Agomelatine
A Preliminary Review of a New Antidepressant

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Abstract

Agomelatine is a new antidepressant that is a potent agonist of melatonin receptors and an antagonist of the serotonin 5-HT$_{2C}$ receptor subtype. It is in late-phase trials for the treatment of major depressive disorder (MDD).

Symptoms of depression significantly improved with agomelatine compared with placebo in large placebo-controlled trials, and agomelatine appears to be as efficacious in treating MDD as other antidepressants but with fewer adverse effects. Agomelatine appears to improve sleep quality and ease of falling asleep, as measured subjectively in depressed patients. Polysomnographic studies have shown that agomelatine decreases sleep latency, decreases wake after sleep onset (WASO), and improves sleep stability as measured by changes in the cyclic alternating pattern.

Agomelatine is generally well tolerated in patients with MDD; in clinical trials, adverse events were generally mild to moderate in nature, with an overall frequency close to that of placebo. Discontinuation of agomelatine because of adverse effects occurred at a similar rate to placebo.

Major depressive disorder (MDD) is a common disorder, with a lifetime prevalence of 16.6%, which is associated with significant morbidity and mortality.\textsuperscript{[1]} Although many individuals experience the disorder, only a small proportion of patients with MDD present for treatment. Older antidepressants such as the TCAs, although effective, have significant and sometimes life-threatening adverse effects that limit their use. The newer antidepressants such as the SSRIs tend to be better tolerated, but still have significant adverse effects, e.g. sexual dysfunction and nausea, which may limit compliance. Additionally, many antidepressants are associated with significant discontinuation symptoms that may ultimately compromise patient care.

Some symptoms of depression are thought to be related to the disorganisation of homeostatic rhythms. Many patients with depression have a blunted circadian rhythm, as demonstrated by abnormal 24-hour temperature curves and melatonin levels.\textsuperscript{[2-4]} In addition, 40–60% of outpatients with MDD report sleep disturbances, i.e. early morning awakenings and difficulties initiating and maintaining sleep.\textsuperscript{[5]} A new antidepressant would be advantageous if it were effective, had fewer adverse effects than currently available agents, and helped reorganise the body’s internal rhythms.
Agomelatine is a unique antidepressant that is currently in late-phase trials for MDD. It is a potent agonist of melatonin receptors and an antagonist of the serotonin 5-HT2C receptor subtype. This review summarises the pharmacology of agomelatine and the data on its efficacy and tolerability in the treatment of depression.

1. Pharmacodynamic Properties

1.1 Receptor Binding Profile

Agomelatine is a potent agonist of melatonin MT1 and MT2 receptors (inhibition constant [kI] = 6.15 × 10^{-11} and 2.68 × 10^{-10} mol/L, respectively). It is also an antagonist of the serotonin 5-HT2C receptor subtype (concentration that inhibits binding of a ligand by 50% [IC50] = 2.7 × 10^{-7} mol/L), which is concentrated in the frontal cortex, hippocampus and amygdala.

Agomelatine displays low affinity at native (rat)/cloned human 5-HT2A (kI <5.0/5.3 mol/L) and 5-HT1A (kI <5.0/5.2 mol/L) receptors, and negligible (kI <5.0 mol/L) affinity for other serotonin receptor subtypes. In binding studies of cloned human MT1 and MT2 receptors, agomelatine has similar affinity to that of melatonin (kI = 8.52 × 10^{-11} and 2.63 × 10^{-10} mol/L, respectively).

1.2 Effects on Neurotransmitter Levels

In vivo data indicate that agomelatine enhanced the levels of dopamine in the frontal cortex of freely moving rats, whereas these levels were unaffected in the nucleus accumbens and striatum. In vivo data show that extracellular levels of noradrenaline (norepinephrine) in the frontal cortex of rats were dose-dependently enhanced by agomelatine in parallel with acceleration in the firing rate of adrenergic cell bodies in the locus ceruleus. These increases in noradrenaline and dopamine levels are likely to reflect blockade of the inhibitory input of 5-HT2C receptors to frontocortical dopaminergic and adrenergic pathways.

1.3 Effects in Animal Models of Depression and Anxiety

Four published studies have evaluated the effect of agomelatine in animal models of depression, and several studies have been published evaluating the effects of the drug in animal models of anxiety.

Papp et al. evaluated the effects that agomelatine had on chronic mild stress, a rat model of depression. This study showed that administration of agomelatine at 10 or 50 mg/kg for 7 weeks counteracted the stress-induced decrease in sucrose consumption in a dose-dependent manner. This effect was noted whether agomelatine was administered in the morning or evening. The involvement of melatonin receptors in the antidepressant effect of agomelatine was suggested by the fact that concomitant administration of an MT1/MT2 receptor antagonist (S-22153) in the evening diminished the effects of agomelatine on rodent sucrose consumption. However, agomelatine still showed antidepressant activity when concomitantly administered with a melatonin receptor antagonist in the morning, suggesting its antidepressant qualities are mediated through both its agonist action at MT1/MT2 receptors and its antagonist action at 5-HT2C receptors, as shown by animal data. Additionally, the antidepressant-like activity of agomelatine was similar to the other antidepressants used in this study, imipramine and fluoxetine.

Millan et al. published a paper evaluating the effects of agomelatine on several rodent models of anxiety. The social interaction test consists of placing two rats together in a novel environment and measuring the active contact between the animals. In this test, doses of agomelatine of 2.5 and 10.0 mg/kg elicited a significant increase in the time devoted to active socialisation in pairs of animals, indicating...
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An anxiolytic effect. The Vogel conflict test is a test where water-deprived rats are exposed to electrical shocks while drinking water. Agomelatine (2.5–80.0 mg/kg) elicited an increase in punished responses, suggesting that it alleviates anxiety. In these two models of anxiety, agomelatine was found to have dose-dependent anxiolytic activities, with effects comparable to the benzodiazepine clorazepate.

Agomelatine also alleviated anxiety in the plus-maze test, another rodent model of anxiety.\(^{[14]}\) This test consists of placing rodents in the centre of a maze-like structure and recording how frequently they explore different arms of the maze. Agomelatine evoked a modest increase of exploration at higher doses of 40 and 80 mg/kg, but with a less robust effect than clorazepate.\(^{[14]}\) Unlike clorazepate, agomelatine did not decrease levels of serotonin and noradrenaline in the hippocampus and frontal cortex of rats.\(^{[14]}\) These data suggest that the anxiolytic effects of agomelatine are mediated through a different mechanism than those of clorazepate.

1.4 Effects on Neurogenesis

Several clinical studies have shown that patients with stress-induced depression have reduced hippocampal volume.\(^{[16,17]}\) This reduction is thought to occur because of the loss or atrophy of glial and neuronal cells, potentially caused by increases in corticosteroids and excitatory amino acids secondary to stress. Although this has been demonstrated in animals, in humans it is currently still under investigation.\(^{[18,19]}\)

The dentate gyrus of the hippocampal formation is a site of continuous neurogenesis during adult life in humans and is involved in some form of learning and memory.\(^{[20]}\) In animal models, treatment with certain antidepressants can prevent or reverse some of these structural alterations. Remodelling of the hippocampal formation may be a factor in the development of depression and is the basis for the neuroplasticity hypothesis of major depression.\(^{[21]}\)

A recent study published by Banasr et al.\(^{[22]}\) has shown that chronic treatment with agomelatine (40 mg/kg for 3 weeks) increased cell proliferation and neurogenesis in the ventral dentate gyrus, a region implicated in the response to anxiety and emotion, in nonstressed rats. Chronic treatment with agomelatine also increased the survival of these newly formed cells. These findings suggest that the antidepressant and anxiolytic effects of agomelatine may be partially due to effects on the ventral dentate gyrus.

1.5 Effects on Circadian Rhythms in Animals

Because of the agonistic activity of agomelatine at MT\(_1\)/MT\(_2\) receptors, several studies using animal models have evaluated the effects of the drug on the circadian rhythm.

Redman et al.\(^{[23]}\) studied the effect of agomelatine in a rat model of phase advancement and found that it entrained the circadian rhythm similar to melatonin. Martinet et al.\(^{[24]}\) demonstrated that agomelatine entrained the circadian rhythm of freerunning rats to a similar degree to melatonin. Van Reeth et al.\(^{[25]}\) showed that the drug enhanced the ability of old hamsters to phase shift compared with controls. Agomelatine has also been found to advance the circadian rhythm in a rat model of the delayed sleep phase syndrome.\(^{[26]}\)

Overall, these animal studies demonstrate that agomelatine is able to resynchronise a disrupted circadian rhythm and has circadian phase-advancement properties. The chronobiotic effect of agomelatine is mediated through its effects on the suprachiasmatic nucleus via the M\(_1\) and M\(_2\) receptors,\(^{[27]}\) and the extent of the effect is similar to that of melatonin.\(^{[28]}\)
2. Pharmacokinetic Properties

2.1 Absorption and Distribution

Agomelatine is absorbed rapidly after oral administration, with the maximum plasma concentration being observed between 1 and 2 hours after administration. The absorbed fraction is >78%. In vitro, the plasma-to-blood concentration ratio of agomelatine is 1.5, showing a preferential distribution into plasma. In plasma, agomelatine is >95% protein bound irrespective of concentration and this is not modified by age or in patients with renal impairment. Under normal protein concentrations, albumin and α-1 acid glycoprotein contributed 35% and 36%, respectively, to the binding of agomelatine in whole blood. Agomelatine is moderately distributed throughout the body, with a volume of distribution at steady state of about 35L.

2.2 Metabolism and Elimination

Agomelatine is metabolised by the liver and the metabolites are excreted mainly in the urine. The drug is metabolised by 7-O-demethylation (leading to S-21517), hydroxylation (mainly leading to S-21540) and the formation of 3,4-dihydrodiodiol (S-22380). The metabolite S-21517 has about the same affinity for 5-HT2C receptors as agomelatine, while the S-22380 and S-21540 metabolites have no affinity for human 5-HT2C receptors. The S-21540 and S-21517 metabolites have an affinity for melatonin receptors that is at least 100-fold less than the parent drug (dissociation constant \( k_d \) being \( 1.14 \times 10^{-9} \) and \( 6.56 \times 10^{-8} \) mol/L, respectively). The S-22380 metabolite has a low affinity for melatonin receptors \( k_d = 7.98 \times 10^{-7} \) mol/L).\(^{29,30}\) These compounds represent approximately 61–81% of the dose excreted in urine over the first 24 hours. A smaller amount of agomelatine is excreted faecally after being metabolised to S-22380. The mean terminal elimination half-life of agomelatine is 2.3 hours.

Hepatic impairment drastically increased the systemic exposure to agomelatine in a single-dose study.\(^{31}\)

3. Therapeutic Efficacy

The efficacy of agomelatine in the treatment of depression has been investigated in several double-blind, randomised, placebo-controlled studies. Patients had to fulfill DSM-IV criteria for MDD (or bipolar II disorder [depressed]) in the study by Loo et al.\(^{32}\) to be eligible for these studies. In these studies, the primary endpoint evaluated was change in the 17-item HAM-D score from baseline. Secondary endpoints included changes in the Montgomery-Åsberg Depression Rating Scale (MADRS), the Clinical Global Impression-Severity of Illness (CGI-S) score, and HAM-D depressed mood and psychic anxiety item scores. Endpoints were assessed in the intention-to-treat (ITT) population using the last observation carried forward (LOCF) analysis in the observed cases (OC) population.

The antidepressant effects of agomelatine appear to be mediated mainly through its action as an antagonist at the 5-HT2C receptor subtype, although its agonist effect at MT1/MT2 receptors may also contribute to some of its antidepressant properties.\(^{7,10}\) Furthermore, because of its agonist activities at melatonin receptors (MT1 and MT2), agomelatine is a novel antidepressant in that it has been shown to affect circadian rhythms, sleep architecture, total sleep time and subjective sleep quality in human and animal studies (see section 3.2).

3.1 Major Depressive Disorder

3.1.1 Dose-Finding Study

Loo et al.\(^{33}\) performed a randomised, multicentre, double-blind, fixed-dose, 8-week trial in which 711 patients (mean age 42.3 years) received agome-
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Agomelatine, a new antidepressant, was studied in a randomized, double-blind, multicentre, flexible-dose, 6-week trial involving 212 outpatients (mean age 42.5 years). Subjects enrolled in the study had MDD of moderate to severe intensity (HAM-D score of >22) and were initially treated with either agomelatine 25 mg/day or placebo. If the depression failed to improve sufficiently after 2 weeks, the dosage of agomelatine or placebo was doubled (50 mg/day).

In this study, patients treated with agomelatine were significantly more likely to improve than those receiving placebo. Patients who received agomelatine (25 and 50 mg/day) had a significantly lower mean HAM-D score at the study endpoint compared with those who received placebo (14.1 ± 7.7 vs 16.5 ± 7.7).

The groups treated with lower dosages of agomelatine (1 and 5 mg/day) did not have significant decreases in anxiety compared with placebo, (p < 0.05, p = 0.004). The optimal dosage of agomelatine for the treatment of depression and used the established antidepressant paroxetine as a study validator.

Pivotal analysis demonstrated agomelatine 25 mg/day to be the optimal dosage for the treatment of MDD. Although there was a statistically significant difference in the mean HAM-D final score between all three dosages of agomelatine and placebo (p = 0.037), subsequent complementary analyses showed that only agomelatine 25 mg/day was clearly more effective than placebo. Compared with the paroxetine and placebo groups, there was a higher number of responders in the agomelatine 25 mg/day group (56.3% vs 46.3% vs 61.5%, respectively; responders defined as those patients having a HAM-D improvement of ≥50% compared with baseline). Both the paroxetine and agomelatine 25 mg/day groups achieved significantly higher rates of remission than the placebo group (25.7% [p < 0.05], 30.4% [p < 0.01] and 15.4%, respectively; remission was defined as a HAM-D at study end of <7), with the highest percentage of patients achieving remission being in the agomelatine 25 mg/day group.

This study also demonstrated that agomelatine 25 mg/day is clinically effective shortly after initiating treatment. After 2 weeks of treatment, patients receiving this dosage of agomelatine had a significant decrease in mean HAM-D total scores compared with patients receiving placebo. In contrast, patients required 4 weeks of treatment with paroxetine before achieving a statistically significant decrease in mean HAM-D total scores compared with placebo.

Agomelatine at a dosage of 25 mg/day also appeared to be effective in treating anxiety associated with depression, as demonstrated by reductions in the Hamilton Anxiety Rating Scale. Patients treated with agomelatine 25 mg/day and those treated with paroxetine achieved significant reductions in anxiety compared with placebo, (p < 0.05, p = 0.004). The groups treated with lower dosages of agomelatine (1 and 5 mg/day) did not have significant decreases in anxiety compared with placebo.

In summary, the study by Loo et al. determined that agomelatine 25 mg/day was the optimal antidepressant dosage tested. At this dosage, depressed patients taking agomelatine were significantly more likely to achieve remission or have a good clinical response than those receiving placebo, showed an antidepressant response within 2 weeks of initiating treatment (and more quickly than those receiving paroxetine), and had a reduction in anxiety associated with depression to a similar degree as patients taking paroxetine.

3.1.2 Additional Therapeutic Studies

Kennedy and Emsley evaluated the effect of agomelatine compared with placebo in treating depression in a randomised, double-blind, multicentre, flexible-dose, 6-week trial involving 212 outpatients (mean age 42.5 years). Subjects enrolled in the study had MDD of moderate to severe intensity (HAM-D score of >22) and were initially treated with either agomelatine 25 mg/day or placebo. If the depression failed to improve sufficiently after 2 weeks, the dosage of agomelatine or placebo was doubled (50 mg/day).

In this study, patients treated with agomelatine were significantly more likely to improve than those receiving placebo. Patients who received agomelatine (25 and 50 mg/day) had a significantly lower mean HAM-D score at the study endpoint compared with those who received placebo (14.1 ± 7.7 vs 16.5 ± 7.7).

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Additionally, the percentage of responders at week 6 (patients who showed a HAM-D score decrease of ≥50%) was significantly higher in the agomelatine group compared with the placebo group (49.1% vs 34.3%, respectively; p = 0.03).\[34\] Severely depressed patients (defined as having a baseline HAM-D score of ≥25) had a significantly higher percentage of responding following treatment with agomelatine than placebo (48.7% vs 30.7%, respectively; p = 0.024) at 6 weeks.\[34\] The rate of response to agomelatine in this study was comparable to that reported in a meta-analysis of 32 trials of TCAs (46%).\[35\]

In patients who did not respond to agomelatine 25 mg/day (37%), increasing the dosage to 50 mg/day did significantly improve their depression. This was demonstrated by significant improvements in the HAM-D score at week 6 in the agomelatine 25–50 mg/day patient group (from 26.1 ± 2.6 at baseline to 17.5 ± 7.4) compared with the ‘increased placebo’ group (26.7 ± 2.8 to 20.4 ± 6.0; p = 0.045).\[34\] With regard to achieving a full remission (as defined by HAM-D total score <6), at the conclusion of the study patients treated with agomelatine were more likely to reach this endpoint than those receiving placebo (20.8% vs 13.3%); however, this was not a statistically significant difference (p = 0.152).\[34\]

Several secondary measures of depression also demonstrated that agomelatine alleviated depression more effectively than placebo. The CGI-S scores improved significantly in patients treated with agomelatine (4.8 ± 0.7 to 3.2 ± 1.3) compared with placebo (4.8 ± 0.07 to 3.6 ± 1.3) at week 6 (p = 0.017). Although the CGI-Improvement scores tended to improve in patients treated with agomelatine compared with those treated with placebo, this did not reach statistical significance.\[34\]

In summary, Kennedy and Emsley\[34\] demonstrated that treatment with agomelatine 25 mg/day was more effective than placebo in treating depression. Additionally, increasing the dosage of agomelatine to 50 mg/day appeared to be effective and well tolerated in patients whose symptoms failed to show improvement after 2 weeks on a dosage of 25 mg/day.

In another study published by Kennedy\[36\] the efficacy and adverse effect profile of agomelatine versus venlafaxine in the treatment of depression was evaluated. This was a 12-week, multicentre, double-blind, randomised study, which involved 277 patients (age range 18–60 years). Patients had to meet the DSM-IV criteria for MDD (MADRS score ≥20) and were given either agomelatine 50 mg/day for the duration of the study, or a sustained release formulation of venlafaxine at a dosage of 75 mg/day for 2 weeks and then 150 mg/day for the remaining 10 weeks.

With regards to clinical efficacy, this study demonstrated that patients with MDD who underwent 12 weeks of treatment with agomelatine 50 mg/day or venlafaxine 150 mg/day had similar rates of response (82.5% and 79.9%, respectively; responders defined as those achieving a 50% reduction from baseline MADRS score). Additionally, patients in each group achieved similar rates of stable remission at week 12 (78 of 137 [57%] vs 83 of 140 [59%] subjects, respectively; stable remitters were defined as those patients who were responders [50% reduction from baseline MADRS score] at week 10 and who had a MADRS score of ≤12 at week 12).\[36\]

Guilleminault\[37\] reported on the effects of agomelatine versus venlafaxine on depression and subjective sleep (onset and quality) in patients treated as outpatients for MDD (n = 332). In this 6-week, double-blind, randomised, multicentre study, subjects received agomelatine 25 mg/day or venlafaxine 75 mg/day for 2 weeks; the dosages were increased to 50 mg/day or 150 mg/day, respectively, after week 2 for the duration of the study if symptoms had not resolved.\[37\] This study showed that
treatment of depressed patients with either agomelatine 50 mg/day or venlafaxine 150 mg/day resulted in comparable antidepressant efficacy after 6 weeks of treatment (final HAM-D score 9.9 ± 6.6 and 11.0 ± 7.4, respectively).[37]

In summary, these studies show that agomelatine is an effective antidepressant, with similar response and remission rates to several other antidepressants. Increasing the dosage of agomelatine from 25 mg/day to 50 mg/day is effective in treating patients with refractory depression several weeks after initiating treatment.

3.2 Effects on Sleep/Circadian Rhythm

Agomelatine is a unique antidepressant in that it has been shown to affect sleep differently from any other antidepressant. This is thought to occur because of its agonist interaction with the MT1 and MT2 receptors. Five published studies have reviewed the effects of agomelatine on human sleep and the circadian rhythm.[37-41]

In the already mentioned study of Guilleminaul,[37] comparing agomelatine to venlafaxine (see section 3.1.2), patients treated with agomelatine reported significant improvements in ‘getting to sleep’ (p = 0.007) and ‘quality of sleep’ (p = 0.015) as assessed by the Leeds Sleep Evaluation Questionnaire (LSEQ) compared with patients taking venlafaxine. These changes were noted 1 week after treatment was initiated and remained statistically significant for the duration of the study.

Cajochen et al.[38] evaluated the effects of agomelatine on sleep architecture in a small, crossover study utilising polysomnography. In this single-dose study, eight healthy nondepressed men (mean age 23–32 years) received agomelatine 5 or 100 mg before bedtime, and reported significantly increased rapid eye movement (REM) sleep with no effect on other stages of sleep.

Leproult et al.[39] published a randomised, double-blind, placebo-controlled, two-period, crossover study evaluating the effect of agomelatine on the circadian rhythm and sleep parameters of healthy, nondepressed older men (n = 8, mean age 60 years). This study demonstrated that evening administration of agomelatine affects the circadian rhythm. In this study, patients received daily treatment for 15 days with either agomelatine 50mg or placebo. The medication was administered at 1830 hours and parameters assessing circadian rhythm were analysed over a 24-hour period. Following evening administration of agomelatine, a phase advancement of nearly 2 hours was observed for body temperature and phase advances of 1.5–2.0 hours were noted for cortisol secretion. This study clearly demonstrated that evening administration of agomelatine advances the circadian rhythm as measured with several physiological variables. Sleep parameters measured by polysomnography, including total sleep time and sleep stages, were not significantly affected in this study.

Additionally, Leproult et al.[39] showed that patients treated with agomelatine had increased growth hormone secretion during the wake period, with levels changing from 155 ± 41μg while patients were receiving placebo to 295 ± 75μg while receiving agomelatine. The clinical effects of the increase in growth hormone level are unknown, but theoretically the increase may have beneficial effects on metabolic variables dependent on the growth hormone axis, such as muscle strength and bone metabolism.

Quera-Salva et al.[40] evaluated the effects of agomelatine on sleep architecture and other sleep parameters in patients with MDD. This study involved 15 outpatients (mean age 36 years) who were treated with agomelatine 25mg at bedtime. Sleep architecture and other sleep parameters were measured by polysomnography, while subjective sleep perception was evaluated by the LSEQ. After 42 days of treatment with agomelatine, sleep efficiency increased by 4% (95% CI 0.03, 8.69), and wake after
Sleep onset (WASO) decreased from 42 to 19 minutes. Slow-wave sleep increased by 16 minutes (95% CI 1.79, 26.06) and no changes were noted in REM sleep. Subjectively patients felt their sleep had improved with respect to ‘sleep quality’ and ‘easiness falling asleep’. These changes were recorded 7 days after initiation of agomelatine and lasted for the duration of the study.

Lopes and colleagues[^41] reported on the effect of 42 days of treatment with agomelatine 25 mg/day on the cyclic alternating pattern (CAP) in non-REM (NREM) sleep (measured by polysomnography) in 15 depressed patients. CAP was measured at baseline and compared with CAP measured in 15 matched controls, and also compared to results obtained at night 7 and night 42 of agomelatine treatment. This study revealed a significant decrease in CAP time and CAP cycle after 7 and 42 nights of treatment with agomelatine compared with the baseline night. A trend toward a further decrease of CAP rate was seen between night 7 and night 42. At day 42, comparison of CAP rate, CAP time and distribution of phases A between controls and subjects with MDD were not significantly different, as opposed to what was present at baseline. These findings suggest that agomelatine normalises NREM sleep in depressed patients.

In summary, agomelatine had a significant impact on the sleep of patients with MDD, and this effect was seen very early after administration of the drug. As early as 7 days after administration, the changes in CAP (indicated by the change in CAP rate and by the change in the percentage of phase A subtypes of CAP, factors indicative of sleep disruption) returned to the values observed in control subjects. This suggests normalisation of NREM sleep.[^41] Sleep efficiency was significantly improved by day 14, and all studied variables were significantly improved by day 42. The changes in NREM sleep variables preceded the improvements seen on the 17-item HAM-D obtained in the study.

These changes are of interest for several reasons. First, they indicate that agomelatine has an action on NREM sleep that occurs soon after starting the medication. There is a change of sleep structure, with a more consolidated sleep seen within 7 days of starting the medication, as shown by the CAP study.[^41] The changes seen on polysomnography correlate with the subjective improvement of sleep and improvement of LSEQ scores. The use of two visual analogue scales that assessed daytime alertness in the study of venlafaxine versus agomelatine indicated less daytime sleepiness in patients tested with agomelatine compared with patients treated with venlafaxine at all post-baseline visits. Interestingly, the disappearance of the NREM sleep disruption precedes improvements in subjective mood (as demonstrated by improvement in the HAM-D score), suggesting that a component of the antidepressant effect of agomelatine is mediated through its ability to improve sleep structure. Although the subjective results of sleep improvement were noted in several larger double-blind comparative investigation trials, the results of the studies that evaluated sleep architecture must be viewed cautiously as the polysomnographic study reported above was an open study and involved a small group (n = 15) of patients, and the CAP evaluation was performed blind and evaluated only 15 patients.

### 4. Tolerability

Agomelatine was generally well tolerated, with a good safety profile in clinical trials. Adverse effects in patients receiving agomelatine occurred at a similar rate to those in patients receiving placebo.

In the dose-finding study by Loo et al.,[^33] the frequency of adverse effects such as anxiety, headache, abdominal pain and diarrhoea in patients treated with agomelatine was statistically similar to that in patients receiving placebo. In the reported adverse effects there were no significant increases for a given adverse effect in patients treated with...
Agomelatine compared with those treated with placebo. Patients who reported at least one emergent adverse event were slightly less numerous in the agomelatine 25 mg/day (51%) and placebo (54.7%) groups than in the paroxetine (66.0%) group, indicating that agomelatine may be better tolerated than paroxetine. Additionally, the discontinuation rate in the agomelatine 25 mg/day group (8.0%) was similar to that in the placebo group (6.5%).[33]

In the study by Kennedy and Emsley,[34] dizziness, nasopharyngitis and influenza were more commonly reported in patients treated with agomelatine than placebo (9.3% vs 4.8%, 6.5% vs 3.8%, and 6.5% vs 2.9%, respectively), although none of these differences was statistically significant. However, headache, nausea, fatigue, dry mouth and diarrhoea occurred more frequently in the placebo group. Severe treatment-related adverse events were reported by two patients in the agomelatine group (one case of dizziness and one of pruritus) and by six patients in the placebo group.

Another study by Kennedy[36] evaluated the sexual side effects of agomelatine utilising the Sex Effects Scale in 111 sexually active patients treated for depression. Sexual dysfunction with respect to a desire-arousal factor occurred in a significantly lower percentage of patients treated with agomelatine than treated with venlafaxine 150 mg/day (20% vs 41.2%, respectively; p = 0.015).[36] In addition, a significantly lower number of patients treated with agomelatine complained of orgasm dysfunction as compared with those treated with venlafaxine (20% vs 47%, respectively; p < 0.002). However, this study did not report if the sexual dysfunction reported in the agomelatine or venlafaxine groups reflected emergent or residual symptoms.

In summary, agomelatine appears to be well tolerated in patients with depression, with an adverse effect profile similar to that of placebo. In all treatment studies, there were no reported cases of serotonergic syndrome in patients taking agomelatine.

4.1 Discontinuation Symptoms

One study evaluated discontinuation symptoms when patients abruptly stopped taking agomelatine.[42] This was a double-blind, placebo-controlled, multicentre study that involved 192 patients receiving either agomelatine 25 mg/day or paroxetine 20 mg/day (mean age 42.55 years). Patients received either active medication or placebo during the discontinuation portion of the study. Discontinuation symptoms were measured 1 and 2 weeks after abruptly stopping 12 weeks of treatment. Of the 88 patients in the agomelatine group, 27 were randomised to have agomelatine discontinued. Forty-three of the 104 patients treated with paroxetine were randomised for medication discontinuation. Patients were eligible for the study if they had initially fulfilled the DSM-IV diagnostic criteria for MDD and had mild to moderate depression as determined by an entry MADRS score of 18–27. Furthermore, patients must have achieved sustained remission during the 12-week treatment period. Discontinuation symptoms were assessed by the total number of discontinuation emergent signs and symptoms (DESS) occurring in the first and second week after discontinuing the antidepressant.

No statistically significant difference in the number of emergent discontinuation symptoms was seen 1 week after treatment interruption between patients discontinuing agomelatine and those continuing agomelatine (3.0 ± 4.2 and 4.4 ± 5.7, respectively; p = 0.250). In contrast, patients discontinuing paroxetine experienced significantly more symptoms than those continuing paroxetine (7.3 ± 7.1 and 3.5 ± 4.1, respectively; p < 0.001).[31] Two weeks after treatment interruption, there were no statistically significant differences in the number of observed emergent discontinuation symptoms between patients discontinuing agomelatine and those continuing
agomelatine (2.0 ± 2.3 and 3.0 ± 4.4, respectively; \( p = 0.312 \)). However, discontinuation symptoms were more prevalent in patients who stopped paroxetine compared with those continuing paroxetine (6.5 ± 6.1 and 3.3 ± 3.2, respectively; \( p = 0.004 \)).\[21\] No emergent serious adverse events occurred in either group during the discontinuation period.\[21\] Additionally, relapse rates were not significantly higher in the subjects discontinuing treatment of agomelatine compared with those who continued taking the medication.\[21\] This study clearly indicates that patients who abruptly discontinue agomelatine do not experience significant discontinuation symptoms.

5. Conclusion

Agomelatine appears to be an effective antidepressant with a unique mechanism of action. It is reported to be well tolerated and, according to comparative trials, to have an adverse effect profile that is related to traditional and some newer antidepressants, specifically venlafaxine and paroxetine, although adverse effects appear to be less frequent than with these other agents. Additionally, agomelatine has positive effects on subjective reports of sleep quality and shortens sleep latency. Agomelatine has been shown to affect sleep architecture, as scored by the traditional polysomnographic staging of Rechtschaffen and Kales (as shown in the studies by Cajochen et al.\[38\] and Quera-Salva et al.\[40\]) and also improves the stability of NREM sleep as evaluated with usage of the more contemporary method of CAP scoring. The changes in sleep patterns seem to occur early after administration of the drug and precede the changes in HAM-D score. This is of clinical and theoretical interest, as there has been a suggestion that chronic sleep disruption and chronic insomnia can lead to depression; the demonstration that improvement of sleep precedes improvement of mood would be an important fact with potential therapeutic implications. However, the clinical effects of these sleep parameters require further investigation.

Despite these exciting and optimistic findings, the current published data on agomelatine are somewhat limited. Specifically, published information on efficacy and tolerability is only available from short-term trials; data from a 12-month study performed recently by the drug developer are not yet available. Also, although older subjects (up to 83 years of age) have been involved in trials, a specific study focusing only on the elderly has not yet been reported. Similarly, systematic investigation of the effects of agomelatine in children and teenagers aged 17 years and younger has not been published.

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