Agomelatine: a new treatment for depression

Professor Bill Deakin,
Neuroscience and Psychiatry Unit, Manchester University

It is estimated that depression carries the greatest burden of disability in established economies. A range of treatments are available, and selective serotonin reuptake inhibitors (SSRIs) are currently the most commonly prescribed class of antidepressant. In this article, the author discusses agomelatine, a novel antidepressant recently licensed by the European Medicines Agency (EMEA), the evidence for its use, and its potential place in therapy.

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Depression can have a significant effect on quality of life.

Agomelatine, a new antidepressant, has four novel properties:

- It does not inhibit the reuptake of serotonin or monoamines
- It is a potent melatonin receptor agonist and has moderate antagonist affinity for the 5-HT_{2c} receptor
- It has no antihistamine activity
- It has a very short half-life of about two hours.

The implications are that agomelatine has a novel mechanism of action not shared by most other antidepressants: it requires only a fleeting presence in the circulation, and it lacks the pharmacological actions associated with side-effects of many other antidepressants.

Unmet need in the treatment of depression

The WHO estimates that depression carries the greatest burden of disability in established economies and globally only respiratory and diarrhoeal disease carry a greater burden.[1] Mild levels of depression show high placebo response rates and immediate treatment with drugs is unnecessary. In moderate and severe depression, current antidepressant drugs approximately double the chance of remission in short-term studies compared to placebo, but even so about 30–40% fail to respond: lack of efficacy is clearly an unmet need. So far there is little evidence that some classes of antidepressant have greater efficacy than others. Meta-analytic studies suggest that the mixed noradrenaline-5-HT uptake inhibitor, venlafaxine, is more effective than SSRIs, however 17 patients would need to be treated with venlafaxine to obtain one extra response over treatment with an SSRI.[2] Switching to a different class of antidepressant from an SSRI is slightly more effective than switching to another SSRI.[3] Commonly used add-on augmenting strategies have a very modest benefit in patients who failed to respond to an SSRI.[4] These modest effects may simply reflect that nearly all treatments target the enhancement of monoamine content in the synapse, even though antidepressant drug classes differ in how this is achieved. Radically new mechanisms of action seem the best hope for broader efficacy, and for efficacy in those resistant to current treatments.

Lack of tolerability of antidepressants is a major unmet need in the medical treatment of depression. SSRIs are the most commonly prescribed class of antidepressant and NICE guidance recommends them as first-line treatment for depression. They work by increasing the synaptic availability of 5-HT. However, this also causes unwanted effects including sexual dysfunction, nausea, and initial anxiety, dysphoria and insomnia. In practice only approximately 35% of SSRI prescriptions are repeated, although this a major advance on the 10–15% repeat rates for older drugs.[5] Similarly noradrenaline uptake inhibitors have side-effects related to their therapeutic action in enhancing noradrenaline release, including urinary frequency, and anxiety and agitation.

Mirtazepine is a combined 5-HT_{2c} antagonist like agomelatine, but it also blocks alpha noradrenergic and histamine receptors. It is thought to work by indirectly increasing monoamine release. It induces weight gain and this has been related to combined 5-HT_{2c} and histamine antagonism. These actions may also contribute to the marked sedative actions of the drug. Clearly new drugs that have minimal pharmacological actions that focus on relevant brain mechanisms of depression offer the best hope of minimising side-effects.

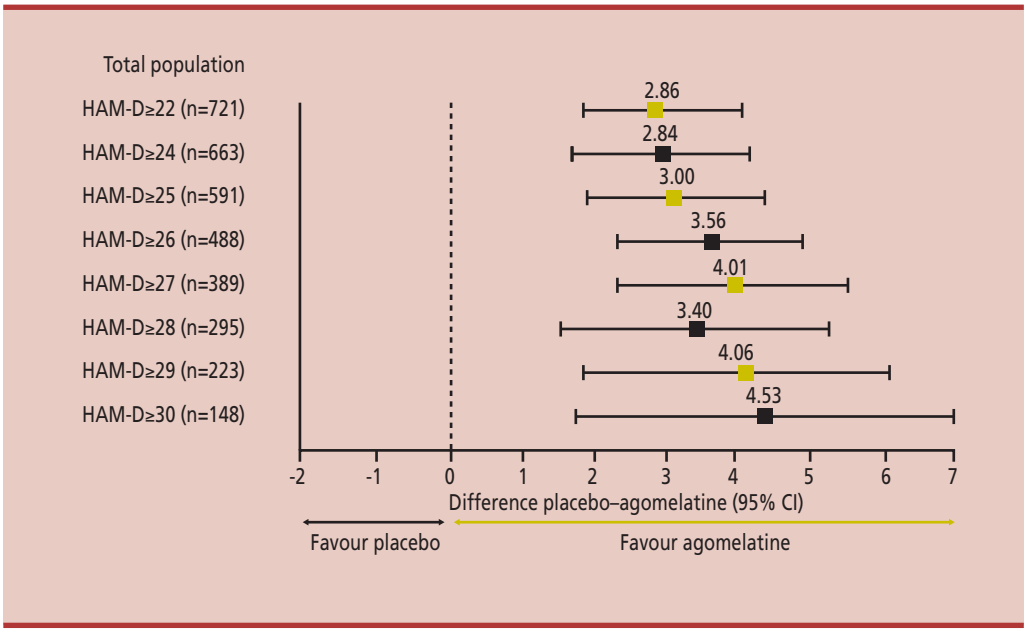


Figure 1. Agomelatine efficacy according to severity of depression: differences, placebo–agomelatine, on HAM-D total score according to HAM-D entry pool[15]

Efficacy of agomelatine

Short-term efficacy

Three definitive double-blind, placebo-controlled phase III studies show clear short-term (six-week) efficacy of agomelatine compared to placebo in treatment groups exceeding 100 patients.[6–8] The aggregated effect size over all three studies was a superiority over placebo of 2.9 on the Hamilton Depression rating scale (HAM-D) at the end of the trials.[9,10] This is comparable to effect sizes seen in trials of established antidepressants such as SSRIs.

An effective response is commonly taken as a 50% reduction in HAM-D scores and in the pivotal studies this was achieved in 56% of agomelatine-treated patients compared to 39% of those on placebo. Remission of symptoms to a HAM-D score of less than six was achieved in 23% of those taking agomelatine and in 14% of those taking placebo.

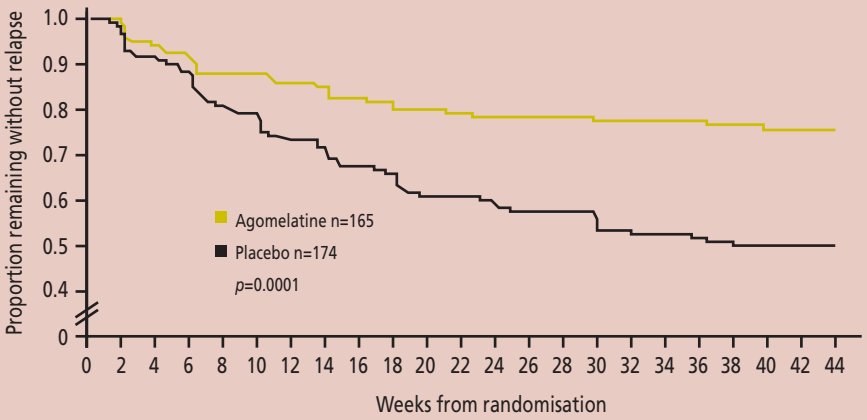
In three unpublished studies, greater improvement on agomelatine compared with placebo was not statistically significant, but in two of these the reference antidepressant also failed to show efficacy. This is a common occurrence in clinical trials of antidepressants, with about one-third of trials failing to show efficacy of effective drugs, often due to large improvements seen with patients on the placebo.[11]

In the third negative study, fluoxetine showed a statistically significant improvement compared to placebo, however, the greater improvement of agomelatine over placebo did not reach statistical significance on the HAM-D, which was the primary outcome measure. However, on the Clinical Global Impression of Improvement (CGI-I) rating, a secondary outcome measure, agomelatine was superior to placebo.

Meta-analysis of all the six placebo-controlled studies showed the statistically significant overall efficacy of agomelatine compared to placebo, with no evidence of inhomogeneity between studies.[10]

Comparative efficacy

One of the three pivotal studies included paroxetine as a reference antidepressant and the outcomes were almost identical and superior to placebo.[7] Both of the placebo-controlled studies versus fluoxetine were inconclusive as noted. In two large head-to-head comparisons against venlafaxine, agomelatine showed trends towards superiority



The incidence over time of patients in the overall population having relapsed over six months was significantly lower with agomelatine compared to placebo (21.7% versus 46.6%, log rank test p=0.0001), the risk of relapse reduced by 54% (Cox model hazard ratio: 0.458 [0.305;0.690]).

* HAM-D total score ≥16, suicide or suicide attempt. *P* values for the comparisons with placebo, Logrank test. Data on file.

Figure 2. Long-term efficacy and relapse prevention with agomelatine versus placebo[16]

in both, and there were notable benefits for agomelatine on the primary outcome measures, which concerned sleep and sexual side-effects.[12,13]

In a comparison with sertraline, treatment with agomelatine demonstrated a significant superiority on CGI ratings and the HAM-D total score over six weeks of treatment.[14]

Efficacy in severe depression, upon sleep, and in the elderly

Two important efficacy findings emerge upon analysis of the pivotal studies. Firstly, agomelatine was more effective compared to placebo in patients over 60 years of age with severe depression (MADRS >30; CGI 5+), and a HAM-D effect size of 4.5 compared to the overall effect of 2.9. Secondly, agomelatine showed greater efficacy in more severely ill patients.[15] For example, Figure 1 shows that those with initial HAM-D scores greater than 30 showed greater improvements over placebo than those with lesser severity.[15]

The effect of agomelatine on sleep is of considerable interest in view of its potent melatonin agonist effects. It is noteworthy that all clinical studies have been carried out using early evening dosing, based on the preclinical evidence that evening melatonin resets or entrains circadian rhythms. Lemoine *et al* used the Leeds Sleep Evaluation Questionnaire (LSEQ) to compare the effect of flexible dose agomelatine 25–50mg with venlafaxine 75–150mg over six weeks in major depressive disorder.[12] All four self-rated domains of sleep improved more in the agomelatine-treated patients and differences between groups were significant by the end of week one. Importantly, the LSEQ domains include both ease of wakening and daytime function as well as ease of sleep onset and quality of sleep. Thus, improved sleep was not associated with daytime sedation, which could reflect the short half-life of agomelatine.

Long-term efficacy

Two formal discontinuation studies have been carried out in which depressed patients who had previously recovered on agomelatine were randomised to continue for a further six months or to switch to placebo. The first study was inconclusive because very few patients relapsed after the switch to placebo. The second study showed a highly significant protective effect (p<0.001) of continuation, which more than halved the number of relapses over six months.[16] There was no evidence of rapid relapse among the patients in the first weeks of discontinuation as is usually seen with other antidepressants, but rather a slow, even rate of relapse distributed over the six-month period, as can be seen in Figure 2.[16] These findings add to the short-term efficacy data and show that efficacy is maintained by continuing agomelatine. Most interestingly, perhaps, the lack of acute relapse following discontinuation points to a novel mechanism of action.

Tolerability

Agomelatine has consistently shown a favourable side-effect profile in clinical studies, and in comparison with reference antidepressants.[17] Part of this may be attributable to the fact that all clinical studies have involved evening dosage, so that little agomelatine remains three half-lives later during the day, and no accumulation in the circulation can occur. The most common adverse events are headache, nausea, and fatigue (Table 1),[17] but the number of events actually occurring is low and they are of

mild-to-moderate intensity, mostly resolving in two weeks, and are not that much different from those experienced while on placebo. Also, discontinuation due to adverse events has been very low at, for example, 8.0% in the Lôo *et al* study compared to 6.5% on placebo.[7,18]

A major problem with SSRIs and antidepressants in general is that abrupt discontinuation is followed by a withdrawal syndrome which includes nausea, vomiting, dizziness, restlessness and attacks of perspiration. Montgomery *et al* showed that patients who had fully recovered during treatment with agomelatine showed no emergent symptoms when switched to placebo, whereas switching from paroxetine was associated with substantially more symptoms.[19] This finding is corroborated by the previously mentioned definitive long-term efficacy study showing no abrupt increase in relapse after discontinuation.[16]

Adverse event	Patients reporting emergent adverse event (%)		
	Agomelatine (25mg/day)	Placebo	Paroxetine (20mg/day)
Total	51.1	54.7	66.0
Headache	6.6	8.6	8.2
Anxiety	3.6	3.6	2.7
Abdominal pain	3.6	3.6	3.4
Diarrhoea	3.6	2.9	4.1
Nausea	2.9	4.3	17.0*
Somnolence	2.9	5.0	7.5
Depression	2.9	2.7	4.3
Insomnia	2.9	2.9	4.8

[a] % patients in the safety set; data from all patients who received at least one dose of treatment (even without efficacy evaluation). *$p \geq 0.005$ (compared with placebo).

Table 1. Main emergent adverse events[a] reported by at least 3.5% of patients in any of the treatment groups[7,17]

Mechanism of action

Short half-life

As has been noted, the short half-life of agomelatine together with the absence of pharmacologically active metabolites very likely contributes to its favourable side-effect profile, especially after early evening dosing. However, it also implies a mechanism of action which requires only brief occupancy of melatonin or 5-HT_{2c} receptors, or even both, to set recovery in motion. There is one argument that the resetting of diurnal rhythms may contribute to efficacy. However, recent evidence suggests that only brief occupancy at dopamine D_2 receptors is sufficient for efficacy of clozapine and quetiapine in the treatment of schizophrenia.[20] Thus, it seems possible that transient occupancy of receptors will become a desirable principle of drug action in the future, and that it will indeed be possible, at least for some receptors and second messenger systems.

Melatonin receptor agonism

Agomelatine has a high affinity for MT1 and MT2 receptors, and it mimics the effects of melatonin in behavioural assays, for example, in entraining circadian rhythms in experimental rat models.[21] Anxiolytic-like effects of agomelatine in animal models are not blocked by melatonin antagonists, suggesting that melatonin agonism might not contribute to anxiolytic effects of the drug as demonstrated in a recent clinical trial in generalised anxiety disorder.[21]

Depression has been seen as a disorder of circadian rhythms perhaps involving desynchronisation of hormone, sleep–wake and body temperature cycles, but a consistent picture of phase advance or delay has yet to emerge.[22] There is little consistent evidence from the few studies that have measured melatonin concentration in patients that secretion is abnormal in depression.[23,24] In one study, it was found that venlafaxine did not modify melatonin secretion.[25]

In another study in patients, fluoxetine, duloxetine, and *Hypericum perforatum* (St John's wort) increased excretion of a melatonin metabolite more than placebo, but the groups did not differ in improvement in depression.[26] This suggests that some antidepressants may increase melatonin secretion but that in fact this is a pharmacological effect unrelated to improvement.

It appears unlikely that agomelatine works directly by reversing a disease-related abnormality of melatonin secretion in humans, or through a melatonin-mediated effect shared with standard antidepressants. There are no industry-standard clinical trials of melatonin as an antidepressant, and few effects have been seen in experimental studies of depression-related disorders.[27] Nevertheless, the potency of agomelatine at melatonin receptors may yet prove relevant to its antidepressant effects and it has stimulated renewed interest in depression as a disorder of diurnal rhythms.

Melatonin clearly has the ability to induce sleep in humans,[28] thus melatonin receptor agonism at the least may contribute to the superior efficacy of agomelatine over venlafaxine in improving sleep patterns in those who suffer from depression.

5-HT$_{2c}$ receptor antagonism

Agomelatine has modest antagonist affinity for the 5-HT$_{2c}$ receptor and shows functional antagonism in animal models.[21] Whether clinical doses of agomelatine decrease 5-HT$_{2c}$ function in humans is not known but this is amenable to direct experimental testing.[29] Animal studies strongly implicate 5-HT$_{2c}$ receptors in mechanisms of anxiety and it has been suggested that anxiety and depression may involve exaggerated 5-HT$_{2c}$ neurotransmission.[30] Some studies have shown that exaggerated 5-HT$_{2c}$ mediated hormonal responses to drug challenges are compatible with increased 5-HT$_{2c}$ neurotransmission in depression.[31,32]

Regardless of whether excessive 5-HT$_{2c}$ function is involved in the pathogenesis of depression, most effective antidepressants downregulate 5-HT$_{2c}$ function with repeated treatment, and this may contribute to their antidepressant efficacy. Such an action may contribute to the antidepressant effects of mirtazepine, a potent 5-HT$_{2c}$ antagonist. Selective 5-HT$_{2c}$ antagonists, for example, olanzapine and ritanserin, increase the restorative slow-wave component of sleep.[33,34] Furthermore, olanzapine decreased rapid-eye movement (REM) sleep and delayed REM onset, which is a classic effect typical of antidepressant drugs.[22] Both of the actions are shared by agomelatine and this suggests that 5-HT$_{2c}$ antagonism may contribute to improved slow-wave sleep and reduced REM sleep, as induced by agomelatine, and hence also to its antidepressant actions.[35] The studies also indirectly suggest that agomelatine has the ability to decrease 5-HT$_{2c}$ function at clinical doses.

Overview of agomelatine

Novel mechanism of action
- Melatonin agonist – improved sleep onset & biorhythms
- 5-HT$_{2c}$ antagonism – anxiolytic, antidepressant, improved sleep architecture
- Short half-life – minimises side-effects
- No effect on 5-HT uptake, thus no sexual side-effects

Effective in depression
- Effective in the severely ill[15]
- Effective in the elderly[15]
- Comparable efficacy to SSRIs and venlafaxine[12–14]
- No discontinuation symptoms or rapid relapse[16]
- Improved sleep quality with no daytime sedation[12]

Well tolerated
- Mild side-effects reflecting pharmacological profile
- No sexual dysfunction
- Minimal weight gain
- Minimal sedation

Downstream effects on monoamine release

Mirtazepine, agomelatine and selective 5-HT$_{2c}$ antagonists share the ability to increase noradrenaline and dopamine release in the frontal cortex in dialysis studies in experimental animals.[36–38] This appears to be mediated in part by disinhibition of 5-HT-mediated restraint of dopamine and noradrenaline cell body firing in the ventral tegmental area and locus coeruleus. In keeping with this, the SSRI citalopram, which does not block 5-HT$_{2c}$ receptors, does not enhance dopamine release in the frontal cortex. It is noteworthy that 5-HT$_{2c}$ antagonists do not affect the basal firing rate of 5-HT neurones or influence the release of 5-HT, whereas citalopram suppresses 5-HT cell firing but increases 5-HT release. Furthermore, there is evidence that behaviourally active doses of mirtazepine do not alter 5-HT release, in contrast to earlier claims to the contrary.[37,38]

These studies suggest that agomelatine, and possibly mirtazepine, has a profile quite distinct from SSRIs. Agomelatine increases frontal catecholamine release without affecting the 5-HT release, whereas SSRIs increase 5-HT release without affecting frontal catecholamine release. Some drugs with significant 5-HT$_{2c}$ antagonist properties such as olanzapine, risperidone, and mirtazepine are known to induce weight gain. In contrast, agomelatine shows no tendency to induce weight gain, possibly because in contrast to the other agents, it is devoid of antihistaminic properties, which are implicated in weight gain. In addition, the low circulating concentration of agomelatine during the day may not affect the regulation of food intake.

Melatonin agonism–5-HT$_{2c}$ antagonism synergy

As the two known primary pharmacological properties of agomelatine

are not individually associated with standard antidepressant actions, the possibility that the two receptors interact through second messenger systems to account for the efficacy of agomelatine is an active area of research.

Conclusion

Agomelatine is an effective antidepressant drug which has a unique pharmacology and a short half-life. In addition, it has a beneficial effect on sleep and a favourable side-effect profile.

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