Agomelatine: a new approach to depression

In a Servier-sponsored satellite meeting at the Latest Advances in Psychiatry Symposium in London in March, Professor Bill Deakin, Professor of Psychiatry and Director of the Neuroscience and Psychiatry Unit at the University of Manchester, reviewed a recent addition to the antidepressant armamentarium – agomelatine – a drug that that shows a unique pharmacological profile. Medical writer, Mark Greener, reports.

The monoamine hypothesis, which dominated psychopharmacological thinking about depression for 40 years, inspired several classes of relatively effective antidepressants. Nevertheless, many patients exhibit inadequate symptomatic improvement, develop dose-limiting adverse events, or show poor adherence with conventional antidepressants. Therefore, there is clearly a need for innovative approaches to the management of affective disorders.

Patients with major depression generally show pervasive, profound and persistent disturbances in several circadian rhythms including sleep-wake cycles and cortisol secretion. Uniquely among currently available antidepressants, agomelatine directly modulates the activity of the suprachiasmatic nucleus, the area of the hypothalamus responsible for synchronising circadian rhythms. Specifically, agomelatine is an agonist of melatonergic MT_1 and MT_2 receptors (see Figure 1). As a result, agomelatine has the potential to normalise disturbed circadian rhythms in depressed patients.

Agomelatine also antagonises 5-HT_{2C} receptors in the frontal cortex – an area involved in mood, anxiety and cognition – which contributes to its antidepressant efficacy. The 'downstream' effects arising from the cortical 5-HT_{2C} blockade include increased release of dopamine and noradrenaline in the frontal cortex.

Unlike most current antidepressants, agomelatine does not influence either extracellular serotonin levels or monoamine uptake. Furthermore, agomelatine is relatively specific, with negligible affinity for histaminergic, adrenergic and cholinergic receptors.

Effective compared with conventional antidepressants

Agomelatine's psychopharmacological profile appears to translate into improved efficacy compared with some conventional antidepressants. A study presented at the 2008 European College of Neuropsychopharmacology (ECNP) meeting compared agomelatine (25mg) and sertraline (50mg). The study defined responders as patients that showed a decrease of at least 50 per cent in baseline HAM-D score.[1] After two weeks, 20 per cent of patients treated with agomelatine met the criteria for responder. This compared with 10.9 per cent of those who received sertraline. Investigators doubled the antidepressant dose if patients showed an inadequate response after two weeks. After six weeks, agomelatine produced a statistically significant 1.68 points difference on the HAM-D_{17} scale compared with placebo. After six months, the responder rate was 12.5 per cent higher with agomelatine (76 per cent) than sertraline (63.5 per cent) (see Figure 2).[2]

Another study presented at the 2008 ECNP meeting compared agomelatine and venlafaxine XR. The researchers defined responders as showing a clinical global impressions (CGI) scale score below 2. After a week, 19 per cent and 9 per cent of those taking agomelatine (25mg) and venlafaxine XR (75mg) responded respectively.[3] Again, the investigators doubled the dose if patients did not show an adequate response after two weeks. After six weeks, 76.4 per cent and 70.6 per cent of the agomelatine and venlafaxine XR groups respectively responded, based on an at least 50 per cent reduction in HAM-D17 score.[4,5] However, agomelatine's numerical superiority was not statistically significant.

Other studies confirm that agomelatine produces a sustained symptomatic improvement. Kennedy and colleagues, for example, reported that 73.0 per cent and 66.9 per cent of patients receiving agomelatine and fixed-dose venlafaxine XR (150mg) respectively had entered remission, defined as a Montgomery-Åsberg Depression Rating Scale (MADRS) total score of 12 or less by week 12.[5] Once again, however, this difference did not reach statistical significance. Furthermore, agomelatine is effective across all levels of baseline severity. In patients with severe depression, the differences in the score between agomelatine and placebo was 2.06 rising to 4.45 points with baseline scores of 22-25 and >30 on HAM-D17 respectively.[6]

The study presented at ECNP also compared agomelatine and venlafaxine XR using the Leeds Sleep Evaluation Questionnaire.[4] A clinically significant improvement on the subscales measuring 'ease of getting to sleep' and the 'quality of

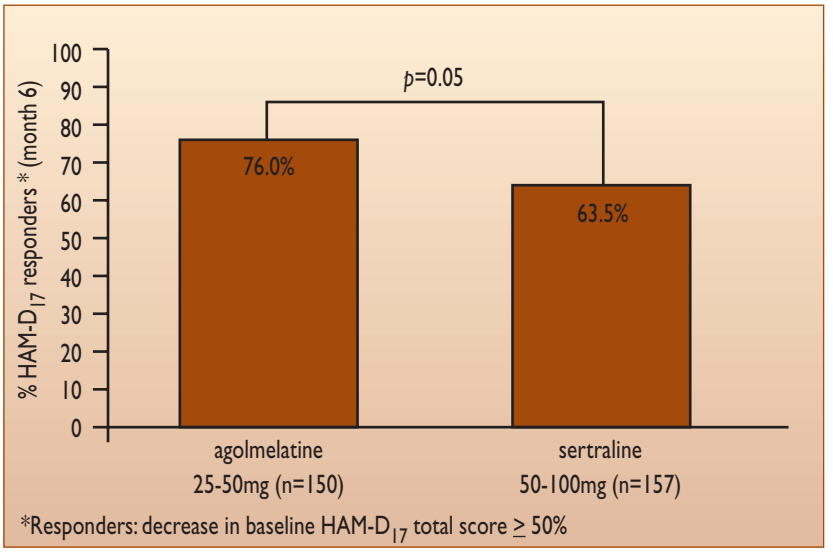

Figure 2. Response rates – agomelatine vs. sertraline (Kennedy SH. *Eur Neuropsychopharmacol* 2008;18(S4):S293.)

sleep' emerged after a week among patients treated with agomelatine. Venlafaxine did not significantly improve these outcomes over this time. This suggests that agonism of melatonergic receptors, rather than the attenuation of depression, is responsible for the improvement in sleep. Agomelatine was not associated with daytime sedation.

Non-adherence is a pervasive problem in depression. However, a meta-analysis of two venlafaxine studies and the trial of sertraline reported a mean compliance rate of 69.4 per cent (range 64.7 per cent - 73.0 per cent) with agomelatine. This compared with 61.5 per cent with the comparator (range 58.3 per cent - 64.7 per cent). This difference is statistically significant.

A well-tolerated treatment

Agomelatine appears well tolerated, in part reflecting the negligible affinity for histaminergic, adrenergic and cholinergic receptors. During eight weeks' treatment, the incidence of reported treatment-emergent adverse events with agomelatine was similar to that of placebo, with the exception of dizziness, which occurred in 6.6 per cent of patients taking agomelatine. Typically, the dizziness was of mild to moderate severity, transient, occurred during the first two weeks of treatment and did not generally result in patients withdrawing from treatment.

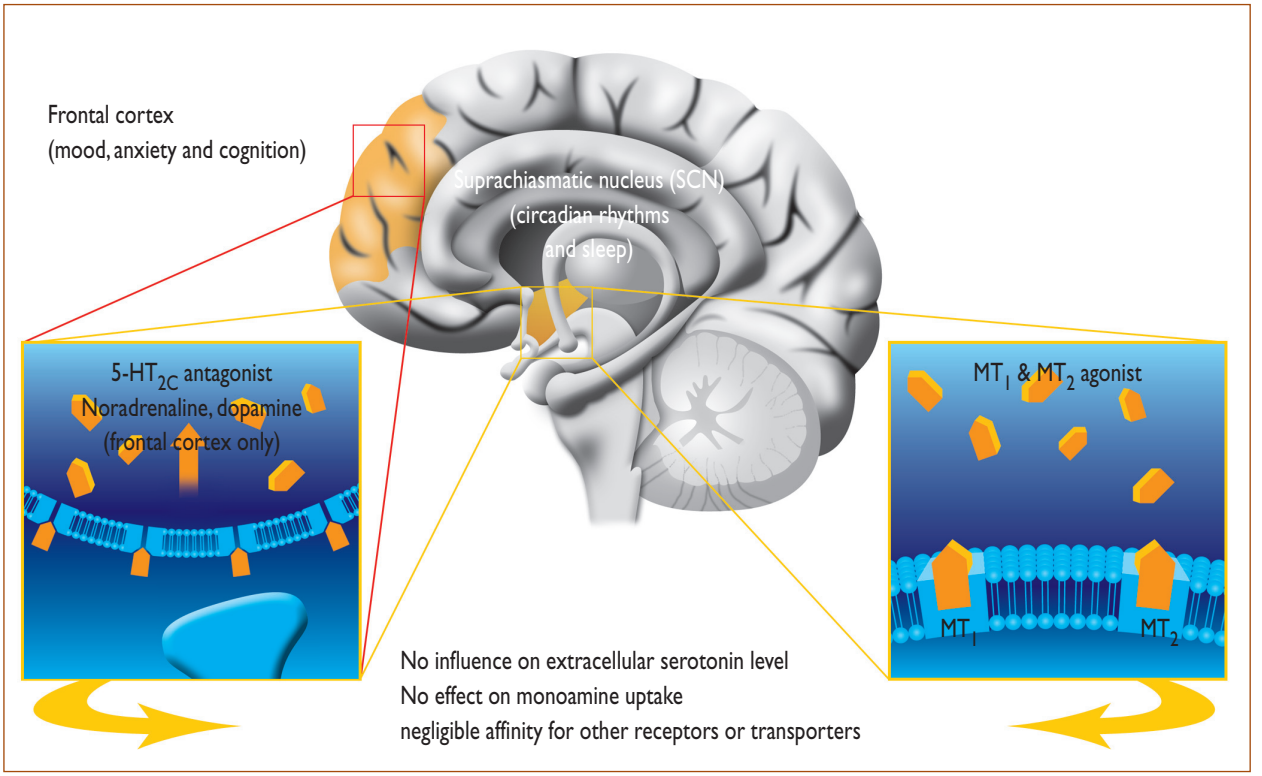

Figure 1. Agomelatine mode of action (Millan MJ, *et al. JPET* 2003;306:954-64. Papp M, *et al. Behavioural Pharmacology* 2006;17:9-18.)

The percentage of patients whose body weight changed during treatment with agomelatine was low and similar to placebo. Furthermore, a pooled analysis of three studies, using the Arizona Sexual Experience Scale, showed that patients treated with agomelatine over six weeks experienced significantly less sexual dysfunction compared with placebo.[7,8] Finally, agomelatine is not associated with emergent discontinuation symptoms.[9] The benign profile on withdrawal contrasts with some other antidepressants, such as paroxetine.

Approximately 80 per cent of a dose of agomelatine is excreted unaltered in the urine. Agomelatine is rapidly metabolised to two inactive metabolites mainly by hepatic cytochrome P450 1A2. As a result, agomelatine is contraindicated with concurrent potent CYP1A2 inhibitors. On the other hand, no significant drug-drug interactions with lithium or lorazepam emerged during the trials.

Elevations in transaminase to more than three times the upper limit of normal (ULN) occurred in 1.1 per cent of patients treated with agomelatine. This compared with 0.7 per cent in the placebo group and was not statistically significant. Cytolytic hepatitis and transaminase elevation to more than 10 times the ULN occur in less than one in 1000 patients taking agomelatine in clinical studies. Against this background, agomelatine is contraindicated in patients with hepatic impairment due to cirrhosis or active liver disease. Other patients should undergo liver function tests at the initiation of treatment, at around weeks 6, 12 and 24 and, thereafter, where clinically indicated.

In conclusion, agomelatine shows a unique psychopharmacological profile. This seems to translate into a rapid onset of antidepressant efficacy (within a week) that is sustained during long-term treatment. Agomelatine shows greater efficacy than SSRIs and venlafaxine in direct comparisons. However, it should be borne in mind that the doses of comparators, albeit recommended starting doses, were relatively low at week one – sertraline 50mg and venlafaxine 75mg. Superiority over venlafaxine 150mg in one study is more impressive but we do not have data comparing it with venlafaxine 300mg.

Agomelatine is effective in severely ill patients and improves sleep quality with no daytime sedation.

Agomelatine is well tolerated, producing mild side-effects and no discontinuation syndrome. Indeed the drug's short half-life of two hours means that there is none in circulation to cause side-effects the day after night-time dose. This also lends support to the emerging theory, which may also be true of antipsychotics, that efficacy does not require 24 hour presence of drug in the circulation; transient occupancy of receptors may be sufficient to trigger a sustained response.

All in all, agomelatine is a potentially valuable addition to the antidepressant armamentarium.

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