 weeks). A total of 165 and 167 patients were randomised to agomelatine and venlafaxine, respectively. The head-to-head comparison for efficacy showed a comparable response between both antidepressants over the 6-week treatment period, for both the HAM-D total score and the responder rate (final HAMD score: 9.0$\pm$5.4 and 8.9$\pm$5.2, respectively) (Lemoine et al. 2007). The second study compared the fixed doses of agomelatine 50 mg and venlafaxine 150 mg over 12 weeks. A total of 137 and 140 patients were randomised to agomelatine and venlafaxine, respectively. Agomelatine 50 mg and venlafaxine 150 mg showed comparable end-of-treatment scores and similar rates of response (82.5 and 79.9%, respectively). Additionally, similar rates of remission at week 12 were achieved (73% vs 66.9%) (Kennedy et al. 2008).

Although the absence of a placebo arm did not allow assessment of assay sensitivity in these studies, the early drop-out rates observed on venlafaxine in both studies and the efficacy results observed on venlafaxine were in line with those reported previously (Mehtonen et al. 2000; Tzanakaki et al. 2000; Stahl et al. 2002).

Regulation of disturbed sleep-wake rhythms in depressed patients. Sleep disturbances are among the most prevalent symptoms and physical signs of depression (Kasper and Wehr 1992). About 70% of the patients with major depression report difficulties in initiating and maintaining sleep as well as early morning awakening and remaining awake (Ohayon and Shapiro 2000). Disturbed sleep has been included as one of the diagnostic criteria in DSM-IV for major depressive episodes. Thus, the development of a safe and effective antidepressant that can improve sleep even before improving mood is highly desirable. The majority of antidepressants have unwanted effects on sleep by causing insomnia,

daytime sleepiness or sedation. As circadian processes participate in the consolidation of sleep, attention to circadian rhythmicity may be beneficial in the treatment of depression.

The melatonergic agonist and 5-HT_{2C} antagonist profile of agomelatine is well adapted to the amelioration of sleep patterns. Melatonin fulfils a pivotal role in the rhythm control of sleep (Borjigin et al. 1999; Cajochen et al. 2003) and can directly induce sleep when the internal drive is weak. However, no antidepressant efficacy has been shown for the use of melatonin in depressed patients. 5-HT_{2C} receptor blockade favours sleep most likely by increasing the frequency of slow wave sleep, as observed in healthy subjects, as well as in major depressed patients (Wilson and Argyropoulos 2005).

Correspondingly, clinical studies have shown that agomelatine, in contrast to SSRIs, does not compromise sleep quality. Agomelatine had a significant positive impact on sleep in patients with MDD, and this effect was already seen very early after administration of the drug. In one study (Quera-Salva et al. 2005), 15 depressed patients were administered agomelatine 25 mg in the evening for 42 days in open conditions and polysomnography was performed regularly throughout the study. In these patients, agomelatine increased the sleep efficiency, the total sleep time (by 4%), and the duration of slow wave sleep (by 16 min). Patients subjectively perceived an improvement in sleep quality as early as 7 days after initiation of the treatment together with a significant decrease in HAMD scores. The objective, quantitative, results showed an increase in sleep efficiency, a decrease in intra-sleep awakenings, an increase in absolute and relative to the total sleep time duration of slow wave sleep and no modification of the total amount of REM sleep, accompanied by a progressive improvement of the delta-sleep ratio. The study showed a regulation of the sleep architecture by normalizing the distribution of the slow wave sleep throughout the night.

The beneficial effects on sleep in depressed patients were more pronounced with agomelatine than with venlafaxine as demonstrated in a randomised double blind trial comparing agomelatine (25–50 mg) with venlafaxine (75–150 mg) (Lemoine et al. 2007). Leeds evaluation questionnaire (LSEQ) and Visual analogue scale (VAS) were used after 6 weeks of treatment to assess the subjective impact of the drugs on sleep patterns and on daytime conditions. A total of 332 patients were included in the study (165 and 167 on agomelatine and venlafaxine, respectively). Agomelatine and venlafaxine had similar antidepressant efficacy after short-term treatment. Compared to venlafaxine, agomelatine produced a significantly better improvement on LSEQ "getting to sleep" and on "quality of sleep" items as early as at the end of the first week of treatment. This effect lasted till the end of treatment. Significant differences in "daytime sleepiness" and "feeling good" LSEQ items were also noted after a few days of treatment only, indicating earlier subjective daytime improvement with agomelatine compared to venlafaxine.

Collectively, agomelatine has a proven regulatory (normalizing) effect on sleep–wake rhythms, with improved sleep maintenance in depressed patients (Kupfer 2006; Lam 2006). Throughout the night, it regulates sleep architecture by resynchronizing slow wave sleep and by increasing sleep efficiency. Agomelatine rapidly relieves sleep complaints of depressed patients without causing any residual daytime impairment.

Tolerability. While people derive therapeutic benefits from antidepressant medications, they may appear rather limited with quite profound side effects for some people. Therefore, there is still an unmet medical need for an antidepressant of adequate efficacy, with high tolerability and lack of discontinuation effects.

So far, the tolerability and safety of agomelatine have been evaluated in more than 4000 patients. The tolerability profile of agomelatine is broadly favourable in both short- and long-term studies. While the overall efficacy of agomelatine in the treatment of depression is comparable to that of available antidepressants, the adverse-event profile is, qualitatively. generally much better than that of current standard treatments, including a lack of weight gain or serotonin syndrome, a low risk of sexual dysfunction, a low incidence of gastro-intestinal adverse events as well as the absence of discontinuation symptoms upon withdrawal. The most common emergent adverse events with agomelatine are nausea, dizziness, dry mouth and diarrhoea, with an incidence close to placebo, the only adverse effect exceeding those seen on placebo relates to dizziness (excluding vertigo). These emergent adverse events tend to occur early in treatment and are transient in nature. In all clinical trials with agomelatine the rate of adverse events leading to discontinuation was close to that of the placebo group. Furthermore, the treatment emergent a adverse events profile is always benign.

Most of the currently available antidepressants produce sexual dysfunction, a side effect that often interferes with recovery from a depressive episode. With the use of antidepressants, all phases of sexual activity are affected. In contrast, with agomelatine, no deleterious effect on sexual function has been observed throughout its entire development. Sexual emergent adverse events were always low and similar

for patients treated with agomelatine or placebo. Indeed, sex scales applied during the short-term efficacy studies even showed that agomelatine induced less sexual dysfunction than placebo (3.0 vs. 8.6%, $P=0.014$). Furthermore, a specific study showed that agomelatine 50 mg administered for 12 weeks to sexually active depressed patients had an antidepressant efficacy comparable to that of venlafaxine 150 mg but offered a superior sexual functioning profile in remitters using the sexual function scale SEXFX to assess pre-orgasm or orgasm scores (Kennedy et al. 2008).

The side effect that greatly influences the acceptability of a drug by a patient is the number and severity of symptoms that are intensified after discontinuation of the drug. Therefore, any antidepressant without discontinuation symptoms will be highly beneficial for patients.

Withdrawal syndrome following abrupt discontinuation of a treatment with agomelatine was evaluated in a specific phase III study (Montgomery et al. 2004). MDD patients were treated for 12 weeks, under double-blind conditions, with agomelatine 25 mg or paroxetine 20 mg. Only those who had remitted at week 8 and showed sustained remission at week 12 were randomised to placebo or the initial active treatment for an additional 2-week double-blind period. Discontinuation symptoms were assessed at the end of the first (primary endpoint) and second week of discontinuation using the Discontinuation Emergent Signs and Symptoms check-list (DESS) (Rosenbaum et al. 1998). This study showed that abrupt discontinuation of agomelatine does not cause withdrawal symptoms. By contrast, discontinuation of paroxetine induced clear-cut emergent symptoms when compared to the patients continuing drug administration (Montgomery et al. 2004).

The absence of discontinuation symptoms associated with agomelatine use is a characteristic that is not shared by any other available antidepressants and, consequently, makes agomelatine a preferable choice for patients who might be concerned by poor compliance.

Conclusion

A very exciting concept for the treatment of depression is the novel antidepressant agomelatine, a compound that exhibits a strong agonistic activity at melatonergic receptors and antagonistic property at 5-HT_{2C} receptors. The drug has been shown to effectively treat patients with major depressive disorder, with a particularly robust efficacy in more severely depressed subgroups, those for whom the clinician has indeed particular concerns. Agomelatine also addresses one of the core symptoms in depression by restoring disturbed sleep in depressed patients. Agomelatine may also improve sexual dysfunction. Agomelatine is well tolerated with a low adverse event burden, which is reassuring for a drug with a novel mechanism of action. The lack of demonstrable effects when discontinued is an equally important attribute. The good safety profile of agomelatine, due to its unique receptor profile, predicts a higher patient acceptability and a better compliance.

To summarize, available data on agomelatine make this innovative compound a very promising antidepressant for the near future.

Disclosures

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