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EXPERT OPINION



# Agomelatine: a new option for treatment of depression?

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A number of diverse antidepressants with different mechanisms of action are available today. However, the mechanisms of action of US FDA-approved antidepressants still mainly rely on targeting monoamine neurotransmitters. The inadequate remission and response rates achieved by antidepressant treatment for depression have been well known through a number of manufacturer-sponsored randomized, placebo-controlled, clinical trials (RCTs), independent RCTs, some large practical clinical trials and many meta-analyses. In the light of the limited efficacy of currently available antidepressants and the need for an antidepressant with a novel mechanism of action, the availability of agomelatine is prudent and timely for clinical practice. Although agomelatine has been approved for the treatment of depression in Europe and some other countries, its clear efficacy has been questionable based on results from individual RCTs and meta-analyses. However, agomelatine may be more beneficial in specific populations such as those who suffer from unwanted adverse events (AEs) (i.e., sexual dysfunction) by current antidepressants or elderly populations who are vulnerable to AEs. Based on currently available findings, agomelatine may not be recommendable as the first-line antidepressant for treating depression; especially, its putative benefits compared with other antidepressants must be thoroughly studied in adequately powered and well-designed future clinical trials.

**Keywords:** agomelatine, depression, efficacy, first-line treatment, novel mechanism

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## 1. Background

Currently, the biological treatment for major depressive disorder (MDD) is primarily antidepressants such as selective serotonin reuptake inhibitors (SSRIs), dopamine–norepinephrine reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors (SNRIs) and noradrenergic and specific serotonin antagonists, all of which are based on the monoamine hypothesis [1]. Previous placebo-controlled clinical studies and the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) and Combining Medications to Enhance Depression Outcomes trials have clearly demonstrated limited therapeutic outcomes of antidepressant treatments in patients with MDD. Specifically, lower response (or remission) and higher relapse rates were observed in patients who required additional treatment steps in the STAR*D trial. Thus, most treatment guidelines recommend that nonresponders or partial responders should be considered for a switch, combination, or augmentation of treatment based on the patient's clinical situation.

Multiple monoamines, such as serotonin, norepinephrine and dopamine, are thought to be related to the pathophysiology of depression and, as such, are relevant targets for pharmacological intervention for depression [1]. This hypothesis has provided the rational for the development of medications that enhance neurotransmission of all three systems in an effort to provide reliable efficacy and a rapid therapeutic effect [1]. Thus, triple reuptake inhibitors (TRIs) have been also

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proposed as a viable treatment for depression. Although no TRI has yet been approved, it is possible that such drugs may have a greater side-effect burden than selective agents, without improving efficacy. The monoamine theory has many limitations, and several mechanisms, including hypothalamic–pituitary–adrenal axis dysfunction and neurodegenerative and inflammatory alterations, may be associated with the pathogenesis of mood disorders [1].

In view of the limited efficacy of currently available antidepressants and the need for an antidepressant with a novel mechanism of action, the emergence of agomelatine is a timely development. Agomelatine is a novel melatonin-MT1 and MT2 receptor agonist and 5-HT2C receptor antagonist that has chronobiotic, antidepressant and anxiolytic effects but has no effect on monoamine reuptake and no affinity for α, β-adrenergic, histaminergic, cholinergic, dopaminergic and benzodiazepine receptors, based on binding studies [2].

## 2. Clinical development

Agomelatine was approved for the treatment of MDD in Europe and Australia in 2009 and 2010, respectively. However, clinicians should note that agomelatine approval was twice rejected by the European Medicines Agency's Committee for Medical Products for Human Use because of its weak efficacy compared with placebo, although adverse effects were not of particular concern. The rights to market agomelatine in the USA were sold by Servier to Novartis in 2006, but the development phase was discontinued in October 2011, although it was scheduled for submission to the FDA no earlier than 2012.

Typical therapeutic doses in these trials are 25 – 50 mg of agomelatine. According to the results from 6 to 8 weeks registration trials of agomelatine (25 – 50 mg/day) for MDD [3-5], agomelatine demonstrated its efficacy and safety for treating MDD compared to placebo treatment (last observation carried forward [LOCF] in the intent-to-treat); the differences of the primary end point of Hamilton Depression Rating Scale (HAMD) between agomelatine and placebo ranged from 2.4 to 3.4, favoring agomelatine. In addition, the differences in response and remission rates between agomelatine and placebo ranged from 14.8 to 19.0% and from 7.5 to 15%, respectively, favoring agomelatine. However, here is the hidden aspect in the efficacy of agomelatine: among 10 RCTs with various doses (1 – 25 mg/day) of agomelatine, 5 RCTs gave negative results (and unpublished) and one trial yielded inconclusive results in terms of the primary end points [6]. This is a crucial issue in antidepressant trials, as several studies have illustrated the strong influence of publication bias on the overall estimates of treatment effect, and this may also apply to agomelatine trials [6,7].

It is hard to determine the relative efficacy of newly approved antidepressant before conducting double-blind parallel comparisons against the major classes of existing antidepressants such as the SSRIs and the SNRIs. According to the recent pooled analysis of direct comparison of agomelatine with escitalopram, fluoxetine, sertraline and paroxetine [8] (n = 1997), the difference was ~ 1 point (0.86) on the LOCF reduction in HAMD score favoring agomelatine over comparators (p = 0.013). In addition, the difference in response rate between agomelatine and comparators was also significantly different (71 vs 66%). Although they did not present the difference in remission rate between agomelatine and comparators in the paper [8], unfortunately it was not significantly different. In addition, they did not include all available studies indicating a selected pooled analysis.

In the recent 8 weeks study [9], agomelatine was tested in 222 elderly patients for 8 weeks compared with placebo. The difference in reduction of the HAMD score between agomelatine and placebo was 2.8 with statistical significance favoring agomelatine over placebo; the response rate was also significantly higher in agomelatine (59.5%) than placebo (38.6%) but the remission rate was not (magnitude of difference = 6.9%).

Recently, *post-hoc* analyses of agomelatine RCTs have been continuously published. Kasper and Hajak [10] compared two clinical trials (placebo or sertraline-controlled studies) in terms of pretreated versus untreated patients with MDD. In the study, 277 patients were reanalyzed and the mean decrease in the total score on the HAMD over 6 weeks was significantly greater with agomelatine than placebo (difference = 4.435) and 67.5% of patients were responders; however, they were not significantly different in the sertraline-controlled study. These results may present some degree of potential of agomelatine for treating previously treated patients, those who have difficulty in reaching satisfactory improvement in depression symptoms. In the *post-hoc* study with three registered RCTs [11], agomelatine was also statistically superior to placebo in treating patients suffering from severe depression by diverse criteria on the severity; however, we have to note that the pool of only three registered RCTs may give selection bias and also included only 295 and 296 patients for agomelatine and placebo, respectively. Another recent study [12] pooled and reanalyzed results from four trials with identical design where the acute phase, head-to-head study (agomelatine vs fluoxetine, escitalopram and sertraline) had an extension phase up to 6 months (agomelatine n = 627, SSRIs n = 635). In the study, the overall difference between two groups was 1.08 and 1.01 points, favoring agomelatine over SSRIs in the whole patients and the subgroup of patients with severe depression; however, the remission rate was not significantly different between the two groups (4.1 and 2.3% difference in the whole and the subgroup of patients with severe depression, respectively, favoring agomelatine), while the difference in the response rate was statistically marginally superior in agomelatine than in SSRIs (5.1 and 5.1% difference in the whole and the subgroup of patients with severe depression, respectively). The study completion rate and adverse events rate were not different between agomelatine and SSRIs treatment.

Recently, meta-analyses avoiding such publication bias have been continuously published. The first meta-analysis of agomelatine, which involved 3943 patients with severe MDD, showed weak efficacy of the drug compared with the placebo [13]. The analysis revealed that agomelatine was only marginally superior to the placebo, with a small magnitude effect size (ES = -0.26) difference. Moreover, agomelatine was only marginally superior (ES = -0.11) to other antidepressants as a whole (paroxetine, fluoxetine, sertraline, venlafaxine) and was not superior to any individual comparator antidepressant. Howland [14] argued that agomelatine was statistically, but not clinically, superior to the placebo. He stated that, due to its pharmacological characteristics and tolerability profile, agomelatine should be considered only as an alternative treatment for patients who do not respond to or cannot tolerate other antidepressant drugs. These criticisms were confirmed in the most recent meta-analysis, which included the data from all published and unpublished clinical trials to avoid publication bias [6]. This meta-analysis found that acute treatment with agomelatine showed a statistically significant improvement compared with the placebo (-1.5 points difference [99% confidence interval (CI): -2.29, -0.73]); however, the clinical relevance of this small effect is questionable. The analysis of response, remission and relapse rates revealed that agomelatine was statistically superior to the placebo in terms of response rates but no difference was found in relapse or remission rates. The difference in response rates corresponded to an absolute risk difference of 6% and to a number needed-to-treat (NNT) of 15; the NNT is smaller than those found for other newly approved antidepressant, repetitive transcranial magnetic stimulation and atypical antipsychotic augmentation for treating MDD. In a study of regulatory submissions for SSRIs and SNRIs between 1984 and 2003, Melander *et al.* [15]. found that the overall responder difference between antidepressants and placebo was 16% (95% CI: 12, 20). He argued that statistically significant mean differences versus placebo in HAMD score change is not an appropriate basis for evaluation of clinical relevance and is not sufficient for approval [15]. Further, a recent German study [16] found that agomelatine had the potential to cause severe forms of hepatotoxicity and warned that preexisting liver disease is a contraindication for agomelatine treatment, and that increased age, female sex and polypharmacy may be risk factors for agomelatine-related hepatotoxicity [16]; in the recent pooled study of four agomelatine dosages [12], significant emergent transaminase increases (> 3 times the upper limit of normality) were found in 0.3% of patients treated with SSRIs (n = 2), in 1.8% of patients treated with agomelatine 25 mg (n = 8) and in 2.6% in patients treated with agomelatine 50 mg (n = 4).

## 3. Expert opinion

Given the limited efficacy of the available SSRIs and SNRIs and the need for new antidepressants with a novel mechanism of action, agomelatine may be considered as another treatment option for MDD. The circadian system, sleep homeostasis and core stress system, all of which are related to the regulation of mood, are crucial to the current understanding of MDD. Disturbances in circadian rhythms have been associated with MDD and may be an underlying mechanism for the disorder [17]. Thus, resynchronization of circadian rhythms by manipulating melatonin secretion may serve as a new therapeutic approach to MDD. Melatonin is secreted at night and is a stable marker of circadian rhythms [18]. The timing of melatonin secretion can be altered by exogenous melatonin, agonism of specific melatonin receptors in the suprachiasmatic nucleus and its suppression by light and by sleep deprivation. The MT1 and MT2 receptor agonist and 5HT2c receptor antagonist properties of agomelatine make it a novel antidepressant and potential candidate for chronobiotherapy. Because chronobiology is an emerging concept in MDD, most practice guidelines do not address it in detail in relation to MDD yet. Chronotherapeutic recommendations are provisional and, at present, only bright light therapy for seasonal affective disorder is mentioned [19].

Recent findings indicate that epigenetic mechanisms, such as histone modifications and DNA methylation, may affect diverse pathways leading to depression-like behaviors in animal models [20]. Accumulating preclinical and clinical evidence supports a potential role for the *N*-methyl-D-aspartate (NMDA) antagonist ketamine as a 'proof-of-concept' agent for the treatment of depression [21]. In a recent randomized, double-blind, placebo-controlled clinical trial (RCT) [22], patients with treatment-resistant depression randomly received a single intravenous infusion of ketamine or midazolam in a 2:1 ratio (n = 73). The ketamine group showed greater improvement in the Montgomery–Åsberg Depression Rating Scale (MADRS) score than did the midazolam group 24 h after treatment. After adjustment for baseline scores and site, the MADRS score was lower in the ketamine group than in the midazolam group by 7.95 points (95% CI: 3.20 – 12.71). The likelihood of response at 24 h was greater with ketamine than with midazolam (odds ratio = 2.18; 95% CI: 1.21 – 4.14), with response rates of 64 and 28%, respectively. Robust and rapid NMDA antagonist-induced improvement in depression symptoms has been consistently reported in other well-designed clinical trials as well. Thus, insights into the mechanism of action and efficacy of agomelatine will improve, update and expand our current understanding of MDD. Recent data suggest that, in addition to its melatonin-regulating actions, agomelatine may have therapeutic effects in MDD via modulation of glutamatergic transmission in the hippocampus [23], neurogenesis (neuroplasticity) of the hippocampus and prefrontal cortex [24], antioxidative effects [25] and recovery of stress-induced major neurotransmitters disturbance [26].

Further, a recent study found that being a morning type at baseline was an independent predictor of response to treatment in MDD, which may be a trait variable. However, it is

not clear whether the morningness-eveningness construct is therapeutically useful yet [27]. Finally, some promising but exploratory clinical data has emerged supporting the use of agomelatine as a combination agent for difficult-to-treat patients with MDD, treating night eating behavior, anxiety disorders and the treatment of elderly patients because it is well tolerated.

Based on currently available data, the most crucial issues in efficacy of agomelatine in the treatment of MDD should be that none of the negative trials were published and the standardized effect size was more than three times higher in published than in unpublished trials, indicating a strong selection bias [6]. Further, in comparator studies, the remission rates were not different; failure to find difference in remission rates between agomelatine and placebo were also found in > 4 RCTs. Hence, the current agomelatine data need careful attention to interpret and generalize into clinical practice.

The clinical usefulness of agomelatine as a first-line treatment for MDD remains questionable at this point. The clinical relevance and a clear benefit of agomelatine for patients with MDD in comparison with other antidepressants have not been extensively studied till today. Hence, more adequately powered and advanced RCTs as well as more clinical experiences with agomelatine may prove the ultimate clinical usefulness of agomelatine for the treatment of MDD in clinical practice.

## Declaration of interest

C-U Pae states no conflict of interest. This study was supported by a grant of the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (A120004).

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