Agomelatine in the treatment of mood and anxiety disorders

The antidepressant agomelatine combines a novel mechanism of action with certain advantages over currently available antidepressants, in terms of restoration of sleep, absence of treatment-emergent sexual dysfunction, and fewer discontinuation symptoms. What is its potential role in clinical practice?

Depressive symptoms and disorders are common in community settings and in primary and secondary medical care. They cause much distress, are associated with increased morbidity and mortality, reduced quality of life, and have a considerable associated societal burden, but many of those who might benefit from pharmacological or psychological treatment are not recognized or treated. By contrast, some patients receive unnecessary or inappropriate interventions. Evidence-based guidelines for the pharmacological management of patients with unipolar depressive disorder recommend initial treatment with a selective serotonin-reuptake inhibitor (SSRI) in patients with persistent symptoms of at least moderate intensity, or a serotonin-noradrenaline-reuptake inhibitor (SNRI) in patients with more severe depressive symptoms (Anderson et al, 2008).

However, response rates to initial antidepressant treatment can be disappointing and it is still not possible to predict reliably which patients will respond well and which will make only a limited response to treatment. Furthermore, many patients fear or experience unwanted and distressing adverse effects, limiting the effectiveness of pharmacological treatments in clinical practice. Despite the availability of SSRIs, SNRIs and other antidepressants, some of which have tolerability and safety advantages over older drugs such as the tricyclics, there is much room for improvement in terms of effectiveness and acceptability in clinical practice (Baldwin and Thompson, 2003). Agomelatine has been approved for treatment of major depressive episodes in adults: it has a chemical structure remarkably similar to that of endogenous melatonin (*Figure 1*), and a novel mechanism of action which may confer some advantages over other antidepressants in particular groups of depressed patients.

What are the pharmacodynamic effects of agomelatine?

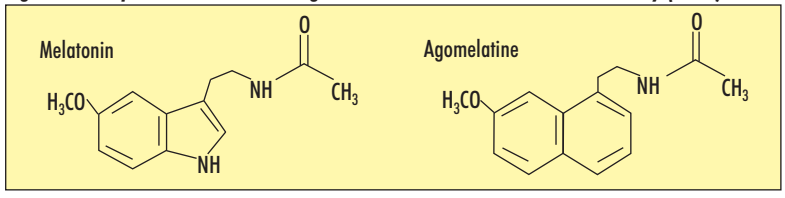
In pre-clinical studies, agomelatine acts as a full agonist at melatonin MT_1 and MT_2 receptors, and inhibits the activity of the suprachiasmatic nucleus to the same degree as melatonin. It also has affinity for the serotonin 5-HT_{2C}, 5-HT_{2B} and 5-HT_{1A} receptors, but unlike many other antidepressants, chronic administration has no effect on number of 5-HT_{1A}, β-adrenergic, 5-HT_{2A} or 5-HT_{2C} receptors. Chronic dosing produces a dose-dependent increase in dopamine and noradrenaline levels in the frontal cortex, and enhances cell proliferation and neurogenesis. It reduces depolarization-evoked release of glutamate, but has no effect on the release of gamma-amino butyric acid, indicating a dampening of excitatory neurotransmission, and a possible role in the treatment of anxiety disorders.

In humans, the 5-HT_{2C} antagonist effects of agomelatine are supported by an increase in slow wave sleep (mediated by 5-HT_2 receptors), the absence of treatment-emergent sexual dysfunction (in contrast to the effects of SSRIs which are probably mediated by the 5-HT_2 receptor) and the decrease in anxiety symptoms in patients with major depression or generalized anxiety disorder. The effects of agomelatine administration on MT_1 and MT_2 receptors are supported by the reduction of body temperature (Leproult et al, 2005), increased total sleep time and decreased awakenings after sleep onset (Quera-Salva et al, 2007), and by the advance in time of the minimum heart rate, as all these effects are also seen with melatonin.

Is this a new combined mechanism of antidepressant action?

Agomelatine has been described as exhibiting 'noradrenergic and dopaminergic disinhibition plus melatonergic agonism' (Stahl, 2007). In essence, noradrenergic and dopaminergic release is inhibited by the tonic release of serotonin onto 5-HT_{2C} receptors. By blocking this tonic

Figure 1. Comparative structure of agomelatine and melatonin. From Kennedy (2007).



Dr David S Baldwin *is Reader in Psychiatry in the Clinical Neuroscience Division, School of Medicine, University of Southampton, Southampton SO14 0YG, and Honorary Consultant Psychiatrist in the Mood and Anxiety Disorders Service, Hampshire Partnership Trust, Southampton and* **Dr Antonio T Lopes** *is Honorary Lecturer in Psychiatry in the Clinical Neuroscience Division, School of Medicine, University of Southampton, and Specialist Trainee in Psychiatry in the Mood and Anxiety Disorders Service, Hampshire Partnership Trust, Southampton*

Correspondence to: Dr DS Baldwin

inhibition, agomelatine causes 'disinhibition' and thus enhances noradrenergic and dopaminergic neurotransmission, as do some other psychotropic drugs (e.g. fluoxetine, mirtazapine, trazodone and most second generation antipsychotics). However, the melatonergic properties of agomelatine, although unlikely to be primarily responsible for its antidepressant effects, may bring further benefits in reducing the intensity of some troublesome depressive symptoms, such as sleep disturbance.

What are the pharmacokinetic properties of agomelatine?

Agomelatine is absorbed rapidly after oral administration, t-max being reached 1–2 hours after a broad range (5–1200 mg) of single doses, with much inter-individual variation in plasma levels. It is subject to ~95% plasma protein binding across the 5–2000 ng/ml range, with no alteration of levels of other plasma protein-bound drugs. It has a short plasma half-life (1–2 hours) and non-linear kinetics at higher doses as a result of saturation of the hepatic first-pass effect. Plasma clearance is 1001–1186 ml/min after intravenous administration, up to 80% being eliminated in urine as various metabolites. The elimination half-life is unaffected by dosage or longer administration, with no evidence of drug accumulation or auto-induction. Metabolism by cytochrome CYP 450 1A2 and CYP 450 2C9 isoenzymes involve initial hydroxylation (1A2) and demethylation (2C9), followed by glucuronide conjugation and sulphonation.

Is particular caution needed in specific patient groups?

In elderly subjects, the C-max is reduced if agomelatine is taken with food. Hepatic impairment causes a substantial increase (71–140 times) in the area under the curve but this is increased only slightly in patients with renal impairment (those with a creatinine clearance <30 ml/min). Cigarette smoking reduces exposure by a factor of 3.6, as a result of induction of the cytochrome CYP 450 1A2 isoenzyme, so levels may rise markedly if someone stops smoking while taking agomelatine. The C-max is increased by the SSRI fluvoxamine (a potent 1A2 and 2C9 inhibitor), but unaffected by either the SSRI paroxetine (a moderate 1A2 inhibitor) or fluconazole (a potent 2C9 inhibitor). There is no clinically relevant interaction with lithium, and neither alcohol nor alprazolam alter its pharmacokinetic properties.

What do animal models indicate about its potential efficacy in humans?

Antidepressant-like effects include reversal of behavioural changes in the forced swim and learned helplessness tests, antagonism of the decrease in conditioned behaviour induced by light, antagonism of the increase in corticosterone in the olfactory bulbectomized rat, and reversal of decreased sucrose consumption in the chronic mild stress model (Le Strat and Gorwood, 2008). Anxiolytic-like effects include increased time spent in the open (exploratory) arms of the elevated-plus maze, antagonism of behavioural changes in the social defeat model, and increased responses in the ultrasonic vocalisation test (Millan et al, 2005). These putative antidepressant and anxiolytic effects of agomelatine in animal models are confirmed by its efficacy in reducing depressive and anxiety symptoms in randomized placebo-controlled trials in major depressive disorder and generalized anxiety disorder.

Agomelatine differs from other antidepressants in exerting pharmacological effects which lead to resynchronization in several animal models of circadian rhythm disturbance. For example, in a dose-dependent manner, it reduces the delay in onset of nocturnal activity of rats returned to normal light/dark cycles after being kept in prolonged darkness (Armstrong et al, 1993), and improves responsiveness of the circadian clock to dark and light stimuli in older hamsters (Van Reeth et al, 2001).

So how effective is agomelatine as an antidepressant?

The reduction in depressive symptom severity on primary outcome measures in randomized placebo-controlled and comparator-controlled trials of the acute treatment of patients with major depressive episodes with agomelatine is broadly similar to that seen with the SSRI paroxetine and the SNRI venlafaxine. Within the clinical trial database of six randomized placebo-controlled investigations, a daily dose of 50 mg appears to have advantages over the 25 mg dose. When compared to venlafaxine in two double-blind trials, the overall response rates with agomelatine were similar – 82.5% *vs* 79.9% (Lemoine et al, 2007) and 73% *vs* 66.9% (Kennedy et al, 2008) – which is encouraging, as the SNRI is often regarded as having superior efficacy to most antidepressants. Preliminary pooled analysis of two studies, in which change in depressive symptom severity was a secondary outcome measure, suggests that agomelatine (25–50 mg/day) may have superior efficacy to sertraline (50–100 mg/day) and venlafaxine (75–150 mg/day) (Kasper and Lemoine, 2008). Furthermore, in the pooled clinical trial database, there was a consistent trend for a larger effect to be seen with agomelatine in the more severely ill patients (Montgomery and Kasper, 2007).

For a drug to be licensed as an antidepressant there has to be clear evidence that it is also effective over longer-term treatment, and able to prevent early relapse of depressive symptoms and the later recurrence of depressive episodes. The long-term efficacy of agomelatine in prevention of relapse in patients with recurrent unipolar disorder has been investigated in two placebo-controlled studies: in the first, agomelatine only had superior efficacy in the more severely ill patients, but in the second, significantly greater efficacy was seen across the patient sample, 21.7% relapsing while continuing with agomelatine, compared to 46.6% relapsing having switched to placebo (Goodwin et al, 2007).

Might it have particular advantages in certain patient groups?

Disturbed sleep is a common and often distressing symptom in depressed patients, which tends to persist despite otherwise successful pharmacological or psychological treatment (Mayers and Baldwin, 2006). The 5-HT_{2C} antagonist and MT_1/MT_2 agonist properties of agomelatine should have beneficial effects on sleep during treatment of depressed patients, and this appears to be the case in both open-label and double-blind randomized comparator controlled studies. Polysomnographic (sleep electroencephalogram) studies show that agomelatine treatment appears to normalize the distribution of slow wave sleep while preserving rapid eye movement sleep, which is suppressed by most antidepressants (Lopes et al, 2007; Quera-Salva et al, 2007); and subjective assessments indicate it has advantages over venlafaxine in improving quality of sleep and in reducing sleep awakenings (Lemoine et al, 2007).

Anxiety symptoms are usually reported by patients experiencing major depressive episodes, and like sleep disturbance, can be hard to treat. SSRI and SNRI antidepressants can worsen anxiety in the first week or so of treatment, and this may cause some patients to stop antidepressants too soon for them to have a beneficial effect. The anxiolytic-like effects of agomelatine in animal models are supported by the findings of randomized controlled trials, in which it relieves anxiety symptoms in patients with major depression (Lôo et al, 2002), and reduces the severity of psychological and somatic symptoms in patients with generalized anxiety disorder (Stein et al, 2008).

How well tolerated is agomelatine?

The tolerability profile in both acute and longer term treatment seems broadly favourable. The most frequently reported adverse events with agomelatine (headache, nausea and dizziness) are not significantly more common than with placebo, nor is the pattern of change in weight during double-blind treatment (Kennedy et al, 2008). Agomelatine may have certain advantages over other antidepressants, having a lower incidence of treatment-emergent sexual dysfunction and significantly fewer troublesome discontinuation symptoms on stopping treatment.

Most of the currently available antidepressants have untoward effects on sexual functioning in a large minority of patients (Baldwin, 2004). Agomelatine appears to exert no adverse effect on sexual behaviour, and is associated with significantly less treatment-emergent sexual dysfunction than is seen either with venlafaxine in male and female depressed patients (Kennedy et al, 2008) (*Figure 2*) or with paroxetine in healthy male volunteers (Montejo et al, 2007). This relative advantage probably arises from its 5-HT_{2C} antagonist actions, as compounds with this property are sometimes used to reverse sexual dysfunction associated with SSRI and other antidepressants, although agonism of melatonin receptors facilitates sexual activity in some animal models (Drago and Busa, 2000).

Discontinuation symptoms on stopping treatment are common with many classes of antidepressant drug, including SSRIs and SNRIs. Although symptoms are typically mild and transient, many patients report severe and distressing symptoms, despite gradual discontinuation through tapering the prescribed dose of medication. It is hard to predict which patients will be most affected, and the role of the nature of the diagnosis, longer duration of treatment, higher dosage, and the mechanism for withdrawal is less clear-cut than previously thought (Baldwin et al, 2007). No discontinuation syndrome has been observed with agomelatine, and there are no significant differences in discontinuation symptoms and signs between patients who stop agomelatine and those who continue it, in marked contrast to paroxetine (Montgomery et al, 2004).

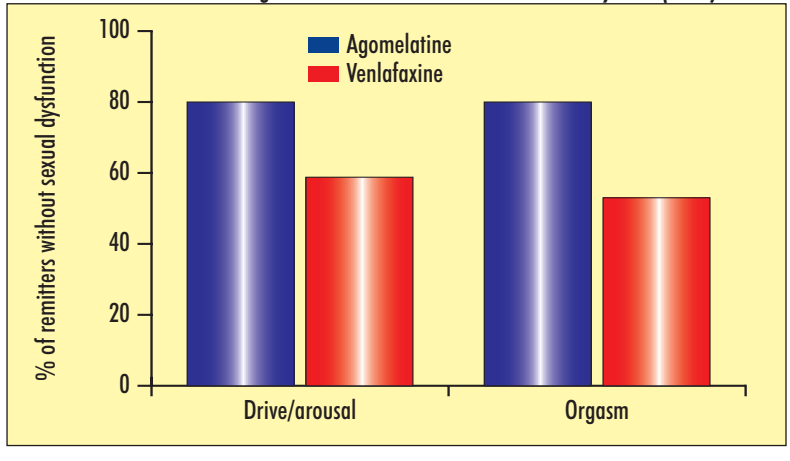
Are there any particular concerns about agomelatine?

When giving a positive opinion for clinical use of agomelatine in November 2008, the European Medicines Agency noted that abnormalities of some liver function tests (elevation of transaminase enzymes beyond three times the upper limit of normal) were fairly common, and that instances of greater elevation had occurred, leading to the requirement for monitoring of liver function tests during treatment at all doses. Hepatic impairment alters the pharmacokinetic properties of agomelatine, and for these reasons it would be wise to avoid its use in patients with established liver disease, and in those considered to be at greater risk of developing it, while waiting for more data to become available from post-marketing pharmacovigilance studies. However, many other antidepressants have been associated with transient asymptomatic and reversible alterations of the activity of hepatic enzymes, and a few with more severe hepatic reactions.

What is its likely role in clinical practice?

Most local formulary and district prescribing committees currently recommend an SSRI for initial treatment in patients with moderate or more severe depressive symp-

Figure 2. Proportion of remitted patients with deterioration in sexual functioning during double-blind treatment with agomelatine or venlafaxine. From Kennedy et al (2008).



toms, on the basis of proven efficacy, reasonable tolerability, safety and established cost-effectiveness. Agomelatine has comparable efficacy to standard SSRIs and appears to have certain tolerability advantages, with relatively less treatment-emergent sexual dysfunction, greater effects in resolving sleep disturbance and fewer discontinuation symptoms. Many doctors and patients will be keen to try a new antidepressant with a novel mechanism of action, when established antidepressants have been found wanting, although this may not be the optimal patient group in which to give a new drug a fair trial of assessment.

The current need to monitor liver function tests during agomelatine treatment is a significant hassle compared to the relative ease of prescribing SSRI antidepressants, and it is hoped that the findings of pharmacovigilance studies will allow this stipulation to be only short-lived. For the moment, it seems reasonable to reserve agomelatine for second-line or third-line treatment, in patients who are concerned to preserve sexual function, or to improve sleep, or to avoid discontinuation symptoms when antidepressant treatment is no longer required (McAllister-Williams et al, 2010). **BJHM**

Conflict of interest: Dr D Baldwin has attended an Advisory Board organised by Servier, the manufacturers of agomelatine, and has received personal honoraria for this and for speaking at a satellite symposium hosted by Servier at the 2008 Summer Meeting of the British Association for Psychopharmacology. Dr A Lopes has no interests to declare. The views expressed in this paper are solely those of the authors and should not be construed as representing those of any other individual, company or organization.

Anderson IM, Ferrier IN, Baldwin RC et al (2008) Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2000 British Association for Psychopharmacology guidelines. *J Psychopharmacol* **22**(4): 343–96

Armstrong SM, McNulty OM, Guardiola-Lemaitre B, Redman JR (1993) Successful use of S20098 and melatonin in an animal model of delayed sleep-phase syndrome (DSPS). *Pharmacol Biochem Behav* **46:** 45–9

Baldwin DS, Thompson CV (2003) The future of antidepressant therapy. *World Psychiatry* **2:** 3–8

Baldwin DS (2004) Sexual dysfunction associated with antidepressant drugs. *Exp Opin Drug Safety* **3**(5): 457–70

Baldwin DS, Montgomery SA, Nil R, Lader M (2007) Discontinuation symptoms in depression and anxiety disorders. *Int J Neuropsychopharmacol* **10**(1): 73–84.

Drago F, Busa L (2000) Acute low doses of melatonin restore full sexual activity in impotent male rats. *Brain Res* **878**(1-2): 98–104

Goodwin G, Rouillon F, Emsley R (2007) Long-term efficacy of agomelatine, a novel antidepressant, in the prevention of relapse in out-patients with major depressive disorder. *Eur Neuropsychopharmacol* **17**(suppl 4): S361–362

Kasper S, Lemoine P (2008) Comparative efficacy of the antidepressants agomelatine, venlafaxine and sertraline. *Eur Neuropsychopharmacol* **18** (suppl. 4): S331–S332

Kennedy S (2007) Agomelatine: an antidepressant with a novel mechanism of action. *Future Neurol* **2**(2): 145–51

Kennedy SH, Rivzi S, Fulton K, Rasmussen J (2008) A double-blind comparison of sexual functioning, antidepressant efficacy, and tolerability between agomelatine and venlafaxine XR. *J Clin Psychopharmacol* **28**(3): 329–33

Lemoine P, Guilleminault C, Alvarez E (2007) Improvement in subjective sleep in major depressive disorder with a novel antidepressant, agomelatine: randomized, double-blind comparison with venlafaxine. *J Clin Psychiatry* **68**(11): 1723–32

Leproult R, Van Onderbergen A, L'hermite-Baleriaux M, Van Cauter E, Copinschi G (2005) Phase shifts of 24-h rhythms of hormonal release and body temperature following early evening administration of the melatonin agonist agomelatine in healthy older men. *Clin Endocrinol (Oxf)* **63**(3): 298–304

Le Strat Y, Gorwood P (2008) Agomelatine, an innovative pharmacological response to unmet needs. *J Psychopharmacol* **22**(suppl 7): S4–S8

Lôo H, Hale A, D'haenen H (2002) Determination of the dose of agomelatine, a melatoninergic agonist and selective 5-HT2C antagonist, in the treatment of major depressive disorder: a placebo-controlled dose range study. *Int Clin Psychopharmacol* **17**(5): 239–47

Lopes MC, Quera-Salva MA, Guilleminault C (2007) Non-REM sleep instability in patients with major depressive disorder: subjective improvement and improvement of non-REM sleep instability with treatment (agomelatine). *Sleep Medicine* **9**: 33–41

McAllister-Williams RH, Baldwin DS, Haddad PM, Bazire S (2010) The use of antidepressants in clinical practice: focus on agomelatine. *Hum Psychopharmacol* (in press)

Mayers AG, Baldwin DS (2006) Antidepressants and their effect on sleep. *Hum Psychopharmacol* **20**(8): 533–59

Millan MJ, Brocco M, Gobert A, Dekeyne A (2005) Anxiolytic properties of agomelatine, an antidepressant with melatoninergic and serotonergic properties: role of 5-HT2C receptor blockade. *Psychopharmacol (Berl)* **177**(4): 448–58

Montejo A, Prieto N, Terleira A et al (2007) Better sexual acceptability of agomelatine compared to paroxetine in healthy male volunteers using the PRSexDQ Scale. *Eur Neuropsychopharmacol* **17**(suppl 4): S349

Montgomery SA, Kennedy SH, Burrows GD, Lejoyeux M, Hindmarch I (2004) Absence of discontinuation symptoms with agomelatine and occurrence of discontinuation symptoms with paroxetine: a randomized, double-blind, placebo-controlled discontinuation study. *Int Clin Psychopharmacol* **19**(5): 271–80

Montgomery SA, Kasper S (2007) Severe depression and antidepressants: focus on a pooled analysis of placebo-controlled studies on agomelatine. *Int Clin Psychopharmacol* **22**(5): 283–91

Quera-Salva M-A, Vanier B, Laredo J et al (2007) Major depressive disorder, sleep EEG and agomelatine: an open-label study. *Int J Neuropsychopharmacol* **10**(5): 691–6

Stahl SM (2007) Novel mechanism of antidepressant action: norepinephrine and dopamine disinhibition (NDDI) plus melatonergic agonism. *Int J Neuropsychopharmacol* **10:** 575–8

Stein DJ, Ahokas AA, de Bodinat C (2008) Efficacy of agomelatine in generalized anxiety disorder. A randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol* **28**(5): 561–6

Van Reeth O, Weibel L, Olivares E, Maccari S, Mocaer E, Turk FW (2001) Melatonin or a melatonin agonist corrects age-related changes in circadian response to environmental stimulus. *Am J Physiol Regul Integr Comp Physiol* **280**(5): R1582–91

KEY POINTS

- Agomelatine is a new antidepressant with a novel mechanism of action. It acts as an agonist melatonin MT_1 and MT_2 receptors, which are involved in regulation of circadian rhythms, and as an antagonist at the $5HT_{2C}$ serotonin receptor.
- In large randomized, controlled clinical trials, agomelatine appears to be an efficacious antidepressant, comparable to standard selective serotonin-reuptake inhibitor and serotonin-noradrenaline reuptake inhibitor drugs, and also reduces anxiety symptoms in patients with major depression or generalized anxiety disorder.
- When compared to other antidepressants, it appears to have an impressive tolerability profile, with typically only mild and transient side effects, and minimal impact on weight and sexual function, and it produces significantly fewer discontinuation symptoms on abruptly stopping treatment than selective serotonin-reuptake inhibitor antidepressants.
- Like many other antidepressants, agomelatine is associated with some mild effects on hepatic transaminase enzymes, and its use should be avoided in depressed patients with known hepatic problems.