

Agomelatine as monotherapy for major depression: an outpatient, open-label study

Jan Pecenek
Vladimir Novotny†

Clinic of Psychiatry, Faculty of Medicine, Comenius University and University Hospital, Bratislava, Slovakia

Vladimir Novotny† passed away on 17 April 2012

Background: Agomelatine is a novel antidepressant agonist to MT1 and MT2 subtypes of melatoninergic receptors (MT1 and MT2) and antagonist to 5-HT_{2C} subtype of serotonergic (5-HT_{2C}) receptors, which has shown antidepressant efficacy in short-term and long-term trials as well as in clinical practice. The purpose of this study was to assess the antidepressant efficacy, safety, and the influence of agomelatine on the functioning of patient in common clinical practice.

Methods: In this open-label, 8-week, multicenter, Phase IV trial, 111 patients with mainly moderate to severe major depressive disorder (39% treatment-naïve) were treated with agomelatine 25–50 mg/day for up to 8 weeks. The primary endpoint was the mean change in total Montgomery and Åsberg Depression Rating Scale (MADRS). Secondary endpoints included assessment of clinical response (defined as a reduction in total MADRS score of $\geq 50\%$), and change in Clinical Global Impression scales, Global Assessment of Functioning scale, Sheehan Disability Scale, and CircScreen sleep questionnaire scores. Safety and tolerability were also monitored.

Results: Of the 111 patients enrolled, 94 completed the study. The total MADRS score significantly decreased by the first week of treatment and continued to decline significantly until study completion, with an estimated mean change of 3.9 ± 3.9 and 17.2 ± 8.0 at the first and eighth week of the study (last observation carried forward analyses). All other secondary endpoints significantly improved from early treatment evaluation to study completion. A clinical response was observed in 14.1% of patients after the first week, rising to 74.5% of patients at study completion. There were 31 spontaneously reported adverse events in 17 patients, and most were mild to moderate in severity.

Conclusion: This study showed good short-term efficacy for agomelatine in outpatients with major depressive episodes. Treatment with agomelatine achieved early and consistent responses for symptoms of depression and other dimensions of clinical and functional status. Agomelatine achieved significant improvements in daily functioning of patients, and had good tolerability. Clinically, no hepatic events were observed.

Keywords: agomelatine, monotherapy, depression, remission, functioning

Introduction

Depression is a major mood disorder affecting about 350 million people worldwide.¹ The World Health Organization has ranked depression as the fourth leading cause of disability, and expects it to become the second leading cause of disability by 2020.² Chronic and recurrent depression affects the physical, mental, and social functioning of patients and their families.^{3,4} Hence, depression should be diagnosed and treated at the earliest opportunity. The goal of treatment for major depressive disorder is remission of all symptoms with complete recovery from social and vocational dysfunction.⁵

Correspondence: Jan Pecenek
Clinic of Psychiatry, Faculty of Medicine,
Comenius University and University
Hospital, Bratislava, Slovakia
Tel +42 19 0556 3757
Fax +42 12 5729 0288
Email jan.pecenek@sm.unb.sk

Among the antidepressants used, tricyclic antidepressants are less selective and are limited by anticholinergic and cardiac side effects, sedation, weight gain, sexual dysfunction, and drug interactions.⁶ Selective serotonin reuptake inhibitors, although considered cost-effective and relatively safe in overdose, are associated with side effects like sexual dysfunction, gastrointestinal disturbance, and weight gain.⁷ Approximately 15% of patients taking selective serotonin reuptake inhibitors cannot tolerate their side effects and therefore may stop taking the drug.⁶

Furthermore, many patients treated for depression do not achieve complete remission and even fewer patients remain in remission. Significant numbers of patients show inadequate response or discontinue medication due to intolerable side effects. Residual symptoms and poor treatment adherence are two of the main risk factors for relapse with current therapies.^{8,9} Impaired functioning also has a negative impact on quality of life.¹⁰ Hence, there is an unmet need for an antidepressant that is relatively more efficacious and better tolerated.

Major depression is accompanied by alterations in circadian rhythms of behavior, sleep, core temperature, and secretion of cortisol and other hormones. Reoordination of these biological rhythms contributes to treating depression.¹¹ Agomelatine is a (melatonergic) MT1 and MT2 receptor agonist and a 5-HT_{2C} serotonergic (5-HT_{2C}) receptor antagonist which has shown antidepressant efficacy in placebo-controlled 8-week and 24-week trials,^{12–16} in comparative studies with venlafaxine and sertraline where change of severity in depression were the secondary endpoints^{17,18} and in an observational trial.¹⁹ This efficacy is achieved through its unique mode of action based in the synergy of its mechanism of effect at the behavioral, molecular, and electrophysiologic levels,^{20,21} and there is evidence concerning the influence of neuroplasticity processes.²²

Treatment with agomelatine would be likely to provide more sustained, longer-term remission because antidepressant efficacy is combined with fewer residual symptoms and better tolerability and adherence.⁸ This trial explored the antidepressant efficacy and safety of agomelatine in treatment of patients with major depressive episodes in clinical practice. The efficacy of treatment with agomelatine and the return of patients to normal social functioning were assessed in this study by both clinician-based rating scales and patient self-rating scales.

Materials and methods

This was an open-label, multicenter, 8-week, Phase IV trial of agomelatine in outpatients with moderate to severe major

depressive disorder attending 13 hospital psychiatric clinics in Slovakia. All patients provided their written informed consent prior to participation in the study and the protocol was approved by the local ethics committees. The study was registered at the Slovak State Institute of Drug Control (code IC4-20098-542) and was monitored by Clinical Research Associates. Psychiatrists working at outpatient offices affiliated to the inpatient departments of psychiatry participated as investigators and were paid for participation by the sponsor. No remuneration was provided to the patients.

Inclusion criteria

Outpatients aged 18–65 years and diagnosed with major depressive disorder as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR),²³ suitable for monotherapy with agomelatine in the clinical opinion of the treating psychiatrists, and who agreed to sign their informed consent were eligible for inclusion in this study. Diagnosis of major depressive disorder was confirmed by the Mini International Neuropsychiatric Interview.²⁴ Severity of depression had to be moderate or severe, as defined by a total Montgomery and Åsberg Depression Rating Scale (MADRS) score of ≥ 20 .

Exclusion criteria

Patients with other types of depressive episode or depressive disorder (bipolar disorder, dysthymia, depressive episode in schizoaffective disorder, substance use, or organic depression) and those with chronic depression (duration > 2 years) or treatment-resistant current episode of depression (no adequate response to two different antidepressants given at an adequate dose for 4-week intervals) were excluded.

Patients with the following characteristics were also excluded from participation:

- Patients with higher risk of suicidal attempt according to a score of ≥ 2 on item 10 “Suicidal thoughts” of the MADRS or by clinical assessment involving clinical status and family history
- Patients with a current DSM-IV diagnosis of panic disorder, obsessive compulsive disorder, post traumatic stress disorder, acute stress disorder, or acute or chronic psychosis
- Patients with a diagnosis of antisocial, borderline, or histrionic personality disorders according to the DSM-IV
- Serious physical symptoms/diagnosis which could interfere with the evaluations as well as substantial neurologic disorder or dementia

- Pregnancy, breastfeeding, or women of child-bearing age with no adequate contraception
- Treatments with electroconvulsive therapy within 3 months before inclusion, initiation of psychotherapy in the same time frame, and light therapy 2 weeks before inclusion
- Increased aspartate transaminase and alanine transaminase levels as well as other signs of hepatic impairment, severe and uncontrolled organic disease, porphyria, alcohol, or drug abuse.

Treatment

Agomelatine was administered orally as a 25 mg tablet before sleep. The dose could be increased at the discretion of the physician to 50 mg after 2 weeks of treatment. No other antidepressant therapy was allowed. Previous treatment with antidepressants had to be stopped at least 14 days before the start of the study for fluoxetine and at least 3 days before for other antidepressants.

Patients using anxiolytics (hypnotics) at baseline could continue with this treatment up to day 14 of the study, at which point the medications had to cease or the patient had to be excluded from the study. No other psychopharmacologic drugs, such as antipsychotics, mood stabilizers, antiepileptics, or potent inhibitors of the cytochrome P450 1A2 metabolic system, were allowed.

Efficacy assessments

The primary objective was to assess change in total MADRS score²⁵ from baseline to study completion. Using the MADRS score, assessments were also made of the clinical response defined as a reduction in total MADRS score of $\geq 50\%$, and remission rate defined as the percentage of patients with total MADRS score ≤ 7 .²⁶ Secondary objectives included assessment of the efficacy of treatment measured by change in Clinical Global Impression-Severity (CGI-S) and Clinical Global Impression-Improvement (CGI-I) score.²⁷ Change in functioning was measured on the clinician-rated Global Assessment of Functioning (GAF) scale²⁸ and patient-rated Sheehan Disability Scale (SDS).²⁹ The patient-based evaluation of sleep (CircScreen³⁰ [screening of Sleep and Circadian Rhythms Disorders]) was also used. Patients were evaluated on clinician-rated scales (MADRS, GAF, CGI-S, and CGI-I) and patient-rated scales (CircScreen and SDS) at baseline and at weeks 1, 2, 4, and 8 (see Table 1).

Safety and tolerability

The safety and tolerability of treatment with agomelatine was evaluated by recording spontaneously reported adverse

Table 1 Patient evaluation protocol

Evaluations	Week of study					
	Baseline – W0	W1	W2	W4	W6	W8
Clinician-rated scales	MADRS	X	X	X	–	X
	GAF	X	–	X	–	X
	CGI-S	X	X	X	–	X
	CGI-I	–	X	X	–	X
Patient-rated scales	CircScreen	X	X	X	–	X
	SDS	X	X	X	–	X
Adverse events	Spontaneously reported	X	X	X	X	X
Hepatic enzymes	ALAT, ASAT	X	–	–	X	–

Abbreviations: ALAT, alanine transaminase; ASAT, aspartate transaminase; CGI-I, Clinical Global Impression-Improvement; CGI-S, Clinical Global Impression-Severity; CircScreen, Screening of Sleep and Circadian Rhythms Disorders; GAF, Global Assessment of Functioning; MADRS, Montgomery and Åsberg Depression Rating Scale; SDS, Sheehan Disability Scale; W, week.

events and measurement of aspartate transaminase and alanine transaminase levels at intervals recommended in the current summary of product characteristics³¹ at baseline and at week 6 of treatment. Physical attributes including body weight, blood pressure, and heart rate were also monitored at each visit. Adverse events were spontaneously reported by the patients. Patients had to mandatorily withdraw from the study if aspartate transaminase and alanine transaminase values exceeded three times the upper limit of normal.

Statistical analysis

The change from baseline to each evaluation point in all primary and secondary efficacy assessments was evaluated. Data were analyzed for normal distribution using the Kolmogorov-Smirnov test, and according to the results, the Wilcoxon nonparametric test with Monte Carlo calculation of the *P* value for differences was used in further calculations. The last observation carried forward (LOCF) method was used for handling of missing data. Both the frequencies of response and remission were calculated for patients who had finished 8 weeks of treatment ($n=94$). Safety and tolerability data were analyzed descriptively for patients as per the protocol.

Results

In total, 111 patients fulfilled the protocol criteria and were included in the study. Of these, 94 (84.7%) completed the 8-week treatment period. The primary reasons for dropout from the study (two patients in week 1; three patients in week 2; two patients in week 4; four patients in week 6; six patients in week 8) were loss of contact (three patients), patient's request (eight patients), nonefficacy of drug (nine patients), violation of protocol, ie, nonpermitted

additional treatment (one patient), and adverse events (two patients).

The mean age of the patients was 45.8 ± 13.1 (range 19–65) years, and 25.2% were male. Patients had had a mean number of depressive episodes of 2.12 ± 1.7 (range 1–10) in their life history, and agomelatine was the first treatment for depression in 38.7% of patients. In the 6 months before taking the study antidepressant, anxiolytics, hypnotics, and antipsychotics were prescribed for 59.5%, 35.5%, and 5.0% of patients, respectively. One patient gave a history of having received electroconvulsive therapy 13 years earlier.

The mean total MADRS score at baseline was 28.7 ± 4.7 , and according to the Mini International Neuropsychiatric Interview criteria,²⁴ depression was mild, moderate, and severe in 0.9%, 62.2%, and 36.9% of patients. After 2 weeks of treatment, the dose of agomelatine was increased from 25 mg to 50 mg in 28 patients with higher MADRS scores. The total MADRS score in these patients was 22.79 in comparison with 19.46 for patients who continued on the initial dose of 25 mg.

Primary efficacy results

The primary efficacy variable, ie, total MADRS score, improved significantly as early as the first week of treatment ($Z = -8.11$; $P < 0.001$) and significant improvement continued in all following assessments (Table 1). The mean total MADRS score in week 8 of treatment was 11.5 ± 8.9 by LOCF analysis (Table 2) and 9.8 ± 7.5 for observed cases. The mean changes in total MADRS score are presented in Figure 1. The rate of achieving the given criteria for response (total MADRS score $\leq 50\%$ of baseline) and remission (total MADRS score ≤ 7) for patients who continued in the study for 8 weeks ($n=94$) is shown in Figure 2. Clinical response by definition was observed in 14.1% in the second week of

treatment, and by week 8, the response was achieved in 74.5% of patients. By week 8 of treatment, 46.8% of patients had achieved remission.

The mean total MADRS score in patients who achieved a response and finished the study ($n=72$) was 27.8 ± 4.5 . In 22 patients who finished the 8 weeks of observation but did not achieve a response, the mean total MADRS score was 32.7 ± 4.0 at baseline and 20.3 ± 4.3 by week 8 of treatment. In five of 17 patients who dropped out during the 8 weeks of the study, remission was achieved in week 2 or 4 of treatment.

Secondary efficacy results

The significant reduction in depressive symptoms as measured by MADRS score was reflected in a positive change in overall clinical status as measured by the CGI scales. Improvement of global clinical status on the CGI-I scale was documented by a change in mean score to 3.3 in the first week (corresponding to “very minimally improved” or “no change”) and to a mean score of 1.8 (corresponding to “very much improved” or “much improved”) at week 8 (Table 2). Also, the mean CGI-S score improved from 4.63 at baseline to 2.18 at week 8, with a significant difference found as early as the first week of treatment ($Z = -5.369$; $P < 0.001$, Table 2).

A positive and significant change in functioning was recorded when measured by physician-rated GAF scale and all three domains of the patient-rated SDS scale. The mean GAF score increased from 60.51 at baseline to 80.2 at 8 weeks (LOCF), with a significant difference compared with baseline achieved at the first measurement in the second week of treatment ($Z = -7.252$; $P < 0.001$, Table 2 and Figure 3). Mean SDS scores decreased from baseline to week 8 of treatment for work, social, and family dimensions. In all three dimensions, a statistically significant difference was found in the

Table 2 Mean values and SDs of scores of scales used for primary and secondary parameters in the study (LOCF)

	Baseline	Week 1	Week 2	Week 4	Week 8
MADRS mean score (SD)	28.7 (4.7)	24.8 (6.0)	20.7 (7.1)	15.7 (8.2)	11.5 (8.9)
CGI-S mean score (SD)	4.63 (0.7)	4.3 (0.9)	3.7 (1.0)	2.9 (1.1)	2.2 (1.2)
CGI-I mean score (SD)	–	3.3 (0.7)	2.8 (0.7)	2.2 (0.9)	1.8 (1.0)
GAF	60.51 (7.2)	–	67.4 (9.4)	74.8 (11.4)	80.2 (12.6)
SDS Work mean (SD)	7.3 (1.2)	6.5 (1.7)	5.7 (2.0)	4.2 (2.3)	3.0 (2.5)
SDS Social mean (SD)	7.7 (1.4)	6.7 (2.0)	6.1 (2.2)	4.4 (2.4)	3. (2.7)
SDS Family mean (SD)	7.0 (1.2)	5.3 (1.9)	6.35 (1.7)	3.7 (2.2)	2.6 (2.4)
CircScreen mean (SD)	12.9 (3.4)	9.7 (4.1)	7.1 (4.2)	5.2 (3.9)	3.7 (3.8)

score for sum of items 1–5

Abbreviations: MADRS, Montgomery and Åsberg Depression Rating Scale; CGI-S, Clinical Global Impression-Severity; CGI-I, Clinical Global Impression-Improvement; GAF, Global Assessment of Functioning; SDS, Sheehan Disability Scale; CircScreen sum 1–5, sum of items, difficulties falling asleep, repeated awakening, waking early in morning, difficulty in being fully awake in the morning, and feeling sleepy during the day (Screening of Sleep and Circadian Rhythms Disorders); SD, standard deviation; LOCF, last observation carried forward.

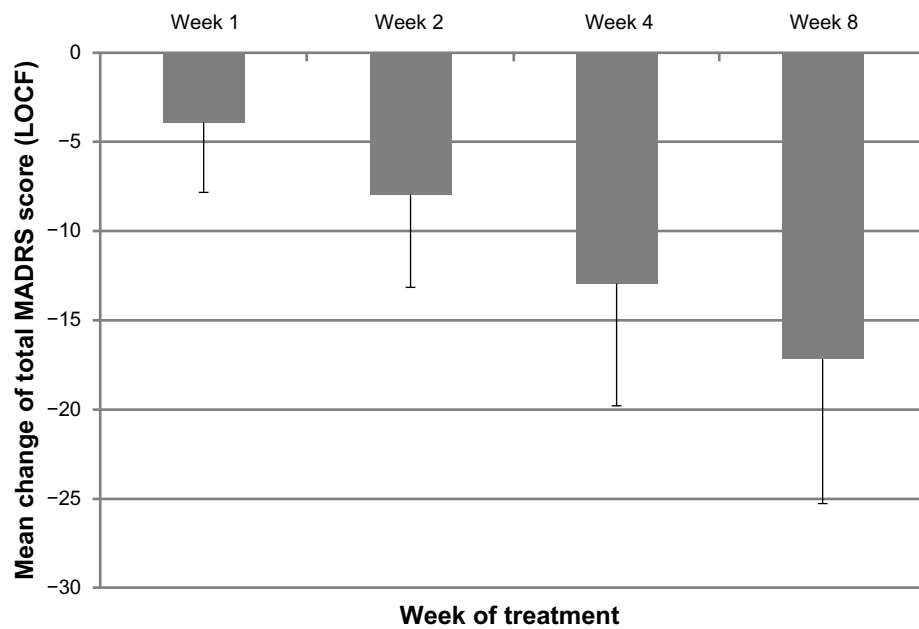


Figure 1 Mean change of total MADRS score from baseline. **Note:** Error bars represent standard deviations. **Abbreviations:** MADRS, Montgomery and Åsberg Depression Rating Scale; LOCF, last observation carried forward.

first week of treatment ($Z=-6.788$, $Z=-8.215$, and $Z=-8.527$, respectively; $P<0.001$, Table 2 and Figure 4).

The change in mean sum of the five CircScreen questionnaire items (difficulty falling asleep, repeated awakening, waking early in morning, difficulty in being fully awake in the morning, and feeling sleepy during the day) was rated by the patient on a scale of 0 (very rarely) to 4 (very often). The sum of items 1 to 5 of CircScreen (LOCF) decreased

from 12.9 at baseline to 3.7 at week 8. The difference versus baseline scores was significant from the first week of treatment ($Z=-7.727$; $P<0.001$, Table 2 and Figure 5).

Safety and tolerability

Agomelatine was generally well tolerated, with most adverse events being mild to moderate in severity. There were 31 spontaneously reported adverse events in 17 patients.

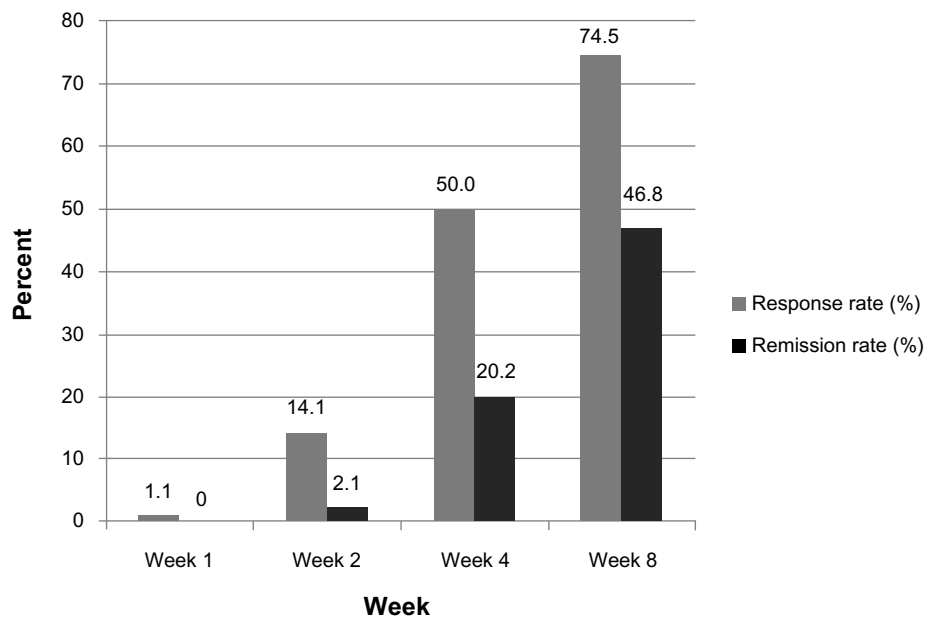


Figure 2 Response and remission rate (observed cases, n=94).

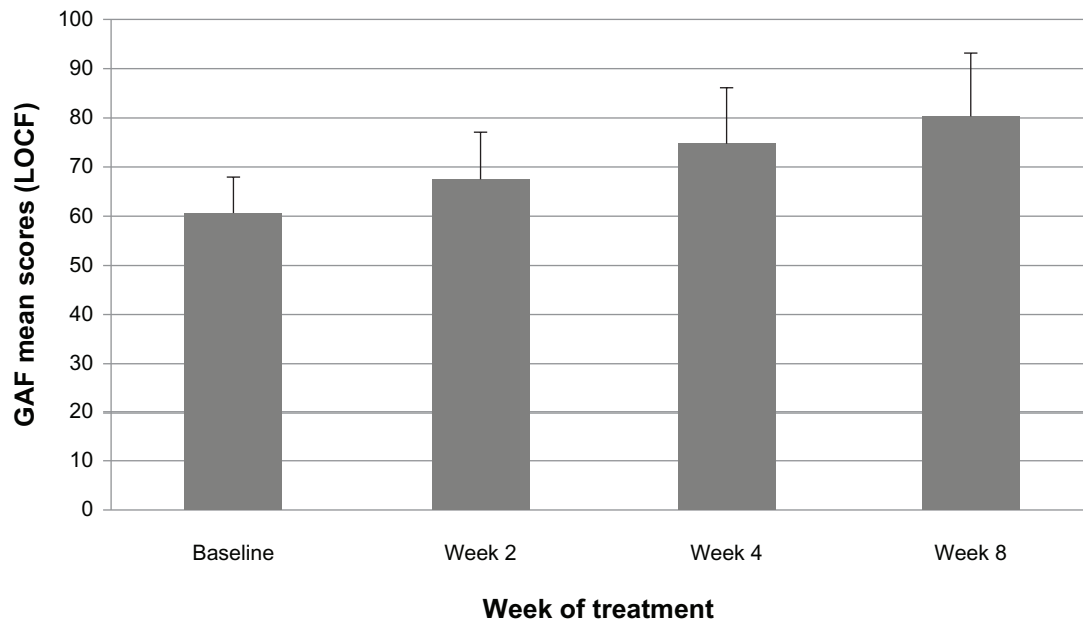


Figure 3 Mean GAF scores from baseline to week 8.

Note: Error bars represent standard deviations.

Abbreviations: GAF, Global Assessment of Functioning; LOCF, last observation carried forward.

The most frequent adverse events were headache and tension (n=6) and anxiety (n=4). Two patients experienced adverse effects which resulted in termination of their participation in the study; one of these patients had nausea and diarrhea and the other patient had nightmares. No adverse effect was serious as evaluated by the treating psychiatrist. No elevation of aspartate transaminase or alanine transaminase greater than three times the upper limit of normal values was observed.

There were no overt or clinically significant changes in body weight, blood pressure, or heart rate. The physical measures are summarized in Table 3.

Discussion

The efficacy of agomelatine has been the subject of a number of clinical trials.^{15,32-39} In this open-label study of agomelatine monotherapy in patients with moderate to severe major

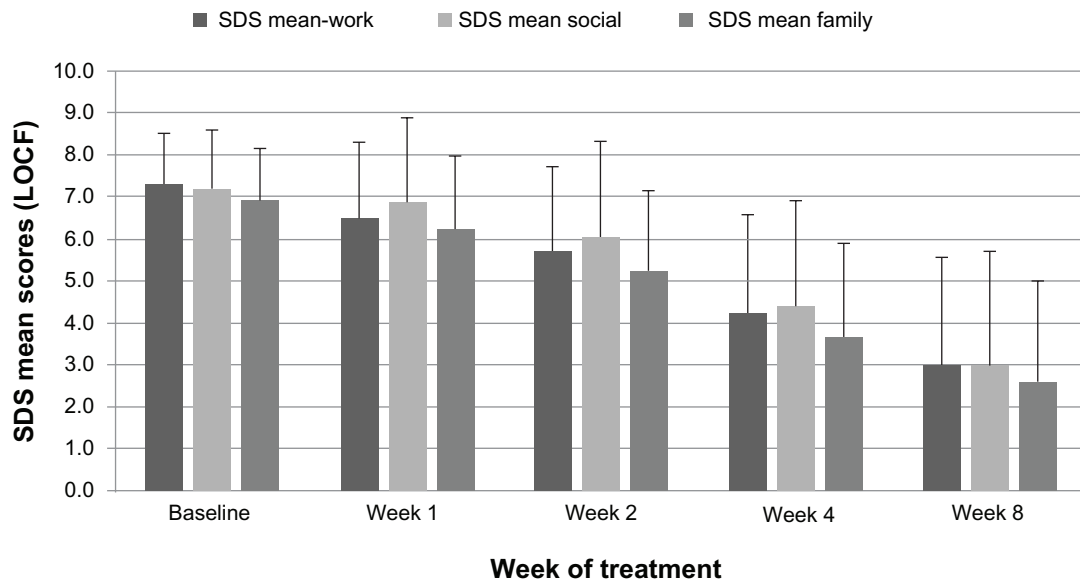


Figure 4 Mean Sheehan Disability Scale scores baseline to week 8.

Note: Error bars represent standard deviations.

Abbreviations: SDS, Sheehan Disability Scale; LOCF, last observation carried forward.

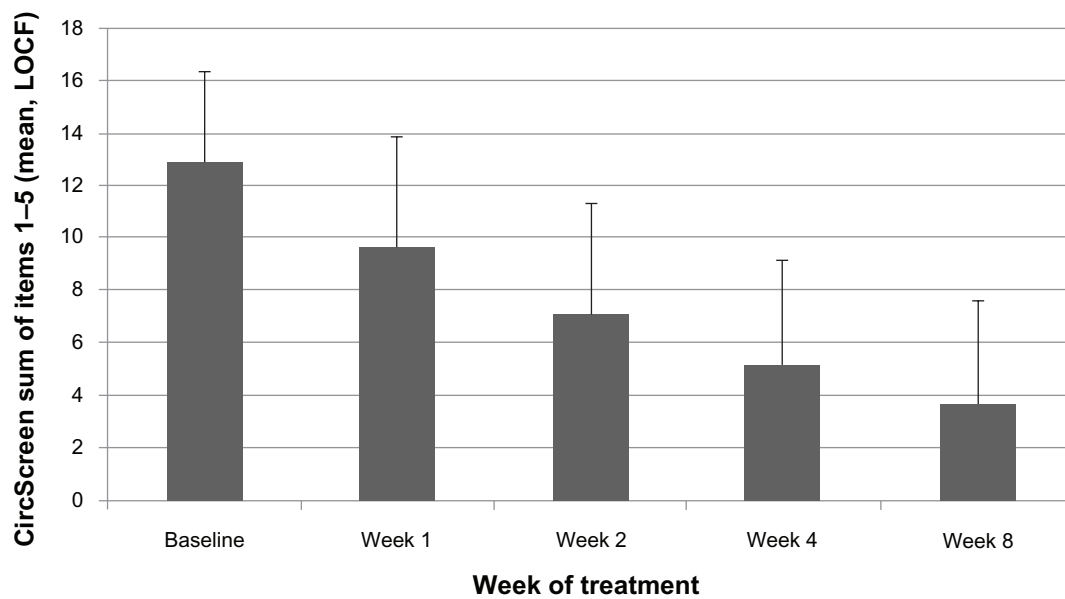


Figure 5 Mean sum of items 1–5 of CircScreen questionnaire.

Note: Error bars represent standard deviations.

Abbreviations: CircScreen, Screening of Sleep and Circadian Rhythms Disorders (items 1–5: difficulties falling asleep, repeated awakening, waking early in morning, difficulty in being fully awake in the morning, and feeling sleepy during the day); LOCF, last observation carried forward.

depressive disorder, MADRS scores and CGI-S scores decreased significantly as early as the first week of treatment and this improvement continued over 8 weeks of treatment. Thus, agomelatine monotherapy was effective in managing patients with moderate to severe major depressive disorder. The difference in mean total MADRS score at week 8 of treatment compared with baseline was 17.2 points, which is a very similar result to the findings of a 12-week observational study of agomelatine involving 3,317 patients in Germany.¹⁹ A substantial proportion of patients achieved a clinical response and remission (Figure 2). The response and remission rates during antidepressant treatment can be expected in broad variety.⁴⁰ The response rate in the current study was much higher than in the 6-week and 8-week double-blind, placebo-controlled studies of agomelatine^{13,36} and higher than in an observational study of different antidepressants where a 38.2% early remission rate and a 20.5% early response rate were found at week 6 of treatment,⁴¹ but similar to a

double-blind study comparing agomelatine with venlafaxine in patients with severe depression.⁴² The higher response and remission rates in the current study could be explained by its open design with involvement of patients who were suitable for treatment with agomelatine in the opinion of the treating psychiatrists. Early response to treatment with agomelatine has been reported in previous studies.^{40,43} Generally, the time taken for antidepressants to start showing a clinical effect is at least 2 weeks.⁴⁴ This delayed onset of action is due to various factors, eg, the time needed for downregulation of several types of receptors and the time needed for neuroplasticity changes to occur, which are postponed because of a change in activity of receptors/transporters due to the action of different antidepressants.⁴⁵ Early improvement of depressive symptoms is very desirable because delayed onset of antidepressant treatment is linked with several negative factors, from prolonged social and working dysfunction to increased risk of suicide and additional deleterious neurobiologic changes.⁴⁶

In recent years, there has been a growing interest in not only using symptom reduction as a traditional outcome measure for efficacy of treatment but also evaluating other important needs and concerns of patients, like social life and working capacity.⁴⁷ Significant changes in scoring of two different measures of functionality used in this study accompanied the changes in symptomatology. The GAF scale is evaluated by professionals and is considered to reflect the severity of symptomatology

Table 3 Physical measures

	Baseline (SD)	Week 8 (SD)
Mean weight (kg)	72.2 (14.9)	71.6 (14.7)
Mean systolic blood pressure (mmHg)	124.8 (10.7)	123.9 (8.5)
Mean diastolic blood pressure (mmHg)	78.6 (7.8)	77.1 (5.5)
Heart rate (bpm)	73.5 (6.4)	73.8 (5.0)

Abbreviations: bpm, beats per minute; SD, standard deviation.

more than genuine functionality.⁴⁸ The SDS has been selected as the most relevant global self-reported assessment of functioning in trials of antidepressants. Most studies have measured social functioning every second week. This was the first study to administer the SDS scale in the first week after the start of the study, with significant changes found in all three dimensions. Social functioning as part of the health-related concept of patient-reported quality of life should constitute an endpoint in trials of antidepressants to help clarify the goals of treatment in patients with major depression.⁴⁹ Agomelatine with its melatonergic activity is supposed to improve the quality of sleep, which was confirmed by patient-rated questionnaire (Table 2 and Figure 5).

Published studies of agomelatine have confirmed good tolerability of the drug.^{13,16} In this study, patients treated with agomelatine did not have any overt or clinically significant changes in body weight, blood pressure, or heart rate. A lot of evidence for a bidirectional association between depression and obesity exists,⁵⁰ and agomelatine could be considered as a weight-neutral antidepressant. The minimal effect of treatment with agomelatine on weight was also confirmed in a long-term study.¹⁴ Agomelatine was generally well tolerated, with most adverse events being mild to moderate in severity. No adverse effect was evaluated as serious by the treating psychiatrist. There was no statistically significant change in hepatic enzyme values in any of the patients, and no patient withdrew due to elevation of hepatic enzymes.

This study has several limitations. An open-label, non-randomized design could be associated with various sources of bias. Registration of patients offered entry to the study but refused it for whatever reason was not part of the protocol, so comparison of the study sample with these patients cannot be done. In general, these data should be interpreted for a selected population of patients who are considered by clinicians to be suitable for treatment with agomelatine, so allocation of patients to treatment was intrinsically biased. Positive expectations of a new antidepressant on the part of treating psychiatrists could also have had an influence. Observational and reporting bias is a characteristic of these types of studies, and small sample size is another limitation precluding generalization of the present data. On the other hand, well documented observational studies from everyday clinical practice can bring a new comprehension of clinical practice and could be perceived as an important complement to randomized, controlled clinical trials.⁵¹ Different measures are needed for different dimensions to demonstrate the efficacy of treatment in short-term studies.⁵² The compact and significant improvement in symptomatology, functioning,

and sleep found in this observational study could reflect the efficacy of agomelatine in the treatment of selected patients with depression in outpatient settings.

Conclusion

In this open-label study of agomelatine monotherapy in patients with moderate to severe major depressive disorder, there was a simultaneous and significant improvement in symptoms of depression and daily functioning. Agomelatine was generally well tolerated. Agomelatine has a unique position among the currently available antidepressant drugs because it has primary antidepressant properties based on its synergic mechanism of action on MT1 and MT2 receptors and specific antagonistic effect at 5-HT_{2C} receptors.⁵³ These results in patients from routine clinical practice can be considered as a marker of the effectiveness of agomelatine in the treatment of major depressive disorder. They also support the use of agomelatine monotherapy for patients with moderate to severe major depressive disorder.

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Author contributions

The late Professor Vladimir Novotny, Clinic of Psychiatry, Faculty of Medicine, Comenius University and University Hospital, Bratislava, Slovakia was the main collaborator and his contribution to this study is acknowledged. JP and VN were involved in the creation and translation of the protocol, training of participating psychiatrists, analyses of data, drafting of the manuscript and JP created and approved the final version.

Disclosure

JP has received educational grants or has participated on advisory boards or speakers' bureaus for AstraZeneca, Eli Lilly, Janssen, Lundbeck, and Servier. This study was supported by Servier Slovakia. The authors report no other conflicts of interest.

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