Agomelatine: a review for general practitioners

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Abstract

Agomelatine is a novel melatonergic antidepressant that restores disrupted biological rhythms, essentially by resetting the circadian clock. Two different, non-monoaminergic, and possibly synergistic pathways, appear to be involved in its mechanism of action. Agomelatine is a melatonin 1 (MT_1) and melatonin 2 (MT_2) receptor agonist and serotonin (5-hydroxytryptamine) 2C ($5\text{-}HT_{2C}$) receptor antagonist. It is effective in treating moderate-to-severe depression, alleviating the symptoms of anxiety, and restoring the disrupted sleep patterns that often result from this potentially devastating disease. Agomelatine is generally well tolerated with little, if any, propensity for antidepressant-induced sexual dysfunction, weight gain, or discontinuation reactions. However, it has the potential to cause temporary hepatotoxicity, and liver functions need to be monitored as a result. Clinically, meaningful drug interactions are unlikely, with the exception of co-administered potent cytochrome P 1A2 (CYP1A2) enzyme inhibitors, which may increase agomelatine's plasma levels significantly. Agomelatine represents an interesting addition to the antidepressant market.

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Introduction

Depression is a major disorder of mood, affecting approximately 340 million people worldwide. It is the third leading cause of burden from disease, and accounts for 4.5% of all human suffering.[1] The most recent estimated lifetime prevalence of major depression in South Africa is 9.7%, with a 12-month prevalence of 4.9%, which tends to be higher in women, than in men, as well as in those with a low level of education.[2] This chronic, debilitating, and sometimes fatal illness, is associated with considerable costs to patients, their families, and to society, and is often difficult to treat.

Traditional theories about the pathogenesis of depression include the monoamine hypothesis, which implicates a lack of noradrenaline and serotonin (5HT), and the receptor hypothesis, which proposes the upregulation of certain noradrenergic and serotonergic receptors, and their subsequent downregulation in response to treatment.[3,4] The two theories are not mutually exclusive, and have arisen from attempts to elucidate the mechanisms of action of serendipitously discovered, as well as more innovative antidepressants.

Most antidepressant agents act by increasing the availability of the monoamines at neuronal synapses, particularly in the locus coeruleus (noradrenaline) and raphe nucleus (serotonin). The pioneering tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) inhibit their reuptake and metabolism, respectively. The more recent antidepressants, including selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), noradrenergic and specific serotonergic antidepressants (NaSSAs) and noradrenaline reuptake inhibitors (NARIs) also act chiefly through these monoaminergic mechanisms. The noradrenaline and dopamine reuptake inhibitor (NDRI), bupropion, is slightly unusual because it also increases dopamine neurotransmission, chiefly in the nucleus accumbens and prefrontal cortex.

An alternative or perhaps additional approach to the pathogenesis of depression is rooted in circadian biology. This hypothesis focuses on the circadian regulation of biological rhythms, and its relationship with depression and the monoamine systems.

Normal circadian rhythms and the role of melatonin

The 24-hour rhythms of life, including the timing of sleep induction, wakefulness, hormone secretion, thermoregulation, glucose homeostasis and fat metabolism, are governed by external environmental time signals

(*zeitgebers*), particularly fluctuations in light intensity (photic *zeitgebers*). These bodily rhythms are also controlled by an internal circadian timekeeping system, that comprises a host of peripheral, tissue-specific molecular clocks that are able to operate independently of external time cues, and a central (anterior hypothalamic) master clock-like pacemaker, the suprachiasmatic nucleus (SCN) that is synchronised to geophysical or solar time, chiefly via photic input.[5]

Melatonin (*N*-acetyl-5-methoxytryptamine), produced from the neurotransmitter serotonin, acts as a non-photic message, and interacts with photic signals in the control of circadian and diurnal cycles. It is a critical synchroniser of biological rhythms, including the sleep-wake cycles, and its secretion from the pineal gland is closely linked to light-dark and seasonal cycles. During the day, non-image-forming light (photic *zeitgeber)* activates the retino-hypothalamic tract that connects the eye to the SCN. The SCN inhibits the pineal gland indirectly, via inhibition of noradrenergic input from the superior cervical ganglion. In this way, light suppresses the production and release of melatonin from the pineal gland. Dark has the opposite effect and causes a surge of melatonin, which usually peaks in the middle of the night and gradually falls during the second half. In turn, once stimulated by dark, melatonin binds to an important population of melatonin receptors, including M_1 and M_2, in the SCN, where it is able to reset circadian rhythms in phase with the prevailing environmental conditions. Melatonin is also able to acutely inhibit SCN neuronal firing, which may increase the SCN's sensitivity to other phase-shifting stimuli.[5,6]

Two other modulators of SCN function are the daily behaviours themselves, and perhaps more pertinently, serotonin (5HT), the synthesis of which is highly circadian. Serotonergic projections from the raphe nucleus are able to modify SCN responses, and this is thought to be mainly via serotonin binding to the 5-HT_{2C} receptor subtype. In rats, it has been suggested that $5HT_{2c}$ receptor agonists may actually mimic light, and induce a phase shift.[7] Interestingly, activity at $5HT_{2c}$ receptors appears to be increased in depression, and decreases in response to certain antidepressant therapies, including clomipramine, mirtazapine, sleep deprivation, and electroconvulsive therapy. $5HT_{2c}$ antagonists appear to favourably influence mood, circadian resynchronisation and sleep quality, while preserving sexual function.[6]

Circadian rhythms in depression

Circadian function is often disrupted in depression. The internal circadian timekeeping system responds poorly to environmental cues, resulting in phase shifts. Diurnal variations occur earlier (phase advance) or later (phase delay) than in healthy individuals. Patients with depression often show larger daytime mood variation, disturbances in hypothalamic-pituitary-adrenal (HPA) axis function, more severe cognitive difficulties, and sleep-wake cycle disturbances, which may manifest as delayed onset of sleep, difficulty in maintaining sleep, and early morning awakening. The degree of circadian misalignment correlates with the severity of depression, although the causal relationship remains unclear.[8] Thus, circadian abnormalities may partially be a consequence of alterations in behaviour and sleep patterns that accompany depression. They may also be triggered by an intrinsic disorganisation of the SCN. Importantly, depression is associated with an altered diurnal rhythm of melatonin output, including a suboptimal night-time surge. It appears that increasing levels of endogenous melatonin are associated with effective conventional antidepressant therapy. It is noteworthy that commercially available melatonin, which binds to melatonergic receptors, may improve sleep function, but appears to be ineffective in alleviating depression, indicating that the circadian stabilising effect of $5HT_{2c}$ antagonism remains therapeutically important.[9] Overall, the circadian hypothesis supports the notion that resetting circadian function is a relevant strategy to treat depression.[6]

Agomelatine

Agomelatine, the first regulatory approved melatonergic antidepressant, is a naphthalene derivative of melatonin. Therefore, it is more lipophilic and shows improved brain penetration compared to the indole of melatonin. It is a potent full agonist of the human melatonergic receptors, melatonin 1 (MT_1) and melatonin 2 (MT_2). Like melatonin, agomelatine acutely and dose-dependently inhibits the firing rate of SCN neurons (MT_1) and directly resynchronises and normalises disturbances of circadian rhythm (MT_2).[10] The greatest effectiveness appears to coincide with the onset of the elevation in night-time melatonin secretion, presumably the period of highest melatonin receptor density. A transient and short activation of melatonergic receptors at this critical time appears to be sufficient for its enduring effects, illustrated by a reduction in body temperature, increased total sleep time, fewer awakenings after sleep onset, and by the advance in time at which the minimum heart rate occurs during the 24-hour cycle.[6,11]

Agomelatine also binds to $5HT_{2c}$ receptors, albeit with substantially lower affinity than to the melatonin receptors. Nonetheless, it acts as an antagonist of these receptors, which contributes to its resynchronisation of circadian rhythms, enhancement of dopaminergic and adrenergic input to the frontal cortex, induction of hippocampal neurogenesis, and ultimately, to its antidepressant effect.[6]

$5HT_{2c}$ antagonism is also beneficial for alleviating other symptoms associated with $5HT_{2c}$ overstimulation, including anxiety, insomnia and sexual dysfunction. Thus, the additive or perhaps even the synergistic action of agomelatine at both the melatonin and $5HT_{2c}$ receptors, appears to be necessary for its efficacy in treating depression.[6]

Agomelatine is licensed for the treatment of major depressive episodes in adults. It received European Union marketing authorisation in February 2009, and is now licensed for use in South Africa.[12]

Efficacy of agomelatine in treating major depression

Several published clinical trials in almost 6 000 depressed patients, have examined agomelatine's efficacy compared to placebo, SSRI and SNRI treatment, both in the acute and long-term or maintenance setting. It is worth noting that five unpublished trials did not find agomelatine to be superior to placebo, even though in two of these trials, the active comparitors were more effective than placebo. One clinical trial, showing lack of efficacy in relapse prevention, was also not published.[13] This highlights the issue of reporting and publication bias, and the role that it plays in evidence-based decision making. The results below are based on the published literature.

Acute efficacy vs. placebo

In three 6-8 week, double-blind randomised placebo controlled studies, agomelatine used at a dose of 25-50 mg at bedtime, demonstrated significantly superior efficacy compared to placebo in both moderate and severe depression, using the Hamilton Depression Rating Scale (HAMD-17) as the primary outcome measure.[14-16] A clinically relevant 2.86 point mean difference was shown.[17] The onset of antidepressant action appeared to be more rapid (week two) than the active comparator, paroxetine, in one of these studies.[14] More recent placebo-controlled trials showed significant efficacy, including positive effects on sleep, with good tolerability in moderate to severe depression.[18,19]

Acute efficacy vs. other antidepressants

Agomelatine (25-50 mg) showed non-inferiority compared to the SSRI, sertraline (50-100 mg) with a greater proportion of responders at week 2, as well as to the SNRI, venlafaxine (75-150 mg) in clinical trials of 6-12 weeks' duration.[20-23] Compared to venlafaxine XR, fewer patients in the agomelatine group discontinued treatment because of adverse events (agomelatine 2.2%, vs. venlafaxine XR 8.6%), although both treatments resulted in equivalently high rates of remission (agomelatine 73%, venlafaxine XR 66.9%).[23] Agomelatine was effective across the range of severities of depression, including in patients with severe depression. It also accounted for early improvements in daily functioning and sleep, compared to sertraline and venlafaxine.

Other comparators have included paroxetine and fluoxetine.[14,24,25] Eight weeks of agomelatine showed superior antidepressant efficacy, compared to fluoxetine in treating patients with a severe episode of major depressive disorder. However, there were no differences in response rates, remission rates and dropouts, due to treatment (emergent adverse effects between the two drugs).[25]

Long-term efficacy

In a 24-week relapse prevention study, patients who continued taking agomelatine showed a twofold lower relapse rate (21.7% vs. 46.6%) compared to those who were switched to placebo, and they maintained this advantage for up to 10 months.[26] In another 24-week study, agomelatine also demonstrated non-inferiority compared to escitalopram.[27]

Sleep disturbances

Many years ago, acute placebo-controlled studies in healthy volunteers showed that agomelatine increased rapid eye movement (REM) sleep propensity and advanced sleep termination, and resulted in earlier regulation of the endogenous circadian nocturnal decline in core body temperature with circadian phase advance.[28,29] These findings were corroborated a decade later in a study of depressed patients, where although the six-week efficacy of agomelatine was similar to venlafaxine, sleep quality measured with the Leeds Sleep Evaluation Questionnaire was subjectively better among patients treated with agomelatine.[22] In a small, single-blinded study, agomelatine improved slow-wave sleep without causing daytime drowsiness, while an open-label polysomnography and qualitative electroencephalogram study in patients with depression, demonstrated improvements in sleep efficiency and fewer intra-sleep awakenings.[30,31] More recently, this was confirmed in a large multicentre randomised double-blind study comparing the effects of agomelatine and escitalopram for a period of 24 weeks.[27] Agomelatine improved sleep latency from the second week, did not affect REM sleep or sleep cycles, and also did not lead to daytime drowsiness.

Symptoms of anxiety in depressed patients

Anxiety symptoms in depressed patients are common, and are associated with a worse prognosis, increased disability, and higher use of medication. In addition, a common early side-effect of antidepressants that increase serotonin, is treatment emergent anxiety, thought to be partly due to the

overstimulation of post-synaptic $5HT_2$ receptors. Six large multicentre studies, each with a duration of six to eight weeks, involving approximately 2 000 patients with major depressive disorder, assessed the efficacy of agomelatine in treating the symptoms of anxiety in depressed patients. Among these, more than 900 patients were classified as severely anxious, defined by a score of at least five points on the anxiety subscale of the Hamilton Depression Rating Scale (HAM-D).[32]

Three of the six studies compared agomelatine to the SSRIs, sertraline and fluoxetine, and the SNRI, venlafaxine. Agomelatine was shown to be more effective in reducing symptoms of anxiety than its comparators. It led to a significant difference on the Hamilton Anxiety Rating Scale (HAM-A) of 1.39 points. The beneficial effects of agomelatine, compared to the comparator drugs, was more pronounced in the highly anxious depressed patients, with a difference of 1.72 recorded on the HAM-A.[32]

In the other three studies where agomelatine was compared to placebo, agomelatine was found to significantly reduce anxiety scores on the HAM-D anxiety subscore, as early as the second week. This rapid improvement resulted in a significant efficacy over the course of the study, which, once again, was even greater in the more anxious subset of patients.[32]

Other disorders

In a robust 12-week, double-blind randomised controlled trial conducted in South Africa and Finland, agomelatine at normal therapeutic dose (25-50 mg) showed significantly superior efficacy compared to placebo in the treatment of generalised anxiety disorder.[33] Agomelatine's efficacy has also been explored in obsessive compulsive disorder in two recent studies.[34,35] Agomelatine has shown promise in seasonal affective disorder in a 14-week open-label study, where patients showed high response and remission rates.[36] Its efficacy in depression in bipolar I patients, in combination with either lithium or valproate, has also been assessed in an open-label study ranging from 6- 46 weeks.[37] In addition, it has been suggested that agomelatine may show efficacy in the long-term maintenance treatment of alcoholism, to prevent alcohol-related brain damage.[38] Other areas of research include its use as an adjunct in autism and benzodiazepine withdrawal.[39,40]

Pharmacokinetics and drug interactions[12]

Agomelatine, formulated as a 25-mg film-coated tablet, is taken orally at bedtime. It is rapidly absorbed with a peak plasma concentration reached within one to two hours of a single dose. Food does not affect its absorption. However, there is substantial inter-individual variation in plasma levels, which is increased with high fat-containing food.

In the therapeutic dose range (25-50 mg), agomelatine's systemic exposure increases proportionately with dose. However, at significantly higher doses (> 200 mg and above), saturation of first pass metabolism occurs, and plasma levels may increase disproportionately.

Agomelatine has a short half-life of one to two hours, which is sufficient for binding to melatonin receptors at the critical nocturnal time point. Biotransformation is predominantly achieved by hepatic cytochrome P1A2 (CYP1A2) isoenzyme hydroxylation (90%), followed by the smaller demethylation contributions of CYP2C9 and CYP2C19 (10%). The major metabolites are inactive, are rapidly conjugated and are eliminated in the urine thereafter.

Absolute bioavailability is low (< 5%) and this is increased in women, and by co-administered oral contraceptives and potent hepatic CYP1A2 isoenzyme inhibiting agents such as the SSRI, fluvoxamine, and the fluoroquinolone, ciprofloxacin. Therefore, agomelatine is contraindicated if the latter two drugs are prescribed. In theory, moderate CYP1A2 enzyme inhibitors (paroxetine, oestrogens, propranolol, grepafloxacin and enoxacin) may result in increased levels of agomelatine, and caution should be exercised when prescribing these agents. In practice, it appears that interactions are only likely to occur with drugs that inhibit both enzyme pathways.

Enzyme inducers (omeprazole and smoking) diminish agomelatine's bioavailability by up to three- to fourfold, and ultimately, the higher 50 mg dose may be necessary to achieve a therapeutic effect. Hypothetically, if these agents are discontinued, the levels of agomelatine may increase and possibly lead to tolerability issues.

Agomelatine itself has no inducing or inhibiting effects on the metabolising CYP450 enzymes mentioned above. The potential for agomelatine to affect exposure to other medicinal products metabolised by these enzymes is negligible. There has been no evidence of drug interactions with agomelatine when it is given concurrently with benzodiazepines, lithium, paroxetine, fluconazole or theophylline.

Agomelatine is distributed moderately, 95% of drug protein-bound. In practice, this is not sufficient to cause displacement of highly protein-bound drugs, such as warfarin and aspirin, nor should these drugs alter the unbound free concentrations of agomelatine. Of note, though, is that the free fraction is doubled in patients with hepatic impairment, presumably because of decreased albumin production, while bioavailability increases 70-140-fold.[11]

Tolerability of agomelatine[12]

Agomelatine has a relatively favourable side-effect profile. It is not associated with weight gain, heart rate or blood pressure changes.

Theoretically, agomelatine is unlikely to cause the sexual dysfunction that is frequently associated with antidepressant use, because it blocks $5HT_{2c}$ receptors. This was borne out in an eight-week, placebo-controlled study in healthy volunteers, that revealed that sexual dysfunction was significantly lower in those taking agomelatine, compared to those taking paroxetine.[41] In a 12-week study in depressed patients, agomelatine showed a superior sexual side-effect profile compared to venlafaxine.[23]

Transient and mild nausea and dizziness are the most common adverse reactions, and these usually occur in the first two weeks and generally do not lead to cessation of treatment. In most studies, the incidence of these effects did not exceed those of placebo-treated patients.

Other common adverse effects include headaches, somnolence, insomnia, fatigue, migraines, emergent anxiety, gastrointestinal symptoms, hyperhidrosis, back pain, and raised liver transaminases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (1.1% on agomelatine vs. 0.7% on placebo).

Liver function

As noted, temporary increases in serum liver transaminases may occur in patients taking agomelatine, particularly the 50 mg dose. For this reason, liver function tests should be performed in all patients prior to the initiation of treatment, and then after the acute phase (at six weeks), at 12 and at 24 weeks, and thereafter, if clinically indicated. If transaminase values increase, liver function tests should be repeated within 48 hours, and closely monitored. Treatment should be discontinued if the levels of transaminases exceed three times the upper limit of normal.

Cautions and contraindications[12]

Agomelatine is contraindicated in patients taking ciprofloxacin or fluvoxamine, as these agents increase the plasma levels of agomelatine substantially.

It should be emphasised that agomelatine is contraindicated in hepatic disease, such as cirrhosis, or in any active liver disease. It may be prescribed cautiously though, to patients with risk factors for hepatic injury, including obesity (fatty liver disease), substantial alcohol intake, or to those on concomitant therapeutic agents that are associated with hepatotoxicity.

The plasma levels of agomelatine may increase by 25% in patients suffering renal impairment (creatinine clearance < 30 ml/minute). Therefore, caution should be exercised in this group of patients, particularly as limited clinical data is available.

Caution should also be exercised in elderly patients, with or without dementia, and in patients with a history of bipolar affective disorder, mania or hypomania, and agomelatine should be discontinued if these symptoms arise during treatment.

The effect of agomelatine on the foetus or breastfed babies has not been determined. Therefore, it should be used with extreme caution in pregnant and lactating women. Although melatonin is known to improve pregnancy rates, animal reproduction studies with agomelatine have not investigated this pro-fertility effect. What has been demonstrated in animals is that agomelatine has no detrimental effects on fertility. Its effects on human fertility are unknown.

Because of dizziness and somnolence, driving and operating machinery may be impaired in patients taking agomelatine.

Close supervision of patients, particularly those who are at increased risk of suicide, should accompany treatment, particularly in the early stages when the risk increases, and following dose adjustments. There is limited experience with agomelatine overdose, although doses up to 2 450 mg have been taken without cardiovascular or biological abnormalities, and spontaneous recovery has occurred. Excessively high doses have resulted in epigastric pain, somnolence, fatigue, agitation, anxiety, tension, dizziness, cyanosis and malaise.

Clinical pearls

Starting treatment

Once liver function tests have been performed, agomelatine should be started at the therapeutic dose of 25 mg, taken at bedtime. If there is no improvement in symptoms after two weeks, the dose may be increased to 50 mg.[12] Several additional factors may influence the dose, including the severity of the depression, its effect on the quality of life, the degree and rate of improvement seen with the existing dose, and any treatment-associated adverse effects. For instance, patients with depression of moderate severity who show an initial partial response to treatment, may not require a dose increase, given that the full antidepressant effect is usually only achieved after four to six weeks, whereas a partial response in a patient with severe illness and suicidal thoughts should probably warrant a dose adjustment.[11] Ideally, treatment should continue for six months after the resolution of symptoms.

Stopping treatment

Usually antidepressants are tapered slowly, rather than discontinued abruptly, in order to minimise the potential for withdrawal symptoms.[42] This is particularly true of agents with short half-lives. One clinical trial assessed discontinuation symptoms in patients following abrupt cessation of either agomelatine or paroxetine, using the traditional Discontinuation Emergent Symptom Scale (DESS) after 12 weeks of successful antidepressant treatment. As predicted, a significant increase in the DESS score was seen in the paroxetine group who switched to placebo vs. those who continued on paroxetine. No significant increase in the score was noted for patients on agomelatine who switched to placebo vs. those who continued on agomelatine.[24] These initial findings were subsequently supported by a relapse prevention study, where after 8-12 weeks of agomelatine treatment, patients were randomised to either a placebo group, or continued with the agomelatine treatment. Patients who were switched to placebo showed no initial increase in symptoms, which reinforces the notion that the drug may be withdrawn abruptly.[26] Nonetheless, until wider experience with the drug is obtained, patients should be advised to consult their doctor if they develop new or worsening symptoms in the week following discontinuation of the agomelatine.

Switching to and from agomelatine

There are various ways of switching from one antidepressant to another. Usually, these are dictated by the pharmacology of the individual drugs and the clinical need. Strategies include switching abruptly from one antidepressant to another; gradually tapering down and stopping the first antidepressant (to avoid discontinuation reactions), before introducing the second drug, tapering down the first agent and introducing the second agent concurrently (either at a reduced or full dose) or incorporating a washout period between the two drugs. In order to avoid discontinuation effects, generally it is not necessary to taper the first drug if the second drug shares similar pharmacodynamic properties, for instance switching between the serotonergic SSRIs and SNRIs. The danger in this scenario is the emergence of serotonin toxicity, particularly with SSRIs, TCAs (clomipramine), SNRIs (venlafaxine and duloxetine), MAOIs, and trazodone. A drug washout period is mandatory when switching from an MAOI to any other agent for this reason. In addition, some SSRIs, such as fluoxetine and paroxetine, are potent inhibitors of CYP2D6, and concurrent administration of these agents with a TCA during the crossover period may result in a dangerous 200-400% increase in TCA plasma levels.[11]

Agomelatine does not increase serotonin levels. Therefore, the risk of serotonin syndrome should not increase if there is concurrent administration of an antidepressant with serotonergic effects during the crossover period. However, discontinuation reactions may be expected if stopping serotonergic agents. Therefore, they should probably be tapered down over a period of four weeks at the time of, or after introducing, agomelatine. The exception to this is fluoxetine, where discontinuation reactions are rare because of the extremely long half-life of its active metabolite. No tapering is required. Of note is that a quick switch from fluvoxamine to agomelatine is potentially dangerous, because of the significant increase in agomelatine's plasma levels when the agents are prescribed concurrently. A gradual withdrawal of fluvoxamine, as well as a washout period of three days, is advised before instituting agomelatine.[11]

Switching from agomelatine to any other antidepressant should not elicit any problems because of its low potential for discontinuation reactions, accumulation (it has a very short half-life), pharmacodynamic and pharmacokinetic drug-drug interactions.[11]

Conclusion

Agomelatine is thought to act primarily by resynchronising the circadian clock, and therefore the abnormal circadian rhythms that are found in depression. However, in common with many other antidepressants, it also stimulates the release of the brain-derived neurotrophic factor, which increases neurogenesis in the brain, normalises cortisol production, and HPA axis function. It has demonstrated good efficacy and tolerability in published trials, yet there is a degree of controversy surrounding previously unpublished data. Monitoring of liver function may be cumbersome, and precludes its use in patients who are not willing to undertake this commitment.

Good candidates for agomelatine therapy are those who have pronounced sleep disturbances and anxiety symptoms accompanying their depression, as well as those who experience sexual dysfunction, either as a result of the depression itself, or induced by SSRI or SNRI treatment. Agomelatine is a welcome addition to the antidepressant market and wider clinical usage will ultimately determine whether it lives up to its promise in the treatment of moderate and severe depression.

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