Agomelatine: The evidence for its place in the treatment of depression

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Introduction: Depressive disorders are among the main causes of disability due to disease. In spite of recent progress in the pharmacotherapy of depression, there is still a high nonresponse rate of ~30% to the first antidepressant treatment. Furthermore, the latency of several weeks until sufficient clinical improvement and the risk of side effects remain unresolved problems. Therefore, there is still further need for the development of new antidepressants. In the last years a variety of melatonin receptor agonists have been synthesized and evaluated for the treatment of sleep disorders. Animal studies suggested that agomelatine (S-20098), a synthetic melatonergic MT_1 and MT_2 receptor agonist with serotonin receptor antagonistic properties, may have additional activating properties and may represent a new approach in the treatment of depression.

Aims: Clinical trials that have demonstrated efficacy and safety of agomelatine for the treatment of depression are reviewed.

Evidence review: In clinical trials, including phase III studies, superior efficacy compared to placebo and good efficacy compared to standard antidepressants was shown for agomelatine for the acute treatment of major depression. In all studies published so far agomelatine was safe and the overall tolerability profile was superior to selective serotonin reuptake inhibitors or selective serotonin and norepinephrine reuptake inhibitors.

Place in therapy: Agomelatine may represent a novel perspective in the treatment of acute depression. The improvement of sleep disturbances, the tolerability in terms of sexual side effects, and the lack of withdrawal symptoms after abrupt discontinuation of treatment may represent important clinical benefits compared to established antidepressants.

Keywords: agomelatine, antidepressants, melatonin, major depression, evidence

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Core evidence place in therapy summary for agomelatine in major depression

Outcome measure	Evidence	Implications
Patient-oriented evidence		
Reduction of depressive symptoms	Clear	Agomelatine more effective than placebo and as effective as paroxetine or venlafaxine
Improvement of sleep	Clear	Earlier and better improvement on subjective getting to sleep and on subjective quality of sleep compared to venlafaxine
Disease-oriented evidence		
Symptom relief in terms of HAM-D reduction	Clear	Agomelatine more effective than placebo and as effective as paroxetine or venlafaxine
Response to treatment	Clear	Agomelatine as effective as paroxetine and venlafaxine
Remission after treatment	Clear	Agomelatine as effective as paroxetine and venlafaxine
Economic evidence Cost effectiveness	No evidence	So far, no information about costs of the drug on European market. Studies required to validate assumption that better tolerability profile will translate into improved cost effectiveness

HAM-D, Hamilton rating scale for depression.

Scope, aims, and objectives

Melatonin secretion underlies strict circadian rhythms[1] and is regulated via the cAMP signal transduction cascade.[2] Several studies have reported beneficial effects of melatonin for the treatment of sleep disorders. However, the therapeutic use of melatonin, which is offered as a supplement in the US, is restricted by its low bioavailability. Therefore, several melatonin agonists have been developed in recent years and examined in clinical trials for the treatment of insomnia (for a current review of melatonin receptor agonist development, see Turek and colleagues[3]). To date, agomelatine (S-20098; Valdoxan®, Servier), a synthetic melatonergic MT_1 and MT_2 receptor agonist,[4] is the best characterized melatonin receptor agonist in terms of preclinical studies. In contrast to melatonin, agomelatine also possesses serotonin (5-HT_{2C}) receptor antagonistic properties[5] within the central nervous system (CNS). Several preclinical studies indicated that agomelatine has activating[6] and antidepressant effects, which are comparable to the antidepressant efficacy of established antidepressants. Therefore, agomelatine may represent a new approach for the treatment of depression. The efficacy and tolerability of agomelatine in the acute treatment of depressive disorders has been evaluated in several controlled clinical trials. In the following article the evidence for agomelatine's antidepressant efficacy will be reviewed and its place in the acute treatment of depression will be discussed.

Methods

The medical literature was reviewed for appropriate articles relating to agomelatine on PubMed (http://www.ncbi.nlm. nih. gov) using the search terms "agomelatine OR S-20098." The search was updated on September 1, 2008. One hundred and sixteen articles were found, of which 11 were written in languages other than English and were therefore excluded. Within those 105 publications, 12 reports from clinical trials and 24 review articles have been identified. Out of the reports from clinical trials, 10 are included and also cited in this review (Table 1). Additionally, congress proceedings focussing on the effects of agomelatine in the treatment of depression were also included where appropriate.

So far no pharamacoeconomic studies of agomelatine have been published. The results of the included clinical trials are reviewed, focussing on clinical efficacy, safety, and tolerability of agomelatine in the treatment of major depression.

Disease overview

Depressive disorders are among the main causes of disability due to disease and the World Health Organization (WHO)

Table 1 Evidence base included in the review

Category	Number of records	
	Full papers	**Abstracts**
Initial search	116	
Records excluded	11	
Records included	105	
Total records included	10	4
Level 1 clinical evidence		
(systematic review, meta analysis)	0	0
Level 2 clinical evidence (RCT)	5	1
Level $\geq$ 3 clinical evidence		
Trials other than RCT	2	
Case reports		
Other outcome than depression	3	3
Economic evidence	0	

For definitions of levels of evidence, see *Core Evidence* website (http://dovepress. com/core-evidence-journal).
Abbreviation: RCT, randomized controlled trial.

estimates that they will be the second most important cause of disability by the year 2020.[7] Chronic depressive episodes are common and are associated with greater illness burden and socioeconomic disadvantage.[8] Throughout Europe, 23% of years of healthy life are lost and approximately one-third of all burden of disease is caused by neuropsychiatric diseases.[9] The 1-year prevalence of depression in Europe is around 5%.[10] The life time prevalence of depression varies widely from 3% in Japan to 16.9% in the US, with most countries in the range between 8%–12%.[11] Despite intensive biologically oriented psychiatric research over the last decades, the etiology of depressive disorders is not yet fully understood, although a multifactorial genesis is supposed. Besides psychologic and social factors, biologic variables apparently play a major role that lead to a disturbed CNS homeostasis. The so-called catecholamine- and serotonin-deficiency hypothesis,[12] which postulates a deficiency of monoamines (norepinephrine and serotonin) within the synaptic cleft, plays a major role in the understanding of the pathophysiology of depression.

Current therapy options

The treatment of depressive disorders consists of a complex multimodal therapy that is determined by the current state of the illness. The treatment of depression includes pharmacotherapy, psychotherapy, and sociotherapy. Whereas pharmacotherapy is not always mandatory for less severe forms of depression, severe depression usually requires pharmacotherapy or electroconvulsive therapy. In addition, a variety

of other biologic interventions, such as sleep deprivation and bright light therapy, may be of use in certain patient subgroups. The discovery of tricyclic antidepressants (TCAs) was a milestone in the treatment of depression. However, in spite of the undoubted effectiveness of TCAs it soon became apparent that their anticholinergic and antihistaminergic side effects may cause problems. As a consequence, new antidepressants were developed with a more selective mode of action, which mainly aimed at avoiding these side effects. Currently, tri- and tetracyclic antidepressants with predominant serotonergic, noradrenergic, or mixed serotonergic/noradrenergic action are available. In addition, selective and reversible inhibitors of the monoamine oxidase A, an irreversible monoamine oxidase B inhibitor, nonselective and irreversible inhibitors of the monoamine oxidase, selective serotonin reuptake inhibitors (SSRI), selective norepinephrine reuptake inhibitors, and antidepressants with a dual mode of action such as selective serotonin and norepinephrine reuptake inhibitors (SNRI), and noradrenergic and specific serotonergic antidepressants acting via blockade of alfa$_2$ and 5-HT$_2$ receptors, are all available.[13–17] The most recently investigated mechanism of action is the agonism at melatonergic MT$_1$ and MT$_2$ receptors and selective antagonism at serotonergic 5-HT$_{2C}$ receptors represented by the antidepressant agomelatine,[5] which is currently under review by authorities in Europe.

Unmet needs

Although newer antidepressants are better tolerated and cause fewer side effects, their specific side-effect profile has to be taken into account during the treatment of depression. In addition, the latency of several weeks until the onset of sufficient therapeutic effects remains a serious and clinically relevant problem. This principle holds true for each antidepressant and each class of antidepressant mechanisms. A further general problem in pharmacotherapy of depression is the possible nonresponse to the first antidepressant treatment.[18–20] Approximately 30% of depressed patients do not show sufficient improvement after the first course of an adequate antidepressant treatment and a further 20% discontinue due to tolerability problems.[21] Adequacy of treatment includes the use of a treatment with proven efficacy during a time interval of at least 4–6 weeks in a sufficient therapeutic dose range including reliable patient adherence to therapy.[19,22,23] Half of patients who do not respond adequately to a first course also fail to respond to a second antidepressant treatment trial. If several antidepressant treatment trials have been inefficacious, even lower response rates after switching to another drug may be observed.[24]

Clinical evidence for agomelatine in the treatment of major depression

Melatonin secretion underlies strict circadian rhythms[1] and is regulated via the cAMP signal transduction cascade.[2] A variety of animal studies and clinical trials in depressed patients suggest that agomelatine, a synthetic melatonergic MT$_1$ and MT$_2$ receptor agonist[4] with 5-HT$_{2C}$ receptor antagonistic properties[5] within the CNS, has activating and antidepressant effects.[6]

In several animal models of depression agomelatine has been shown to possess antidepressant effects that were comparable to those of established antidepressants. In contrast to melatonin the beneficial effects of agomelatine did not depend on the time of administration, indicating that besides the chronobiotic, other properties may contribute to its antidepressant-like activity.[25] Furthermore, agomelatine has been shown to have chronobiotic activity similar to melatonin in animal models of disturbed circadian rhythms.[26,27]

Clinical efficacy assessment

Clinical trials focus on symptomatic relief measured by specific scales, such as the Hamilton Depression Score (Hamilton Depression Rating Scale, HAM-D),[28] and define response and remission in relation to these scores. The traditional definition of response to antidepressant therapy includes a 50% improvement in symptoms (usually 50% reduction of the baseline score). Remission is defined as the absence of depressive symptoms and a full return to premorbid levels of functioning. In most randomized controlled trials an absolute rating scale threshold is defined as remission (eg, HAM-D score $\leq$ 7). Goals of clinical management can be divided into acute, intermediate, and long-term goals. The ultimate goal of acute treatment is to achieve remission, meaning not only being asymptomatic (in the sense of not meeting the criteria for diagnosis of the disorder and having no or only minimal residual symptoms) but also showing improvement in psychosocial and occupational functioning. The intermediate goal is further stabilization and prevention of a relapse, elimination of subsyndromal symptoms, and restoration of the prior level of functioning. The long-term goal is full recovery,[29] to prevent further episodes, maintain functioning, and ensure a satisfactory quality of life.[30–32]

Clinical efficacy of agomelatine in phase II and III trials
Symptomatic relief
The clinical efficacy of agomelatine in the treatment of depressive disorders was first investigated in a multinational,

randomized, double-blind, placebo-controlled trial.[33] In this study three different doses of agomelatine were compared with an active comparator. Seven hundred and eleven patients aged between 18 and 65 years, who were suffering from major depressive disorder (n = 698) or bipolar II depression (n = 13) according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV),[34] with a minimum severity score of 22 in the 17 item HAM-D (HAM-D17)[35] were treated with agomelatine, paroxetine, or placebo. After an obligatory 1-week placebo run-in period, patients were randomized to receive agomelatine 1, 5, or 25 mg once daily in the evening, paroxetine 20 mg/day in the morning, or placebo during the 8-week study period. After exclusion of placebo responders during the run-in period (defined as HAM-D17 improvement >20%) the mean HAM-D17 score at baseline was 27.4 and the mean Montgomery-Asberg Depression Rating Scale (MADRS)[36] score was 31.5, indicating a moderately to severely depressed study population. One-third of the patients had a depressive episode of severe intensity, defined as HAM-D17 score ≥ 25. The treatment groups showed no significant differences in either demographic or clinical variables.

The intent-to-treat analysis using the last observation carried forward method in patients who had received at least one post-randomization treatment and had a baseline and at least one postbaseline rating, showed a statistically significant superiority in the mean scores of all agomelatine-treated patients taken together in comparison to the placebo-treated group. Subsequent distinct analyses of the three agomelatine treatment groups, however, showed clear effectiveness only in the patient group that received 25 mg/day, whereas agomelatine 1 and 5 mg/day did not differ from placebo. The time to first response was significantly shorter in the agomelatine 25 mg/day group in comparison to placebo. In contrast to paroxetine, which first showed significant advantages after 4 weeks, agomelatine 25 mg/day was significantly superior to placebo already after 2 weeks of treatment.

The clinical efficacy of agomelatine in major depression has been confirmed in further randomized, double-blind, placebo-controlled studies. In the study published by Kennedy and Emsley,[37] 212 outpatients were treated with agomelatine 25 mg/day, with the possibility of increasing the dose to 50 mg/day in case of insufficient improvement after 2 weeks of treatment.[38] After a 6-week treatment period, agomelatine was significantly more effective in comparison with placebo. Patients treated with agomelatine had a significantly lower HAM-D score (P = 0.0017) at endpoint (14.1 ± 7.7) compared with patients receiving placebo (16.5 ± 7.4).

Furthermore, there was a significant improvement of severity of disease measured with the Clinical Global Impression Scale (CGI-S) score with agomelatine compared with placebo (3.2 ± 1.3 versus 3.6 ± 1.3; P = 0.0017). Thirty-six (34%) patients in the agomelatine and 38 (37%) patients in the placebo group failed to improve after 2 weeks of treatment. Therefore, in the agomelatine group the dosage was increased to 50 mg/day, while placebo-treated patients continued to receive placebo. Also in this subgroup of increased agomelatine-treated patients, significant improvements in HAM-D score were observed at study endpoint. The HAM-D score decreased in the agomelatine-treated patients from 26.1 ± 2.6 at baseline to 17.5 ± 7.4 at week 6, compared with a decrease from 26.7 ± 2.8 to 20.4 ± 6.0 in the placebo group.

In a further double-blind, parallel-group, flexible-dosing study,[39] an interactive voice response system was used as a novel blinding method. Two hundred and thirty-eight patients with moderate-to-severe major depression were treated with agomelatine over 6 weeks. In case of insufficient improvement at week 2, dose adjustment from agomelatine 25 to 50 mg/day was possible. In terms of HAM-D final scores agomelatine was significantly more efficacious than placebo with an agomelatine-placebo difference of 3.44 (P = 0.001). Furthermore, in terms of severity of disease measured with CGI-S, agomelatine significantly improved CGI and decreased CGI-severity compared with placebo.

Further evidence for the efficacy of agomelatine came from a double-blind, randomized study with the main goal of investigating the effects of agomelatine on sleep improvement.[40] In this flexible-dose study, 332 outpatients suffering from major depression were treated with agomelatine 25–50 mg/day or venlafaxine 75–150 mg/day. After 6 weeks of treatment the antidepressant efficacy of agomelatine in terms of CGI global improvement was comparable to that of venlafaxine.

Response and remission

Analysis of response and remission rates during agomelatine treatment suggested that agomelatine exerts high efficacy in the treatment of depressive disorders. In the first randomized, double-blind, placebo-controlled trial of agomelatine[33] response, defined by an improvement of 50% in the HAM-D score, was achieved significantly more often in the agomelatine 25 mg/day (61.5%) and agomelatine 1 mg/day (62.5%) group in comparison with placebo (46.3%) as shown by pairwise comparison. In contrast, neither agomelatine 5 mg/day (51.4%) nor paroxetine (56.3%) was significantly superior to placebo. In this study remission defined by a HAM-D17

score at endpoint below 7 was achieved significantly more often with agomelatine 25 mg/day (30.4%) and paroxetine (25.7%) than with placebo (15.4%).

Significant efficacy of agomelatine was also found in a randomized, double-blind, multicenter study of agomelatine versus paroxetine published with the main goal of investigating discontinuation symptoms in sustained remitted patients.[41] During the first part of the study 335 outpatients with major depression (DSM-IV) with a mean MADRS score of 23 were treated after a drug-free run-in period with either agomelatine 25 mg/day or paroxetine 20 mg/day once daily for 12 weeks. One hundred and ninety-two patients achieved sustained remission, defined as an MADRS score ≤ 12 at weeks 8, 10, and 12. The rate of sustained remitters was 52.7% in the agomelatine and 61.9% in the paroxetine group. At the time of the second randomization, at entry into the discontinuation period, there were no statistically significant differences between the two groups.

Furthermore, in a recently published study by Kennedy et al,[42] investigating sexual dysfunction in 276 depressed patients during antidepressant therapy with agomelatine 50 mg/day or the SNRI venlafaxine extended release 150 mg/day over a period of 12 weeks, comparable high remission rates (defined as an MADRS score ≤ 12) of 73% in the agomelatine and 66.9% in the venlafaxine group have been observed.

Although it has to be considered that unequal definitions of remission, different dosages, and different treatment intervals might account for differences in the observed remission rates, these study results indicate that agomelatine exerts antidepressant efficacy that leads not only to treatment response but also to a rate of sustained remission similar to that of established antidepressants.

Response rates were also significantly higher with agomelatine 25–50 mg/day (54.3% and 49.1%) than with placebo (35.5% and 34.2%) in two randomized, double-blind, flexible-dosing studies.[37,39]

Specific subgroups of depressed patients

The antidepressant efficacy of agomelatine has also been proven in the subgroup of severely depressed patients, defined by the generally accepted criterion of a baseline HAM-D17 score ≥ 25.

In the study by Loo et al[33] an analysis of the subgroup of severely depressed patients (n = 586) revealed that patients treated with agomelatine 25 mg/day (n = 120) but not those receiving the lower doses differed significantly from placebo-treated patients (n = 114) in terms of HAM-D

final scores (13.14 $\pm$ 8.4 versus 16.1 $\pm$ 9.1). In contrast, the active comparator paroxetine was not significantly superior to placebo in this study population (HAM-D final score 14.1 $\pm$ 8.4).

Similarly, in the study published by Kennedy and Emsley,[37] 76 severely depressed patients were treated with agomelatine and 75 severely depressed patients were treated with placebo. Treatment with agomelatine resulted in a significantly lower HAM-D score at endpoint compared with placebo (14.4 $\pm$ 7.9 versus 17.3 $\pm$ 7.2; $P = 0.024$). Moreover, in the study population with severe depression, the difference in mean HAM-D score at endpoint between agomelatine and placebo exceeded the difference in the full study population (2.72 $\pm$ 1.19 versus 2.30 $\pm$ 1.02) indicating high efficacy of agomelatine in severely depressed patients.

In addition, first results from open-label studies indicated that agomelatine may not only be effective in the treatment of major depression, but also in the treatment of bipolar and seasonal affective disorder (SAD).

Agomelatine 25 mg/day as an adjunctive therapy to lithium (n = 14) or valpromide (n = 7) significantly improved depressive symptoms in bipolar I patients after 6 weeks of treatment,[43] and agomelatine 25 mg/day yielded a significant decrease in depressive symptoms measured with the Structured Interview Guide for the HAM-D SAD-version, CGI-S, and CGI-I in 37 patients suffering from SAD.[44]

Depression-associated sleep disturbances

In view of its pharmacologic profile agomelatine is likely to possess sleep-wake cycle regulating properties. In several animal models of disturbed circadian rhythms agomelatine has been shown to have chronobiotic activity similar to melatonin. These results are also of particular interest for the treatment of affective disorders since a disorganization of circadian rhythms is suggested to play an important role in the pathophysiology of major depression.[45,46]

The influence of agomelatine 50 mg/day on circadian rhythms was investigated in a double-blind, placebo-controlled, crossover study in healthy, older, adult men.[47] At the end of the 15-day active treatment period, significant 2-hour phase advances in the 24-hour profiles of body temperature and cortisol levels were found. Similar trends were seen in thyroid stimulating hormone secretion. Polysomnographic investigations, however, showed no effects of agomelatine on normal sleep patterns suggesting that agomelatine facilitates the realignment of overt circadian rhythms in older adults.

In addition, in patients with major depression treated with agomelatine 25 mg, polysomnography shows regulation of

sleep-wake rhythms increasing the duration of slow wave sleep and normalizing its distribution through the night.[48] After 6 weeks of treatment sleep efficiency, time awake after sleep onset, and the total amount of slow wave sleep increased. In contrast agomelatine did not change rapid eye movement (REM) latency, amount of REM, or REM density.[49]

In addition, in a dose-finding study,[33,50] somatic complaints and symptoms related to sleep disturbances decreased substantially throughout the study, further indicating that agomelatine has beneficial effects in the treatment of depression-related sleep disturbances.

In a double-blind, randomized study in 332 outpatients suffering from major depression, the effects of agomelatine 25–50 mg/day and venlafaxine 75–150 mg/day on subjective sleep quality were compared. In contrast to venlafaxine, agomelatine showed an earlier and better improvement on subjective getting to sleep and on subjective quality of sleep as well as a better improvement of daytime sleepiness.[40] These results indicate that agomelatine may contribute to a normalization of disrupted circadian rhythms in depression via phase-shifting properties without direct sedation and therefore not disturbing the normal day-sleep rhythm.

Safety and tolerability

In all clinical trials published to date, agomelatine has a better safety and tolerability profile than established antidepressants, including the investigated SSRIs and SNRIs.

In a first dose-finding pilot study in 28 patients no modifications of cardiovascular parameters or biologic abnormalities were seen after a 4-8 week treatment period with agomelatine 5 or 100 mg/day.[33,50] Slightly more adverse events and severe treatment-related adverse events were seen in the 100 mg/day group.

In the above mentioned large, double-blind study by the same authors,[33] 56.5% of 711 patients reported at least one adverse event that emerged or worsened during the study such as headache, abdominal pain, nausea, diarrhea, somnolence, or anxiety. No significant difference between agomelatine and placebo was seen, whereas during paroxetine treatment significantly more gastrointestinal adverse events, predominantly nausea, were seen than with placebo. Again no clinically relevant changes in vital signs, weight, or cardiovascular parameters, including electrocardiogram recordings, were seen with agomelatine. In a further placebo-controlled trial, adverse events more common in the agomelatine group compared with placebo were dizziness (9.3% versus 4.8%), nasopharyngitis (6.5% versus 3.8%), and influenza (6.5% versus 2.9%).[37]

Remarkably, although agomelatine ameliorates sleep-related complaints, no sedation has been reported during the daytime. Impairment of sexual function has been reported for antidepressants and represents an important cause of noncompliance.[51] Therefore, the effects of agomelatine on sexual function were studied in a specific trial.[42,52] Using a sexual function questionnaire, sexual dysfunction was compared between agomelatine and venlafaxine extended release.[42] Treatment-emergent sexual dysfunction was significantly less prevalent in the agomelatine group. Desire, arousal, and orgasm scores and the total sexual dysfunction score was significantly greater in venlafaxine-treated patients. In order to distinguish between medication-induced sexual side effects and sexual symptoms associated with depression an additional analysis of sexually active patients who achieved remission (defined by a decrease of at least 50% in the MADRS score compared to baseline and a total MADRS score ≤ 12 after 10 weeks of treatment) was carried out. In this analysis 7.3% of agomelatine-treated patients compared with 15.7% of venlafaxine recipients reported a deterioration of sexual function. While men more often reported a decline in drive and desire, women more often reported deterioration of orgasm.

Discontinuation symptoms were investigated in a randomized, placebo-controlled, double-blind study[41] in 88 patients with major depression who were sustained responders after agomelatine 25 mg/day treatment lasting 12 weeks (the control group received paroxetine 20 mg/day). Sixty-one patients continued agomelatine whereas 27 were abruptly switched to placebo. After 1 week of treatment interruption no statistically significant difference in the number of discontinuation symptoms between patients treated with agomelatine and those receiving placebo was observed. In contrast to these findings, 43 patients discontinuing the SSRI paroxetine experienced significantly more discontinuation symptoms, such as insomnia, muscle aches, dizziness, and nausea, than another 61 patients who continued treatment with the SSRI. After 2 weeks of treatment interruption the agomelatine group continued to show similar results to the placebo group and there were no significant differences between the paroxetine and the placebo group. No significant differences in the rates of relapse or partial relapse were registered in either of the active treatment groups or in the placebo group during the observation period of 2 weeks, which was relatively short for the estimation of the relapse risk. Nevertheless, patients who discontinued from paroxetine experienced a significantly greater worsening in CGI and MADRS scores in comparison to patients continuing

the medication, which might be attributed to the emergent withdrawal symptoms in the paroxetine discontinuation group. Patients discontinuing agomelatine showed the same low severity of depressive symptoms as patients continuing the medication. During the discontinuation period no serious adverse events were recorded.

This study showed agomelatine was not associated with discontinuation symptoms during the observation period of 2 weeks. Because the half-life of agomelatine is 2 hours and the drug has no active metabolites, any discontinuation symptoms would be expected during the first week after discontinuation of the active drug. Therefore, the 2-week observation period seems to be long enough to rule out any emerging withdrawal or discontinuation symptoms. The inclusion of only sustained remitters rules out the likelihood of registering reemergent depressive symptoms during relapses or partial relapses as discontinuation symptoms. Therefore, agomelatine seems to be at lower risk for discontinuation symptoms after abrupt tapering, for example in noncompliant patients. This could be an important safety benefit during antidepressant therapies.

Patient group/population

Agomelatine has been shown to be effective in the treatment of major depression, especially in the subgroup of severely depressed patients. In a pooled analysis of placebo-controlled studies, agomelatine 25–50 mg was significantly more effective than placebo.[53] Agomelatine also ameliorates sleep-related complaints without sedation during the daytime suggesting that it may be of special benefit in agitated patients.

No large-scale studies on the long-term effects of agomelatine in the treatment of major depression have been published so no definite conclusion can be drawn at the moment in relation to long-term safety issues or efficacy in relapse prevention. Because of this, in 2006 the Committee for Medicinal Products for Human Use adopted a negative opinion, recommending the refusal of a marketing authorisation for the medicinal product Valdoxan/Thymanax® (Servier) for the treatment of depression.

However, in a double-blind multicenter study in depressed patients the efficacy of agomelatine in relapse prevention has been investigated.[54] After initial response to agomelatine, 492 outpatients continued treatment with agomelatine or placebo. During the 6-month study period, 46.6% of patients receiving placebo, but only 21.7% of patients receiving agomelatine, relapsed. Therefore, these results indicate that agomelatine might also be effective in the long-term treatment of depression.

Place in therapy

Agomelatine is the first melatonergic and 5-HT$_{2C}$ receptor antagonistic antidepressant. In all clinical trials published to date, including large-scale phase III studies, agomelatine has shown at least equal efficacy to active comparators such as SSRIs and SNRIs. Furthermore, agomelatine is also effective in the treatment of severe depression. In addition, agomelatine is the first antidepressant without antihistaminergic side effects that effectively ameliorates sleep-related complaints without sedation during the daytime.

In all clinical studies the overall tolerability profile of agomelatine was excellent and showed no impact on laboratory parameters, vital signs, blood pressure, heart rate, and QTc time intervals. The rate of treatment-emergent adverse events was not higher than with placebo. The sexual acceptability of agomelatine represents an important clinical benefit as well as the lack of withdrawal symptoms after abrupt discontinuation of treatment.

In summary, agomelatine represents a promising novel strategy in the treatment of depression. For clinicians it is a novel perspective in the acute treatment of depression that will hopefully show good clinical effectiveness paired with excellent tolerability also in the long-term treatment of depressed patients.

Acknowledgments

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