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REVIEW

Profile of agomelatine and its potential in the treatment of generalized anxiety disorder

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Background: Although many generalized anxiety disorder (GAD) patients respond to the available pharmacological treatments, nearly half of them do not present the expected results. Besides, the side effects associated to some drugs have a negative impact on treatment adherence. Therefore, the aim of this review was to report the clinical profile of agomelatine, a selective melatonergic MT_1/MT_2 receptor agonist with serotonin $5\text{-}HT_{2c}$ receptor antagonist activities, as a potential pharmacological option in the treatment of GAD.

Methods: We performed a literature review regarding studies that evaluated the use of agomelatine in GAD treatment.

Results: Two short-term, double-blinded studies and one prevention-treatment trial evaluated the efficacy of agomelatine in the treatment of GAD. Agomelatine was associated with higher rates of clinical response and remission, when compared to placebo. In addition, the long-term use of agomelatine decreased the risk of relapse of anxiety symptoms, even for the severely ill patients. Besides, the tolerability was satisfactory with the absence of discontinuation symptoms, as observed in previous studies.

Conclusion: The efficacy and tolerability profiles of agomelatine in the treatment of GAD were good. However, the scarce number of trials, the small sample sizes, and the use of patients without any comorbid conditions were some limitations that impaired the generalization of the results in the general population. Nevertheless, agomelatine is an attractive off-label option in the treatment of GAD that needs more conclusive evidences to establish its role in future guidelines.

Keywords: agomelatine, generalized anxiety disorder, pharmacological treatment

Introduction

Generalized anxiety disorder (GAD) is a chronic illness, characterized by excessive worry about daily life domains, such as finances, responsibilities, and health of family members.[1] Patients with GAD tend to report feelings of exhaustion and irritability associated to ruminative thoughts and often seek medical assistance.

Pharmacological treatment has the objective to reduce acute symptoms, and to prevent relapses in the long term. Therefore, it should be effective and well tolerated. Although selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and pregabalin are first-line options for GAD treatment, nearly 50% of patients do not respond to them.[2] Also, side effects such as nausea and sexual dysfunction for the antidepressant,[3] and sedation and dizziness for pregabalin, can impact on treatment adherence.

Benzodiazepines represent a second-line option in the treatment of GAD because of their particular clinical efficacy and tolerability profile. They appear to have a greater impact on somatic symptoms of anxiety, mainly in the first 2 weeks of treatment. This feature could be interesting, especially considering the latency of efficacy for the

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antidepressants and their potential of worsening symptoms in the acute use.[4] However, continuous use of benzodiazepines can lead to abuse and dependence.[5] In addition, cognitive problems on the long-term use can impact on treatment compliance.

The unsatisfactory efficacy of treatment, especially when considering remission rates and long-term tolerability of drugs, stimulated new pharmacological approaches, as for example the use of atypical antipsychotics,[6] mood stabilizers, and combination treatment of antidepressants (SSRI/SNRI). Among them, agomelatine has shown evidence of anxiolytic effects. It is approved as an antidepressant; however, its mechanism of action is different from that of the currently approved drugs used to treat depression and anxiety.

Profile of agomelatine

Pharmacodynamics of agomelatine

Agomelatine is a synthetic naphthalene analog of melatonin and agonist of melatonergic MT1 and MT2 receptors with a longer half-life (mean terminal half-life of 140 minutes) and affinity for these receptors than melatonin.[7,8] In animal studies, both substances show antidepressant-like activity, but only agomelatine exhibits this property when administered to rats in the morning.[9] One of the most important pharmacological properties of agomelatine is its prochronobiological effect.[10] Agomelatine accelerates the resynchronization of circadian rhythms of locomotor activity and relevant biological parameters that are compromised in depression.[11,12] The serotonin 5-HT_{2c} receptor antagonist activity of agomelatine seems to play a role, along with its melatonergic property, in the antidepressive efficacy.[13,14] Indeed, other clinically active antidepressant agents such as mirtazapine and amitriptyline exert 5-HT_{2c} antagonist receptors. Evidence suggests that in contrast to other 5-HT receptors, 5-HT_{2c} receptors influence the frontocortical dopaminergic and adrenergic pathway functions, which are compromised in depressive states.[7]

Besides the antidepressant action of agomelatine, animal models have also demonstrated its anxiolytic properties. Indeed, it has been demonstrated that mice genetically lacking 5-HT_{2c} receptors showed reduced anxiety.[15] By this way, the antagonism of 5-HT_{2c} receptors induced by agomelatine, especially in the frontal cortex, may be associated with anxiolytic properties, and through the blockade of 5-HT_{2c} receptors, agomelatine may also enhance extracellular levels of noradrenaline, therefore increasing anxiolytic response.[15] Another possibility is that the anxiolytic effect may be due to the activation of melatonergic receptors in response to anxious states. Therefore, anxiogenic stimuli may enhance pineal release of melatonin.[15,16] Indeed, the synergistic effect of 5-HT_{2c} antagonism and melatonergic agonism, rather isolated actions of both mechanisms, may explain both the anxiolytic and antidepressive effects of agomelatine. Nevertheless, it is possible that, in some extent, the hypnotic and sedative effects of agomelatine may be responsible for its anxiolytic property.[13]

Pharmacokinetics of agomelatine

After oral administration, agomelatine is rapidly (0.5–4 hours) and well absorbed (80%) and the time at which maximum blood concentration was achieved was between 45 minutes and 90 minutes after a single oral dose of 25–50 mg.[17] However, its bioavailability is $<5\%$ at the therapeutic oral dose due to the high first-pass metabolism,[18] which may be of concern especially in elderly patients or in subjects with liver disorders.[10]

It presents a moderate volume of distribution of approximately 35 L, a plasma protein binding of 95%, and the peak plasma concentration is achieved within 1–2 hours.[18] At the therapeutic levels, agomelatine blood concentration increases proportionally with dose; at higher doses, a saturation of the first-pass effect may occur. About 80% of the drug is eliminated through urinary excretion of the metabolites, whereas a small amount of the metabolites undergoes fecal excretion.[3,10] The major enzymes involved in the biotransformation of agomelatine are CYPl A2 (90%), and to a lesser extent, CYP2C9/CYP2C19.[19]

Safety of agomelatine

The safety of agomelatine was observed in 7,900 subjects treated for major depression.[18] Severe adverse reactions were seen, more frequently, with a higher dose of agomelatine. Specifically, clinical studies have documented threefold elevations of transaminases enzymes, particularly in patients taking 50 mg/daily (2.5%), when compared to those taking 25 mg/daily (1.4%). Also, rare cases of hepatic failure were observed.[18] Therefore, agomelatine requires monitoring of liver function, and is contraindicated in patients with impaired liver function,[20] and should be avoided in people over 75 years (although no significant effect has been documented in this group). Others minor adverse drug reactions observed with agomelatine use (seen in between one and ten patients in 100) are related to somnolence, dizziness, headache, fatigue, and gastrointestinal symptoms.[18] One particularity of agomelatine is the different profile of adverse effects compared to SSRIs and SNRIs, commonly associated to weight gain, sexual dysfunction, and psychomotor

agitation.[5] In addition, agomelatine use was not associated with discontinuation symptoms after abrupt treatment cessation.[15,19]

Clinical profile

Animal models for depression have shown agomelatine antidepressant-like activity.[21] In clinical trials for major depression, agomelatine has proven superior efficacy compared to placebos, and has shown equivalent results when compared to conventional antidepressants such as SSRIs.[22–24] In a meta-analysis of agomelatine trials for major depressive disorders, there was a marginal superiority of agomelatine over the group of antidepressants (fluoxetine, paroxetine, sertraline, and venlafaxine), but it lacks clinical relevance.[24,25] This result could be influenced by the use of scales that rely more on rating sleep problems. Agomelatine's favorable profile on sleep could have influenced its superior reduction in the rating scores compared to the others antidepressants. Lastly, eight of nine trials seemed to have pharmaceutical sponsorship, and publication bias cannot be ruled out. Agomelatine proved to be effective in the treatment of the acute phase of depression and its discontinuation increased relapse probability in the maintenance phase.[26]

The first clinical evidence of agomelatine as an anxiolytic medication was observed as a secondary outcome in major depression clinical trials. Specifically, data from six short-term randomized trials for depression were reviewed to evaluate the efficacy of agomelatine on anxiety in depressed patients.[27–31] Agomelatine showed increased efficacy over both placebo and active drugs (fluoxetine, sertraline, and venlafaxine) in reducing anxiety symptoms in depression, using the Hamilton Anxiety Rating Scale (HAM-A).[26] Since then, there is a continuous interest regarding the properties of agomelatine and its anxiolytic function as an optional treatment for anxiety disorders, specially GAD. Therefore, the aim of this literature review was to expose the studies conducted regarding GAD treatment with agomelatine and discuss their results, limitations, and future implications.

Drug interactions

Concomitant treatment with medications that interact with isoenzymes CYPl A2 and CYP2C9/CYP2C19 may decrease or increase plasma concentrations of agomelatine.[27] Fluvoxamine, a potent CYP1 A2 and moderate CYP2C9 inhibitor, markedly inhibits the metabolism of agomelatine resulting in a 60-fold (range 12–412-fold) increase of agomelatine exposure. Also, drugs that are potent inhibitors of CYPl A2, such as ciprofloxacin, amiodarone, mexiletine, or zileuton, should be avoided, as well as moderate CYPl A2 inhibitors – including estrogens – that may also increase the exposure of agomelatine.[32]

Methods

First, we conducted a literature search to identify randomized controlled trials evaluating the efficacy of agomelatine in GAD treatment. Keywords were *agomelatine, generalized anxiety disorder, and anxiety disorders and treatment*. To complement our data, we also included references from selected papers. Electronic research-literature databases included PubMed/Medline. We included papers with no limit of time, and excluded papers that were not written in English. All the authors were involved in the process of selecting the studies and agreed with their inclusion. Some papers that presented redundant data, or did not seem to add information relevant to the purpose of the article were also excluded.

Results

We found three studies, all performed by the same group of researchers, with the criteria above.

First study

The first study, conducted by Stein et al (2008),[33] was a 12-week randomized placebo-controlled trial, with 121 GAD patients diagnosed through a semi-structured clinical interview and scales related to anxiety. Only GAD patients with no psychiatric comorbidities were included, and patients receiving psychiatric medication or on psychotherapy were excluded.

The active drug group (n=63) could have agomelatine increased from 25 to 50 mg daily in a blinded fashion if sufficient improvement of GAD symptoms was not achieved from 2 weeks onward. A majority of the patients (92.6%) completed the study, and both groups presented a decrease in anxiety as measured by the HAM-A at the end of the 12th week; however, the agomelatine group had a higher decrease (–3.28 [1.58]; 95% CI =–6.41 to –0.15; P=0.040). When the comparison was made independently for the subscale scores of HAM-A, the improvement with agomelatine over placebo reached statistical significance only for the somatic symptoms of anxiety (P=0.0015).

In a comparison between groups, agomelatine use was statistically superior from 6th week onward (P=0.040). However, in the secondary efficacy analysis, a higher rate of responders on agomelatine than on placebo was observed

from 2nd week through 12 week, with the rates at the last value also favorable to agomelatine (66.7% vs 46.6%; E [SE] =20.1 [8.8]; 95% CI =2.8–37.4; *P*=0.026). In addition, as observed in major depression trials,[27–32] agomelatine use was associated with markedly improvement on sleep symptoms, including the items for getting off sleep, quality of sleep, and sleep awakening.

Patients from both groups did not differ in percentage related to adverse effects. The most common adverse events reported in the agomelatine group were dizziness (7.9%) and nausea (4.8%). Finally, discontinuation emergent signs and symptoms were lower on agomelatine than on placebo.

Second study

This second multicenter trial aimed to evaluate the long-term efficacy and tolerability of agomelatine (25–50 mg) in a 6-month period in preventing relapse in nondepressed patients with GAD.[34] The first stage of the trial consisted of a 16-week open-label treatment period with a flexible dosage of agomelatine (*n*=477). Patients who met the criteria for clinical response (using HAM-A) were randomized to a 26-week, randomized, double-blind, placebo-controlled maintenance treatment period. Finally, at the end of the 26th week, patients were randomized to receive either placebo or agomelatine (same dose) for 1 week to assess potential discontinuation symptoms.

During the open-label treatment with agomelatine, the HAM-A score decreased from 28.0±3.8 at baseline to 9.7±5.9 at week 16. The rate of responders for the patients with at least one post-baseline assessment was 68.1%. In the double-blind 26-week period, when compared to the placebo group (*n*=114), the agomelatine group (*n*=113) evidenced a lower risk of relapse over 6 months (19.5% vs 30.7%; *P*=0.046), with an estimated risk of relapse at 6 months of 19.7% (3.8) versus 31.7% (4.5) in the placebo group. Also, the risk for relapse over time was reduced by 41.8% for agomelatine-treated patients (OR =0.546, *P*=0.005). Similar results were observed with the severely ill patients, and the risk of relapse was reduced by 59.3% in patients treated with agomelatine versus placebo (OR =0.351, *P*=0.006).

Unlike in the previous short-term study, the tolerability profile was measured for the entire 6-month period. When compared to the placebo group, the agomelatine group presented a higher percentage of, at least, one emergent adverse event (40.7% vs 27.2%; *P*=0.032). The most frequent emergent adverse events with agomelatine were similar to those reported during the first study. Seventeen patients (3.6%) had evidenced abnormal liver enzyme value, without clinical relevance. In addition, there were no discontinuation symptoms in patients switched to placebo, compared to those who remained with agomelatine after the end of the 26-week period.

Third study

The third published study was conducted to confirm the efficacy of agomelatine in GAD treatment, as required by regulatory agencies, and assay sensitivity was evaluated by including an escitalopram group.[35] The design of the study was similar to the first study, including the use of similar instruments to measure anxiety and the same exclusion criteria.

Patients were randomized to receive agomelatine (*n*=139), escitalopram (*n*=142), or placebo (*n*=131) in the evening for 12 weeks; the daily dosage of agomelatine or escitalopram could be increased at the 4th week (agomelatine: from 25 mg to 50 mg; escitalopram: from 10 mg to 20 mg) depending on the lack of a patient's improvement. After week 12, a blind tapering period of 1 week was initiated to avoid possible withdrawal reactions, in which escitalopram dosage was diminished, and the dose of agomelatine remained unchanged, based on previous studies that evidenced that this antidepressant is not associated with discontinuation symptoms, according to the authors.

An improvement in symptomatology was reached by the three groups at the end of week 12, as measured by the HAM-A; however, only the agomelatine (difference vs placebo of 4.71 [1.03], 95% CI (2.69–6.73); $P<0.0001$) and escitalopram (difference vs placebo of 4.77 [1.03], 95% CI (2.74–6.79), $P<0.0001$) groups presented a significant decrease. However, in the subgroup of patients with severe anxious symptoms (HAM-A $\geq$25), remission rates (HAM-A $<$7) were 37.7% for agomelatine, 18.9% for escitalopram, and 20.3% for placebo, and statistical significance was reached only for the comparison between agomelatine and placebo groups (SE =7.23; *P*=0.019). In addition, both agomelatine and escitalopram improved psychic and somatic symptoms of GAD, but agomelatine was more effective on improvement of sleep. Tolerability and safety profiles were similar for agomelatine and escitalopram, but treatment discontinuation due to adverse events was less frequent in the agomelatine group (2.2% vs 7.1%).

Discussion

In our literature review, agomelatine showed efficacy in the treatment of GAD in two short-term studies and in a 2-phase study, with an open-label trial, followed by 26-week

double-blinded study to investigate the prevention of relapse. The reduction of anxiety symptoms was evidenced for all primary and secondary outcomes, including the decrease in the score of HAM-A, and the rates of response and remission. In addition, tolerability and safety were satisfactory, with the majority of adverse events in the mild to moderate range.

One particular feature of agomelatine in the treatment of GAD is worth emphasizing. Whereas most antidepressants act primarily on psychic symptoms of anxiety (measured by HAM-A), agomelatine had shown equal improvements in psychic and somatic symptoms. Although the positive effect on sleep, which is a key feature of GAD, might explain the superior reduction of somatic symptoms, this observation was also evidenced after the exclusion of sleep-related items of HAM-A.

The three studies showed interest in evaluating the clinical efficacy of agomelatine in severely anxious patients. Agomelatine had positive effects in the treatment of severely ill patients when compared to placebo. Indeed, the risk for relapse in those patients was even lower for agomelatine, than for the nonsevere GAD sample. Particularly, the third study – that used escitalopram as an active comparator – showed that only agomelatine differentiated from placebo in the remission rate for patients with severe anxiety symptoms.

The majority of clinical trials of agomelatine have shown similar results on the tolerability and safety profile, with equivalent rates of emergent adverse events. They were mild or moderate, and in some comparisons, similar to the placebo group. An exception was the higher rate for agomelatine emergent adverse events, when compared to placebo, in the 6-month maintenance period. In the only comparison of tolerability with escitalopram, a different distribution of adverse events was evidenced, with the SSRI presenting with a decreased libido and anxiety. Also, a higher number of patients in the escitalopram group (n=11) were withdrawn due to adverse events, compared to placebo group (n=4) and the agomelatine group (n=3). Finally, all studies repeated the investigation for possible discontinuation symptoms, and corroborated previous results that showed that agomelatine is not associated with the risk of abrupt withdrawal symptoms, commonly seen with SSRIs and SNRIs.

Some limitations regarding the studies of agomelatine for treatment of GAD deserve mention. First, patients included in the GAD studies may not be representative of those seen in general psychiatric or medical practice. Significant comorbidity with depression is commonly seen in patients with anxiety disorders.[36] Although most trials in GAD exclude primary psychiatric comorbidity, which helps to compare the results of those three studies with previous results in the literature, it impairs the generalization of the results in real clinical settings. Besides depression, subthreshold GAD was cited as the most frequent mental health disorder in primary care.[37] Also, primary care patients with subthreshold GAD had comorbidity rates of 48.5%.[38] Finally, pharmacological treatment of GAD in patients with clinical comorbidities such as diabetes, obesity, and hypertension should be made cautiously. Hence, more naturalistic studies should be conducted to investigate the efficacy of agomelatine in the general population.

The three studies were conducted by the same group of researchers, and sponsorship played a key role in leading the design and conduction of the study, including data collection, management, and analysis. A recent meta-analysis, reviewing the efficacy of agomelatine in the treatment of major depression, reported that for the ten trials included in the review, only one did not disclosure sponsorship.[24] So, publication bias cannot be ruled out.

The sample sizes of the studies are considered small, and larger and longer-lasting trials were required for a full evaluation of the efficacy and safety profile of agomelatine in the treatment of GAD. Although the sample size of the second study had a larger sample, the study evaluated the efficacy of agomelatine in an open-label phase. Besides, the 6-month double-blind period of that trial did not evaluate agomelatine in the acute phase of GAD, but rather observed the risk of relapse. In addition to the comments for the studies design, the lack of more active-drug arms impairs the comparison of agomelatine to standard pharmacological treatments for GAD.

The current algorithms for the treatment of GAD include several pharmacological options. Unfortunately, inadequate clinical response and different profiles of tolerability may have a negative impact on treatment adherence. Therefore, new potential treatments are needed, especially for those refractory patients. Although the number of trials is scarce, agomelatine proved to be useful in the short- and long-term treatment of GAD, with satisfactory tolerability, even for the more severely anxious patients. The antidepressant property of agomelatine strengthens its use in the treatment of anxiety, as depression comorbidity is common. For instance, pregabalin, a first-line agent for GAD treatment, may not be suitable for the treatment of anxiety in the presence of depression as monotherapy. Agomelatine might be chosen as a second-line agent for GAD in patients who have poor tolerability with SSRIs and SNRIs, especially when other off-label drugs need to be avoided. For instance, despite the efficacy of quetiapine in the treatment of anxiety symptoms, its long-term metabolic effects might

compromise treatment continuation. In addition, one might argue if agomelatine treatment could be associated with less benzodiazepine use, considering its improvement in several sleep measurements in patients with depression and anxiety.

Nevertheless, the potential clinical utility of agomelatine in anxiety treatment is dependent upon the development of future research that can evidence its efficacy in more naturalistic scenarios. In addition, agomelatine should be compared with more active-drug comparator studies to test its efficacy directly against standard pharmacological therapy. Specifically, augmentation treatment trials might be interesting, in order to evaluate agomelatine as an adjunctive treatment for GAD. For now, agomelatine is an attractive option in GAD treatment that still awaits a definitive role in future pharmacological algorithms.

Disclosure

The authors report no conflicts of interest in this work.

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