Expert Opinion

Agomelatine, a melatonin agonist with antidepressant properties

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Agomelatine (β-methyl-6-chloromelatonin), which is structurally homologous to melatonin, is a potent agonist of melatonin MT1 and MT2 receptors as well as an antagonist of serotonin 5-HT_{2C} receptors. Agomelatine appears to improve sleep without causing daytime sedation. It has not been found to be associated with sexual side effects and discontinuation symptoms. Three placebo-controlled trials, one of them a dose finding study and two of them pivotal trials, suggest that agomelatine is an antidepressant at doses of 25 – 50 mg/day. Agomelatine appears to be well tolerated, without sexual or cardiac adverse effects, weight gain or discontinuation syndromes. Animal studies suggest a possible neuroprotective action of agomelatine, although there are more data in favor of an anxiolytic effect. Substantially more research is needed to establish its role in the treatment of mood and circadian rhythm disorders.

Keywords: agomelatine, antidepressant, depression, melatonin, receptor, serotonin

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1. Introduction

Major depressive disorder (unipolar depression) is a common condition that affects 4 – 10% of men and twice as many women. Morbidity and mortality are substantial. For example, major depression causes more disability than arthritis and diabetes, and increased rates of death are attributed to suicide, accidents and excessive mortality from coronary heart disease [1]. Major depression has high rates of comorbidity with anxiety disorders, substance use disorders and chronic medical illnesses. There is a high rate of relapse (return of a partially remitted episode) and recurrence (development of a new episode) after improvement of an index episode of depression. Major depression is associated with basic changes in physiology, including sleep disturbances and desynchronization of circadian rhythms.

Treatment guidelines [2,3] have been consistent in recommending antidepressants both as first-line acute treatments for depression and maintenance therapy to reduce the risk of relapse and recurrence. Manualized psychotherapies such as interpersonal therapy and cognitive behavior therapy have been found to be effective as monotherapy for major depression of mild to moderate severity, and adjunctive interpersonal therapy has been shown to reduce the risk of relapse. Yet, only a minority of depressed patients receives adequate treatment acutely and even fewer patients continue adequate maintenance treatment, in part because of frequent adverse effects. Of those who are treated, rates of response and remission are unacceptably low. The development of currently available antidepressants has been based on the monoamine hypothesis of depression, which has limited explanatory power for both the pathophysiology and treatment of depression [4].

2. Agomelatine: a novel antidepressant

2.1 Overview of the market

There are currently five classes of antidepressant medication available: tricyclic antidepressants, selective serotonin re-uptake inhibitors (SSRIs),

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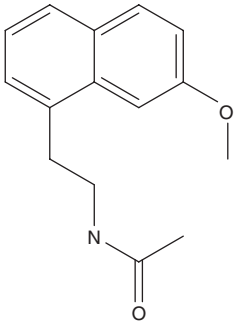
Box 1. Drug summary.

Drug name	Agomelatine
Phase	Phase III
Indication	Depression
Pharmacology description	Melatonin 1 and 2 agonist 5-HT_{2c} antagonist
Route of administration	Alimentary, by mouth Alimentary, sublingual
Chemical structure	
Pivotal trial(s)	It is in US Phase III trials to evaluate efficacy, safety and tolerability in major depressive disorder patients

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serotonin/norepinephrine re-uptake inhibitors (SNRIs), monoamine oxidase inhibitors and antidepressants with receptor antagonism but no direct effects on neurotransmitter re-uptake such as trazodone and mirtazepine [5]. In addition, instrumental therapies such as electroconvulsive therapy and repetitive transcranial magnetic stimulation are approved for the treatment of major depression, vagus nerve stimulation is approved for the treatment of refractory depression, artificial bright light is effective for seasonal affective disorder (major depression during the winter and normal or elevated mood in the spring and summer) and deep brain stimulation is under study as a treatment for severe refractory depression.

Antidepressants that are now on the market have been shown in at least two randomized controlled trials to be superior to placebo in producing a response of depression, which is defined as a 50% or greater reduction in depression rating scale scores. Overall, the response rate to any antidepressant rarely exceeds 60%, and the rate of remission (no or minimal symptoms) is rarely greater than 30%. Persistent psychosocial dysfunction is common even with symptomatic remission, and any residual symptoms, including disturbed role function, increase the risk of relapse and recurrence [6]. Thus far, no antidepressant has been shown to be clearly superior to any other for response or remission of depression.

A factor that contributes to inadequate treatment response is the reluctance of patients to take antidepressants. One factor that contributes to treatment nonadherence is limited tolerability of existing antidepressants. The tricyclic antidepressants have limiting anticholinergic, hypotensive and cardiac effects. With the release of fluoxetine in 1987, it was expected that the introduction of the SSRIs would greatly facilitate the treatment of depression because of greater patient acceptance. However, adverse effects of SSRIs have emerged that range from sexual dysfunction, gastrointestinal syndromes, extrapyramidal syndromes, bleeding disorders and drug interactions which have sobered this expectation [7-11]. Newer antidepressants such as the SNRIs do not appear to be more reliably effective than the SSRIs, and they add noradrenergic and (in the case of venlafaxine, dopaminergic) side effects to serotonergic side effects as well as more complicated dosing. Only a few antidepressants normalize sleep, and there are those that do cause daytime sedation and in some cases weight gain.

Many antidepressants act on the monoamine neurotransmitters norepinephrine, serotonin and dopamine, but some antidepressant therapies (e.g., trazodone, mirtazepine) antagonize serotonin 5-$HT_{2A/2C}$ receptors among others and some (e.g., electroconvulsive therapy, artificial bright light) have no direct action on neurotransmitters or receptors. Nevertheless, many newer antidepressants were developed as variants of existing medications based primarily on neurotransmitter actions, resulting in a series of 'me too' drugs that offer no real advantage over existing treatments. Some newer antidepressants are either enantiomers (e.g., escitalopram) or metabolites (e.g., desvenlafaxine) of existing products of the same manufacturer that were released in anticipation of loss of patent protection of the original medication and, unlike earlier metabolites of existing antidepressants, such as nortriptyline and desipramine (monodemethylated metabolites of amitriptyline and imipramine, respectively), have not yet been shown to have clear advantages over the parent drug. At one time, drugs that seemed more 'selective' in their actions such as the SSRIs were felt to be more specific for depression, but these drugs are not in fact selective pharmacologically or therapeutically because they have multiple actions and are effective for multiple disorders. Subsequently, drugs with more than one demonstrated neurotransmitter action such as the SNRIs were touted as 'broad spectrum' antidepressants. More recently, the hope has been expressed that it might be possible to develop antidepressants with multiple cellular targets that would be more effective for the complex pathophysiology of depression and many other illnesses [12,13]. Indeed, many disorders from hypertension to cancer to refractory major depression do not respond to a single specific treatment and require combinations of treatments with different mechanisms of action. If a single medication combined actions that were known to be relevant to improvement of depression it would reduce potential interactions and problems with adherence associated with medication combinations [14]. However, the assumption that current antidepressants have only one action has been shown not to be correct [15,16]. In a review of this report, the manufacturer suggested that agomelatine (**Box 1**) represents

a multifactorial approach to different dimensions of depression, an assertion that is supported by speculations that enhanced melatonin secretion is associated with an antidepressant response. Conversely, melatonin itself has not been shown to have antidepressant properties and any change in melatonin signaling could be secondary to alterations in norepinephrine neurotransmission and have nothing to do with antidepressant efficacy [12].

2.2 Introduction to agomelatine

It has been recognized for many years that depression is associated with circadian rhythms that are desynchronized from each other and from environmental cues, and that improvement of the sleep-wake cycle and other circadian rhythms may promote improvement of depression [17,18]. Agomelatine is a novel antidepressant that is an agonist of melatonin receptors as well as an antagonist of 5-HT_2 receptors, with minimal affinity for histamine, acetylcholine and norepinephrine receptors.

Melatonin (N-acetyl-5-methoxytryptamine) is synthesized in the pineal gland, with peak release occurring in the dark. Its chronobiotic properties are mediated by two G-protein-coupled melatonin receptors linked to different signaling mechanisms in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus, which comprises the circadian clock that drives the sleep–wake cycle as well as cycles of behavior and hormone secretion [19,20]. MT1 receptors inhibit the SCN, inducing sleep, while MT2 receptors (and possibly MT1 receptors to some extent) induce phase shifts in SCN signaling that entrain the sleep–wake cycle to the cycle of light and dark. These receptors may also participate in the entrainment and coordination of other biological rhythms implicated in depression such as rhythms of hormone secretion, rapid eye movement (REM) sleep and activity. Serotonergic input to the SCN from the raphe nucleus modulates the entraining effect of light on the SCN and serotonin 5-HT_{2c} receptors (the only serotonin receptors with a circadian variation of expression) inhibit melatonin release while antagonists of these receptors decrease the inhibitory effect of light on melatonin production [18,19]. As a result, both serotonin and melatonin modulate circadian rhythmicity [18]. Melatonin secretion is influenced by stress as well as the light–dark cycle [20]. While it may hasten the onset of sleep, melatonin by itself has not been found to prolong sleep or to have antidepressant properties [19].

The observation that major depression is associated with desynchronization of circadian rhythms has stimulated the idea that resetting these rhythms may have antidepressant potential. An antidepressant with positive effects on sleep would be particularly appealing because all of the currently available antidepressants except trazodone, mirtazepine and possibly nefazodone disrupt sleep continuity, REM sleep and/or slow-wave sleep and the sleep disorder of depression may persist after improvement of other symptoms with these medications [21]. Agomelatine was developed by Servier and licensed in the US to Novartis as a treatment for major depression that would have improved tolerability and a low propensity for weight gain or sexual dysfunction [22]. Agomelatine received a positive opinion from the Committee for Medicinal Products for Human Use of the European Medicines Agency on 23 November 2008; it has not yet been approved by the FDA.

2.3 Chemistry and pharmacodynamics

Agomelatine (N[2-7(-methoxy-1-naphtyl)ethyl] acetamide; β-methyl-6-chloromelatonin), a naphthalene homologue of melatonin, is a selective agonist of MT1 (inhibition constant; K_i = 0.06 – 0.1 and MT2 (K_i= 0.12 – 0.27) receptors and with more affinity for these receptors and a longer half-life than melatonin [22,23]. It is also an antagonist of cloned serotonin 5-HT_{2c} receptors (K_i = 6.2) but not to a significant extent of other serotonin receptor subtypes [19,22,24]. Blockade of 5-HT_{2c} heteroreceptors on dopaminergic and noradrenergic neurons in the SCN and limbic system, hippocampus and neocortex enhances release of dopamine and norepinephrine in the frontal cortex but not the limbic system [22], although agomelatine has no effect on any monoamine transporter [19].

2.4 Pharmacokinetics and metabolism

Agomelatine is rapidly absorbed after oral administration, with peak plasma levels being reached in 1 – 2 h. Bioavailability following oral dosing is 5 – 10% due to extensive first-pass metabolism [25]. However, the rate of increase of blood level is greater than the rate of increase in dose, possibly due to saturation of first-pass metabolism. It is 85 – 95% protein bound, with a steady-state volume of distribution of around 35 l. Agomelatine is metabolized by hydroxlylation and demethylation, as well as oxidation by CYP450 1A2 and 2C9 [25]. One metabolite has about the same affinity for 5-HT_{2C} receptors as the parent drug but no pharmacologic activity *in vivo*; no metabolites bind strongly to melatonin receptors. Agomelatine is primarily eliminated by urinary excretioin of metabolites; the mean terminal elimination half-life is 2.3 h [22,25]. However, there is undoubtedly a wide range of half-lifes given the heterogeneity of metabolizing enzymes. Despite the short mean elimination half-life that has been reported, clinical trials of agomelatine have reported clinical efficacy with once daily dosing, raising the possibilities that the dynamic half-life is longer than the elimination half-life and that the active metabolite may have a longer duration of action than the parent drug.

2.5 Clinical efficacy

In animals, agomelatine induces phase shifts in circadian rhythms and accelerates synchronization of circadian rhythms to shifting light–dark cycles [26]. It has also been found to resynchronize circadian rhythms in animals kept in constant darkness [19]. In addition to the sleep–wake cycle, agomelatine phase advances circadian rhythms of hormone secretion that are linked to a different oscillator than the one that drives the sleep–wake cycle. The extent of synchronization of circadian

rhythms is similar to that seen with exogenous melatonin [22]. In one series of animal experiments, agomelatine normalized the increase in cortisol secretion associated with chronic stress, which may be similar to the hypercortisolemia associated with human depression [20]. In a double-blind placebo-controlled crossover study in healthy men, agomelatine 50 mg/day significantly phase advanced the 24 h profiles of body temperature, cortisol and TSH levels at the end of a 15 day trial and stimulated GH secretion and prolactin levels during the awake period [14].

Animal studies suggest that agomelatine can enhance cognition and induce neuroprotective proteins such as brain derived neurotrophic factor (BDNF), which could reverse defective neuroplasticity that has been observed in mood disorders [22]; the latter are associated with downregulation of BDNF, which is corrected by antidepressants [4]. Chronic treatment with agomelatine decreased depolarization-evoked release of glutamate but not GABA in rat hippocampus, suggesting dampening of excitatory neurotransmission, and the medication promoted lesion repair in a mouse model of white matter damage induced by excitotoxicity, an effect that was blocked by melatonin receptor antagonists [27]. Both of these actions, as well as actions on the ERK-Akt-GSK3b signaling pathways, may explain increased cell proliferation and neurogenesis in the ventral dentate gyrus of the hippocampus under basal and stressful conditions with chronic (3 week) but not subacute (1 week) or acute (4 h) treatment with agomelatine in adult rats [28]. This property could have the potential to ameliorate loss of hippocampal neurons in depression [22].

Several studies have found efficacy in rodent models of depression and anxiety [22]. In some animal models, agomelatine and melatonin have antidepressant-like activity when given in the evening, but only agomelatine has antidepressant activity when given in the morning [19,29]. However, maximal antidepressant effects in animals are observed when agomelatine is administered at the beginning of the dark period [20]. Agomelatine also has an anxiolytic effect in animal models [30,31], and this effect is blocked by melatonin antagonists in the evening but not the morning [19].

2.5.1 *Phase II studies*

An 8-week double-blind dose finding study of 1, 5 and 25 mg/day of agomelatine in 711 out-patients with major depression (mean Hamilton Depression Rating Scale (HRSD) score 27, or moderately depressed) found 25 mg to be significantly more effective than placebo in reducing anxiety and depression scores, while the two lower doses did not separate from placebo [32]. Remission rates with agomelatine (30%) were similar to paroxetine (26%), an active control used in the study, and superior to placebo (15%). The same group conducted a blinded dose finding study lasting 7 – 11 weeks in depressed inpatients treated with 5 or 100 mg/day of agomelatine and found similar efficacy of both doses with fewer side effects at the lower dose [33]. The smaller sample size and the absence of a placebo or active control make it impossible to compare this result with the previous study and suggest that even if the subjects were in-patients a population with a high placebo response rate may have been selected.

2.5.2 *Phase III studies*

A review [19] of three published randomized placebo-controlled studies in major depressive disorder (total N = 1161), including the dose finding study cited earlier [32] and two 6-week studies of 25 mg/day of agomelatine with the option for a blinded increase to 50 mg/day in the event of inadequate response found that 25 or 50/mg day of agomelatine produced significantly greater reductions of HRSD scores than placebo. Differences in HRSD scores were around 3 – 4 points [34]. In all three studies, there were significantly more responders to agomelatine (49 – 62%) than placebo (34 – 46%). Using last observation carried forward (LOCF) and univariate repeated measures analysis of variance (ANOVA), p values ranged from 0.024 to < 0.01. Self-reports of sleep improved, but more detailed investigation of sleep quality and structure was not performed in these studies.

A pooled analysis of the three controlled studies noted above using changes in HRSD scores as the primary outcome measure found that agomelatine was superior to placebo in the subgroup of patients with more severe depression, defined as a HRSD score ≥ 25 [35]. When the HRSD criterion for severity was increased to 30, the difference between placebo and agomelatine increased from 3 to 4.53 points. A similar finding emerged when severity was defined by increasing scores on the Clinical Global Impressions-Severity scale. Agomelatine was also superior to placebo in the subgroup of patients aged ≥ 60, although there were not enough severely depressed patients in this group to perform a separate analysis of responses to more severe geriatric depression.

A 12-week double-blind comparison of 50 mg/day of agomelatine to 150 mg/day of venlafaxine XR in 276 patients with major depressive disorder found similar rates of remission (67 – 73%) with both drugs [36]. However, the lack of a placebo control and a rate of remission that was much higher than that reported in other antidepressant trials, as well as the relatively low dose of venlafaxine, raises the possibility that the population was unusually responsive to treatment or had a high placebo response rate.

Subjective assessment of ability to get to sleep was the primary outcome measure in a 6-week double-blind comparison of 25 – 50 mg/day of agomelatine and 75 – 150 mg/day of venlafaxine in 332 patients with major depressive disorder [37]. On a visual analogue scale, ability to get to sleep was significantly greater with agomelatine, with a between group difference at the last assessment of 6.36 mm on a 100 mm scale. Ratings of quality of sleep and antidepressant efficacy, which were secondary outcome measures, were similar. Both drugs produced similar response rates, but the absence of placebo makes it

impossible to know whether apparent efficacy represented a placebo response.

The manufacturer is currently conducting an 8-week, placebo- and paroxetine-controlled study of agomelatine in 490 patients with major depressive disorder, and a 52-week, randomized placebo-controlled relapse prevention trial in 600 patients with major depressive disorder [25]. It is expected that these Phase III studies will be completed in late 2009.

In a double-blind multi-center 12-week study of 121 patients with generalized anxiety disorder conducted in Finland and South Africa and sponsored by the manufacturer, reductions of Hamilton Anxiety Rating Scale (HAM-A) scores were significantly greater with 25 – 50 mg of agomelatine than placebo (-16.6 versus -13.2 points, or a difference of reduction of 3.28 points from a mean baseline score of 29) [31]. With the LOCF method of data analysis, significantly more patients responded (≥ 50% reduction in HAM-A score) to agomelatine than to placebo (66.7 versus 46.6%). While statistically impressive, the absolute difference in anxiety reduction between agomelatine and placebo seems small, and there was no consideration of the contribution of improved sleep to the overall reduction in anxiety scores.

Agomelatine 25 mg/day was studied in an open-label protocol in 21 patients with bipolar depression taking lithium or valproate [38]. Following an initial 6-week treatment phase, 81% of patients responded (≥ 50% reduction in HRSD scores). Of the 11 patients who continued open-label agomelatine for an average of 211 days, 84% were responders at the last evaluation. Remarkably, the mean HRSD score at 52 weeks was as low as 2.3, down from a baseline score of 25. Because this kind of dramatic improvement is not typical of other studies of bipolar depression and the study, which was conducted at eight centers, was only able to enroll 21 patients, the generalizability of this finding should only be assessed after controlled research. A similar caution applies to an open study of 37 patients with a mild major depressive episode associated with non-bipolar, nonpsychotic seasonal affective disorder [39]. After 14 weeks of open-label treatment with 25 mg/day of agomelatine, 76% of patients had a 50% reduction in HRSD scores and 70% had about a two-third reduction of depression scores, which was the investigators' *a priori* definition of remission. In addition to the high rate of placebo response and of spontaneous improvement of depression of this severity, the time of year of the study was not reported, making it impossible to know whether seasonal depression was improving anyway after 3 months because springtime was approaching.

In older normal men, 50 mg/day of agomelatine administered in the evening phase advanced rhythms of cortisol, thyroid and body temperature but did not affect sleep [40]. In contrast, open treatment with 25 mg/day of agomelatine for 42 days in 15 moderately depressed outpatients improved sleep continuity and quality and normalized slow wave sleep and δ power, and time awake after sleep onset decreased from 42 to 19 min, without any effect on REM sleep [35,41]. In a similar protocol in what may have been the same 15 depressed patients, agomelatine appeared to normalize non-REM sleep [42].

2.6 Safety and tolerability

The most common adverse effects of agomelatine in controlled studies have been headache, nausea, fatigue and dizziness [19,35]. Insomnia, somnolence, constipation and abdominal pain have also been reported [25], but weight gain, sexual dysfunction and adverse cardiovascular effects have not. In a direct comparison, agomelatine produced significantly less deterioration of sexual function than venlafaxine [36]. Changes in laboratory tests and electrocardiogram have not been reported [31,38]. Like all antidepressants, agomelatine has been noted to induce mania or hypomania when used to treat bipolar depression in patients already taking lithium [38]. Discontinuation syndromes have not been reported in efficacy trials of agomelatine [25]. A double-blind discontinuation study of 192 patients taking 25 mg/day of agomelatine or 25 mg/day of paroxetine for 12 weeks noted discontinuation symptoms 1 and 2 weeks after abruptly stopping paroxetine but not agomelatine [43].

Because of the role of 5-HT_2 receptors in mediating platelet aggregation and coronary artery occlusion [44] and reports of beneficial effects of 5-HT_2, antagonists in promoting coronary blood flow [45] and preventing restenosis following coronary angioplasty [46], agomelatine could prove useful in the presence of coronary heart disease. The same property could have additive antiplatelet effects with other medications used to reduce clotting risk, increasing the risk of bleeding. Neither of these possibilities has yet been explored.

2.7 Conclusion

Agomelatine is a promising new antidepressant that in short-term studies has not yet appeared to have cardiac and sexual side effects or to cause weight gain. Its ability to synchronize circadian rhythms and improve some aspects of sleep, especially slow-wave sleep, is appealing. Neuroprotective effects demonstrated in animals certainly warrant further investigation although it has not been suggested that this might be relevant to humans. More severely depressed patients appear to respond to agomelatine. Side effects that commonly limit acceptability of existing antidepressants such as sexual dysfunction and weight gain may not be as problematic for agomelatine.

Randomized clinical trials have used a design and a method of data analysis (intent to treat with significance assessed by ANOVA) that is standard in antidepressant trials. However, with one exception [32], corrections were not made for multiple comparisons. The fact that response rates in uncontrolled studies were much higher than has been reported in controlled trials of any other antidepressant raises further questions about the samples chosen for these studies. In addition, the magnitude of reduction in depression rating scale scores in controlled studies was not great and the clinical significance of the result is unclear, especially in the absence

of assessments of functioning. Because one of the three published randomized controlled studies was a dose finding study and not really a pivotal trial and most studies provide insufficient detail to evaluate the results thoroughly, more controlled research is needed to define the role of this novel medication in the treatment of depression.

3. Expert opinion

Because mood disorders are associated with desynchronization of circadian rhythms, interventions that resynchronize these rhythms have been thought for some time to be potential therapeutic agents for mood disorders. The best established application of this principle is the use of artificial bright light for seasonal depression. Exposure to bright light in the morning, which phase advances sleep, appears to be the most likely to be effective for winter depression associated with a sleep phase delay. It is possible that melatonin has not been shown to have antidepressant properties in humans because it was not administered in a manner that would correct an abnormal sleep–wake cycle, for example, by giving melatonin in the early evening to phase advance sleep in patients with a sleep phase delay. Agomelatine, therefore, is a combination of a new approach to depression that addresses circadian rhythms with a 'me too' approach to serotonin receptors utilized in existing antidepressants such as trazodone, nefazodone and mirtazepine. Future approaches might focus on the timing of medications whose only action is to alter biological rhythms, and specifically on whether the timing of administration of agomelatine influences its efficacy.

Symptom reductions reported with agomelatine are not substantially greater than those reported with currently available antidepressants, making it unlikely to be preferable in terms of efficacy to existing antidepressants as monotherapy. Despite approval by European agencies, the question arises whether the FDA will consider it to be a sufficient advance to warrant approval in the US. However, the beneficial effects of agomelatine on sleep and circadian rhythms may make it particularly useful for patients with insomnia and sleep phase shifts. Depressed patients with hypersomnia often feel tired even though they sleep excessively because slow wave sleep, which normally occurs earlier in sleep, is replaced by a phase advance of REM sleep. Agomelatine could have the potential to correct this problem and reinstitute restorative sleep. This medication could also have applications in other disorders associated with abnormal sleep such as fibrobyalgia and chronic fatigue syndrome. Agomelatine could also be helpful as adjunctive treatment for patients with a partial response to other antidepressants.

Lithium has also been found to treat both depression and mania, but it is not as effective for the former as are antidepressants. Electroconvulsive therapy is an effective treatment for both mania and depression, and although it sometimes induces mania further treatments usually eliminate emergent mania. In contrast, there is nothing in the pharmacologic or clinical profile of agomelatine to suggest that it would not have the potential to aggravate bipolar mood disorders in long-term treatment. Because medications with 5-HT_2 antagonist properties may also have antipsychotic actions and ameliorate adverse effects of dopamine D_2 receptor blockade, agomelatine could prove effective in combination with antipsychotic drugs in the treatment of psychotic depression.

Research in the pathophysiology and pharmacotherapy of depression is moving away from neurotransmitter and receptor targets and is beginning to focus on second messengers, neurogenesis, synaptic plasticity and epigenetic factors that affect basic neuronal function [12]. Extending this research to new medications such as agomelatine may reveal other actions that could predict additional applications. As is true of other antidepressants, the known actions of this medication are probably not its only actions. Any new medication should be subjected to more extensive studies of its intracellular actions. Manufacturers are often not motivated to support such research once a medication is approved, but studies of actions beyond receptors are taking place.

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Declaration of interest

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Bibliography

1. Dubovsky SL, Dubovsky AN. Concise guide to mood disorders. Washington, DC: American Psychiatric Press; 2002
2. Anderson I, Ferrier IN, Baldwin RC, et al. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2000 British Association for Psychopharmacology Guidelines. J Psychopharmacol 2008;22:343-96
3. Bauer M, Whybrow PC, Angst J, et al. World Federation of Societies of Biological Psychiatry (WFSBP) Task Force on Treatment Guidelines for unipolar depressive disorders. Part 2: maintenance treatment of major depressive disorder and treatment of chronic depressive disorders and subthreshold depression. World J Biol Psychiatry 2002;3:69-86
4. Krishnan V, Nestler EJ. The molecular neurobiology of depression. Nat Insight 2008;455(7215):894-902
5. Dubovsky SL. Clinical guide to psychotropic medications. New York: WW Norton; 2005
6. Coryell W, Endicott J, Keller MB. Predictors of relapse into major depressive disorder in a nonclinical population. Am J Psychiatry 1991;148:1353-8
7. Barbui C, Hotopf M, Freemantle N, et al. Treatment discontinuation with selective serotonin reuptake inhibitors (SSRIs) versus tricyclic antidepressants (TCAs). Cochrane Database Syst Rev 2000;(4):CD002791
8. Clayton AH, Pradko JF, Croft HA, et al. Prevalence of sexual dysfunction among newer antidepressants. J Clin Psychiatry 2002;63:357-66
9. Gill HS, DeVane CL, Risch SC. Extrapyramidal symptoms associated with cyclic antidepressant treatment: a review of the literature and consolidating hypotheses. J Clin Psychopharmacol 1997;17:377-89
10. Lake MB, Birmaher B, Wassick S, et al. Bleeding and selective serotonin reuptake inhbitors in childhood and adolescence. J Child Adolesc Psychopharmacol 2000;10:35-8
11. Taylor D, Lader M. Cytochromes and psychotropic drug interactions. Br J Psychiatry 1994 1994;168(5):529-32
12. Millan MJ. Multi-target strategies for the improved treatment of depressive states: conceptual foundations and neuronal substrates, drug discovery and therapeutic application. Pharmacol Ther 2006;110:135-370
13. Hopkins AL. Network pharmacology: the next paradigm in drug discovery. Nat Chem Biol 2008;4:682-90
14. Morphy R, Kay C, Rankovic Z. From magic bullents to designed mujltiple ligands. Drug Discov Today 2004;9:641-52
15. Santarelli L, Saxe M, Gross C, et al. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science 2003;301:805-9
16. Shelton RC. Intracellular mechanisms of antidepressant drug action. Harv Rev Psychiatry 2000;8:161-74
17. Lader M. Limitations of current medical treatments for depression: disturbed circadian rhythms as a possible therapeutic target. Eur Neuropsychopharmacol 2007;17:743-55
18. Racagni G, Riva MA, Popoli M. The interaction between the internal clock and antidepressant efficacy. Int Clin Psychopharmacol 2007;22(Suppl 2):S9-14
19. San L, Arranz B. Agomelatine: a novel mechanism of antidepressant action involving the melatonergic and the serotonergic system. Eur Psychiatry 2008;23:396-402
20. Fuchs E, Simon M, Schmelting B. Pharmacology of a new antidepressant: benefit of the implication of the melatonergic system. Int Clin Psychopharmacol 2006;21(Suppl 1):S17-20
21. Lam RW. High-quality remission: potential benefits of the melatonergic approach for patients with major depressive disorder. Int Clin Psychopharmacol 2007;22(Suppl 2):S21-5
22. Zupancic M, Guilleminault C. Agomelatine. A preliminary review of a new antidepressant. CNS Drugs 2006;20:981-92
23. Audinot V, Mailliet F, Lahaye-Brasseur C, et al. New selective actions of human cloned melatonin Mt1 and Mt2 receptors. Naunyn Schmiedebergs Arch Pharmacol 2003;367:553-61
24. Millan MJ, Gobert A, Lejeune F, et al. The novel melatonin agonist agomelatine (S20098) is an antagonist at 5-hydroxytryptamine2C receptors, blockade of which enhances the activity of frontocortical dopaminergic and noradrenergic pathways. J Pharmacol Exp Ther 2003;306:954-64
25. Dolder CR, Nelson M, Snider M. Agomelatine treatment of major depressive disorder. Ann Pharmacother 2008;42:1822-31
26. Van Reeth O, Olivares E, Turek FW, et al. Resynchronisation of a diurnal rodent circadian clock accelerated by a melatonin agonist. Neuroreport 1998;9:1901-5
27. Gressens P, Schwendimann L, Husson I, et al. Agomelatine, a melatonin receptor agonist with 5-HT(2C) receptor antagonist properties, protects the developing murine white matter against excitotoxicity. Eur J Pharmacol 2008;588:58-63
28. Banasr M, Soumier A, Herv M, et al. Agomelatine, a new antidepressant, induces regional changes in hippocampal neurogenesis. Biol Psychiatry 2006;59:1087-96
29. Bertaina-Anglade V, la Rochelle CD, Boyer PA, Mocaer E. Antidepressant-like effects of agomelatine (S 20098) in the learned helplessness model. Behav Pharmacol 2006;17:703-13
30. Loiseau F, Bihan CL, Hamon M, Thiebolt M-H. Effects of melatonin and agomelatine in anxiety-related procedures in rats: interaction with diazepam. Eur Neuropsychopharmacol 2006;16:417-28
31. Stein DJ, Ahokas AA, de Bodinat C. Efficacy of agomelatine in generalized anxiety disorder. A randomized, double-blind, placebo-controlled study. J Clin Psychopharmacol 2008;28:561-6
32. Loo H, Hale D, D'Haenen H. Determination of the dose of agomelatine, a melatoninergic agonist and selective 5-HT(2C) antagonist, in the treatment of major depressive disorder: a placebo-controlled dose range study. Int Clin Psychopharmacol 2002;17:239-47
33. Loo H, Dalery J, Macher J-P, Payen A. Blind pilot study comparing the therapeutic effect of two doses of agomelatine, an agonist of melatonin and antagonist of 5HT(2C) receptors, in 30 patients presenting with a major depressive episode. Encephale 2003;29:165-71
34. Olie JP, Kasper S. Efficacy of agomelatine, a MT1/MT2 receptor agonist with 5-HT-2C antagonistic properties, in major depressive

disorder. Int J Neuropsychopharmacol 2007;10:661-73

35. Montgomery S, Kasper S. Severe depression and antidepressants: focus on a pooled analysis of placebo-controlled studies on agomelatine. Int Clin Psychopharmacol 2007;22:283-91
36. Kennedy SH, Rizvi S, Fulton K, Rasmussen J. A double-blind comparison of sexual functioning, antidepressant efficacy, and tolerability between agomelatine and venlafaxine XR. J Clin Psychopharmacol 2008;28:329-33
37. Lemoine P, Guilleminault C, Alvarez E. Improvement in subjective sleep in major depressive disorder with a novel antidepressant, agomelatine: randomized, double-blind comparison with venlafaxine. J Clin Psychiatry 2007;68:1723-32
38. Calabrese J, Guelfi JD, Perdrizet-Chevallier C. Agomelatine adjunctive therapy for acute bipolar depression: preliminary open data. Bipolar Disord 2007;9:628-35
39. Pjrek E, Winkler D, Praschak-Rieder N, Kasper S. Agomelatine in the treatment of seasonal affective disorder. Psychopharmacology 2007;190:575-9
40. Leproult R, Van Onderbergen A, L'Hermite-Baleriaux M, et al. Phase-shifts of 24-h rhythms of hormonal release and body temperature following early eventing administration of the melatonin agonist agomelatine in healthy older men. Clin Endocrinol 2005;63:298-304
41. Salva M-A, Vanier B, Laredo J, et al. Major depressive disorder, sleep EEG and agomelatine: an open-label study. Int J Neuropsychopharmacol 2007;10:691-6
42. Lopes MC, Quera-Salva MA, Guilleminault C. Cyclic alternating pattern in the NREM sleep of patients within major depression disorder: baseline results and change overtime with a new antidepressant: agomelatine. Sleep Med 2005;6(Suppl 2):87-8
43. Montgomery S, Kennedy SH, Burrows GD, et al. Absence of discontinuation symptoms with agomelatine and occurrence of discontinuation with paroxetine: a randomized, double-blind, placebo-controlled discontinuation study. Int Clin Psychopharmacol 2004;19:271-80
44. Golino P, Piscione F, Benedict CR, et al. Local effect of serotonin released during coronary angioplasty. N Engl J Med 1994;330:523-8
45. Kyriakides ZS, Sbarouni E, Antoniadis A, Kremastinos DT. Intracoronary ketanserin augments coronary collateral blood flow and decreases myocardial ischemia during baloon angioplasty. Cardiovasc Drugs Ther 1999;13:415-22
46. Serruys PW, Klein W, Tijssen JP, et al. Evaluation of ketanserin in the prevention of restensosis after percutaneous transluminal coronary angioplasty. A multicenter randomized double-blind placebo-controlled trial. Circulation 1993;88:1588-601

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