

Agomelatine or placebo as adjunctive therapy to a mood stabiliser in bipolar I depression: randomised double-blind placebo-controlled trial

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Background

Adjunctive antidepressant therapy is commonly used to treat acute bipolar depression but few studies have examined this strategy.

Aims

To examine the efficacy of agomelatine *v.* placebo as adjuncts to lithium or valproate in bipolar depression.

Method

Patients who were currently depressed despite taking lithium or valproate for at least 6 weeks were randomised to treatment with agomelatine ($n = 172$) or placebo ($n = 172$) for 8 weeks of acute therapy and 44 weeks of continuation therapy (trial registration: ISRCTN28588282).

Results

No significant differences in improvement of depressive symptoms were observed between the two groups either at 8 weeks or 52 weeks on the primary efficacy measure of change in Montgomery-Åsberg Depression Rating Scale scores from baseline to end-point. Adverse events including switches into mania/hypomania were low and similar in both groups.

Conclusions

Agomelatine adjunctive therapy was not superior to placebo adjunctive therapy for acute bipolar depression.

Declaration of interest

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Although mania is the defining feature of bipolar I disorder, depressive episodes pose the major burden of this condition. Patients with bipolar I disorder experience syndromal or sub-syndromal depressive symptoms three times more commonly than syndromal/subsyndromal manic symptoms.^{1–3} Depressive symptoms in bipolar I disorder are associated with poor functioning⁴ and poorer quality of life⁵ and increased risk of suicide.^{6,7} Yet, only three treatments (quetiapine; olanzapine plus fluoxetine combination; lurasidone) have been approved by the US Food and Drug Administration for treatment of acute bipolar depression. In real-world clinical practice, a significant proportion of patients either does not respond to or does not tolerate the side-effects of these treatments. Thus, other treatments that are safe and effective are urgently needed. Antidepressants in combination with mood stabilisers or atypical antipsychotics are widely used for treating bipolar depression in clinical practice.^{8,9} Yet, the efficacy of such

strategy continues to be controversial.¹⁰ Three large double-blind trials examined the efficacy of antidepressant add-on *v.* placebo add-on to mood stabilisers in treating bipolar depression. Fluoxetine plus olanzapine was more effective than not only placebo alone but also placebo plus olanzapine in improving bipolar depressive symptoms.¹¹ Paroxetine was no more effective than placebo when added to lithium, but superiority of paroxetine to placebo was noted in a *post hoc* analysis of patients with lower serum lithium levels.¹² In the STEP-BD study, durable recovery rates were no different between the paroxetine or bupropion plus mood stabiliser group compared with the placebo plus mood stabiliser group.¹³ Since this study did not have a placebo monotherapy arm, the results could be interpreted to indicate that both treatments were either equally effective or ineffective in improving depressive symptoms. If it was indeed a failed study, it highlights a recognised problem with patient selection for placebo-controlled

studies in mood disorders, which is the recruitment of an assay sensitive population.¹⁴ High placebo response rates and high drop-out rates greatly reduce assay sensitivity. There is now mounting evidence that conduct of trials at non-academic sites may further compromise the quality of recruitment.^{15,16}

Overall there is a paucity of studies comparing the addition of antidepressant *v.* placebo to a mood stabiliser or an atypical antipsychotic as a strategy for managing bipolar depression.¹⁷ Agomelatine represents a novel pharmacology among antidepressants as it is the only compound possessing both melatonin receptor (MT₁ and MT₂) agonist and 5-hydroxytryptamine 2 C (5-HT_{2c}) receptor antagonist properties.¹⁸ The acute and long-term efficacy and tolerability of agomelatine has been clearly demonstrated at doses of 25–50 mg in patients with major depressive disorder^{19–21} and in those with generalised anxiety disorders.^{22,23} The efficacy and safety of agomelatine in patients with major depressive disorder and generalised anxiety disorders compared favourably with other antidepressants.^{23,24} In a preliminary open-label study that assessed the efficacy and safety of agomelatine 25 mg in addition to lithium or valproate in patients with bipolar I depression, a high rate of treatment response (81%) was obtained over a 6-week treatment period, together with good acceptability.²⁵ The primary objective of the present study was to further explore the antidepressant efficacy of 8 weeks of treatment with agomelatine 25–50 mg as an add-on to a mood stabiliser (MS) lithium or valproate (AGO-MS) compared with placebo add-on to a mood stabiliser (PBO-MS) in patients with bipolar I disorder in a current major depressive episode. The secondary objectives were (a) to assess the safety of AGO-MS and (b) to collect preliminary data on AGO-MS maintenance of efficacy and long-term safety over a 10-month double-blind extension treatment period.

Method

This was an international, double-blind, randomised study using a flexible dosage of agomelatine or placebo in combination with a mood stabiliser (lithium or valproate), conducted in 67 centres in 15 countries (Argentina, Australia, Austria, Brazil, Canada, Denmark, Finland, France, Germany, India, Korea, Netherlands, Poland, South Africa, Spain) from July 2006 to December 2008 (trial registration: ISRCTN28588282). The study was performed in accordance with the principles of Good Clinical Practice E6 of the International Conference of Harmonisation (CPMP/ICH/135/95) and the Declaration of Helsinki, Finland. The study was approved by the relevant local ethics committees. All participants provided written informed consent for participation in the study.

Study population

Male or female out-patients eligible for this study were aged 18 (at least 21 years old in Argentina) to 70 years and presented with a bipolar I disorder currently in a major depressive episode according to DSM-IV-TR²⁶ criteria, confirmed with the Mini International Neuropsychiatric Interview.²⁷ The current major depressive episode must have lasted at least 4 weeks but no more than 12 months. At the selection visit, they had to meet the following criteria: 17-item Hamilton Rating Scale for Depression (HRSD-17)²⁸ total score ≥ 18 and Young Mania Rating Scale (YMRS)²⁹ total score 8.

Patients had to be on either lithium or valproic acid treatment for a minimum of 6 weeks before selection visit with a blood level of lithium between 0.5 and 1.0 mEq/L or valproic acid between 50 and 100 g/mL, tested between selection and inclusion visits. No mood stabiliser dose adjustment was allowed after inclusion, unless the serum levels were out of the therapeutic range. In order to ensure stable mood stabiliser concentrations within the

accepted therapeutic range over the course of the study, mood stabiliser blood levels were measured between weeks 6 and 8, between months 5 and 6, and between months 10 and 12. Lorazepam use was allowed as needed between week 0 and week 2 visits only.

Patients were required to be physically healthy or to have stable medical illnesses on the basis of medical history, physical examination, 12-lead electrocardiogram (ECG) and clinical laboratory tests (biochemistry and haematology). Patients were excluded if they had transaminase values > 3 times the upper normal limit, a blood creatinine value higher than 150 $\mu\text{mol/L}$, abnormal thyroid function and/or positive plasma beta-human chorionic gonadotropin.

Patients who met criteria for any of the following DSM-IV-TR disorders were excluded: obsessive-compulsive disorder, alcohol or drug misuse or dependence within the past 6 months. Patients were also excluded if they were at risk of suicide based on the assessment of the investigator or had a rating of four points on item three of HRSD-17. Patients were excluded if they had not responded to the administration of an appropriate dose of two different previous antidepressant treatments at the recommended dosage for the current episode. Patients with neurological disorders (dementia, seizure and stroke) or severe or uncontrolled organic disorders (neoplastic, cardiovascular, pulmonary or digestive disorders, unstable type 1 or 2 diabetes, hypo- or hyperthyroidism, untreated or uncontrolled hypertension) were also excluded. Patients were also excluded if they had received any of the following recent/concomitant therapies: formal psychotherapy, sleep deprivation and light therapy started within 2 weeks, electroconvulsive therapy (ECT) or transcranial magnetic stimulation for the current episode. For psychotropic treatments, a wash-out period of five elimination half-lives of the molecule was required before inclusion.

Study design and allocation to treatment

Patients had a 2- to 10-day run-in selection period between selection and inclusion (week 0) visits. At week 0, eligible patients were assigned to agomelatine or placebo according to a balanced (non-adaptive) randomisation with stratification based on the mood stabiliser (lithium or valproic acid) and the clinical centre. The treatment allocation and the dose increase were done centrally using an interactive voice response system (IVRS) in masked conditions for patients and investigators. From week 0, patients received agomelatine 25 mg/day or placebo. In case of insufficient improvement – determined using masked criteria defined by the sponsor prior to the study start – the dosage of agomelatine was increased to 50 mg/day after 2 weeks. Both the investigator and the patient were masked to dose adjustment. The 8-week double-blind treatment period was followed by an optional 10-month extension period. After study treatment discontinuation, regardless of when it occurred, there was a 1-week follow-up period without study treatment.

Throughout the duration of the study, patients took two tablets orally once a day in the evening (around 20.00 h). Patients received either agomelatine 25 mg (1 tablet of 25 mg + 1 placebo tablet), agomelatine 50 mg (2 tablets of 25 mg) or placebo (2 placebo tablets). The dosage schedule, the appearance of the study medication and the taste were the same from inclusion to the end of the treatment period for all patients. Tablets were packaged in identical blisters with identical labelling.

Efficacy measurements

In order to protect against baseline score inflation, the HRSD-17 was used to determine study eligibility, whereas change in the total

Montgomery–Åsberg Depression Rating Scale (MADRS)³⁰ total score from baseline to the last post-baseline value over the acute 8-week treatment period was used as the primary efficacy measure. The MADRS was administered at each visit by the study investigators.

Secondary efficacy measures included response to treatment (defined as a decrease from baseline in MADRS total score 50%) over the 8-week and 12-month periods, changes in the HRSD-25 (HRSD-17 + 8 items of Reverse Vegetative Symptom Scale), the Clinical Global Impressions scale for Bipolar Disorder – Modified (CGI-BP-M),³¹ the Hamilton Rating Scale for Anxiety (HRSA),³² the Leeds Sleep Evaluation Questionnaire (LSEQ)³³ and the Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (QLESQ).³⁴

Safety measurements

Tolerability and safety evaluations were based on emergent adverse events spontaneously reported by the patient at each visit. Investigators were prompted to report any significant mood elevation according to their clinical judgement as an adverse event. Then, at least 1 week after the onset of the symptoms, the investigators were asked to describe the event by assessing the DSM-IV criteria for mania (hypomanic or manic) and to provide their final diagnosis. YMRS was rated by the investigator at selection, inclusion and each visit up to month 12.

The tolerability and safety evaluations were also based on 12-lead ECG abnormalities, biological samplings and physical examination. Vital signs (body weight, supine heart rate and blood pressure) were assessed at inclusion, week 8 and month 12 or at termination in the case of premature withdrawal.

Sample size calculations

Sample size calculations were performed based on the expected difference in MADRS change scores between baseline and last post-baseline visits over week 0 to week 8 between agomelatine and placebo groups in the full analysis set (using the two-sided Student's *t*-test for independent samples at 5% type I error). It was estimated that 148 patients per treatment group would provide a power of at least 80% if the difference in MADRS scores is at least 3 points with a standard deviation of 9 points. For a similar standard deviation, this number of patients is sufficient to conclude the superiority with a power of at least 90% if the difference is at least 3.5 points.

Statistical analysis

As established in the protocol registration, all efficacy analyses were performed on the full analysis set (intention-to-treat principle) based on the last post-baseline value recorded over the acute 8-week treatment period. The superiority of AGO-MS as compared with PBO-MS was examined on the MADRS total score using a three-way analysis of covariance with treatment and type of mood stabiliser as fixed effects, centre as random effect, with baseline MADRS total score as covariate and without interaction. A similar analysis was performed on the secondary outcome of HRSD-17 total score. In addition, an unadjusted analysis, based on the two-sided Student's *t*-test for independent samples, was performed.

The difference in response rates (as determined by 50% or greater reduction in MADRS scores was estimated, taking into account the last post-baseline value over the acute 8-week treatment period) between AGO-MS and PBO-MS was computed using a chi-squared test. For other comparisons, appropriate parametric and non-parametric statistics were used. Safety data

were provided by treatment group over the acute and extension periods for the safety set of patients (i.e. having taken at least one dose of study treatment).

Post hoc analysis

In order to understand the impact of placebo response, we performed a *post hoc* analysis that included patients from all centres that had randomised at least one patient to each treatment condition (AGO-MS and PBO-MS). We then excluded all patient data from centres that had particular placebo or agomelatine responder rates (responder defined as ≥ 50 improvement on MADRS) i.e. 100%, $\geq 90%$, $\geq 80%$0%. We examined changes in MADRS scores using a three-way analysis of covariance with treatment and type of mood stabiliser as a fixed effect, centre as a random effect and baseline MADRS total score as a covariate and without interaction. Statistical analysis was performed on SAS software, version 9.1. The type I error was set at 5% (two-sided tests).

Results

Clinical and demographic characteristics

Of the 405 patients selected, 344 patients (84.9%) were randomly allocated to receive AGO-MS (172 patients) or PBO-MS (172 patients) (Fig. 1). There were no significant differences in demographic characteristics between patients treated with AGO-MS or PBO-MS (Table 1). The average age of the randomised patients was 45.2 years (s.d. = 12.6) and 61.1% were female.

The average duration of bipolar I disorder in study participants was 16.7 years (s.d. = 11.2, median 14.6). The first episode was more frequently a depressive episode (62.5% of patients). The study patients had experienced 2.6 manic episodes (s.d. = 2.7), 0.8 mixed episodes (s.d. = 1.6) and 4.9 depressive episodes (s.d. = 4.9) during the past 10 years. During the past 12 months, the mean number of mood episodes was 1.7 (s.d. = 0.9). Throughout the study, mood stabiliser blood levels were within the range planned in the protocol (~ 0.7 mmol/L for lithium; between 66 and 79 g/mL for valproic acid).

No clinically relevant differences between the groups were observed regarding physical examination, ECG and other baseline characteristics. Baseline scores for various measures including MADRS, HRSD, HRSA, YMRS, CGI-BP-M depression, mania or general score and QLESQ at inclusion are provided in Table 2. A total of 87 patients out of the 157 (55.4%) randomised to the AGO-MS group and continuing in the study after week 2 had a dose increase.

Efficacy on depression

MADRS total score

Over the 8-week period, mean changes from baseline to last post-baseline value in the full analysis set were clinically relevant and identical in both groups (Table 3). Improvement on the MADRS total score was not significantly different between groups after adjustment for mood stabiliser, baseline score and centre (mean difference: -0.65 (s.e. = 1.13), $P = -0.565$). There was, correspondingly, no significant difference between the AGO-MS and PBO-MS groups in the proportion of responders (61.9% and 60.8%, respectively, $P = 0.837$) or remitters defined as a MADRS total score ≥ 12 , (53.0% and 53.2% in the AGO-MS and PBO-MS groups, respectively).

A total of 244 patients (AGO-MS: 124; PBO-MS: 120) entered the 10-month extension phase and had at least one post week 8 MADRS score. There were no significant differences in MADRS

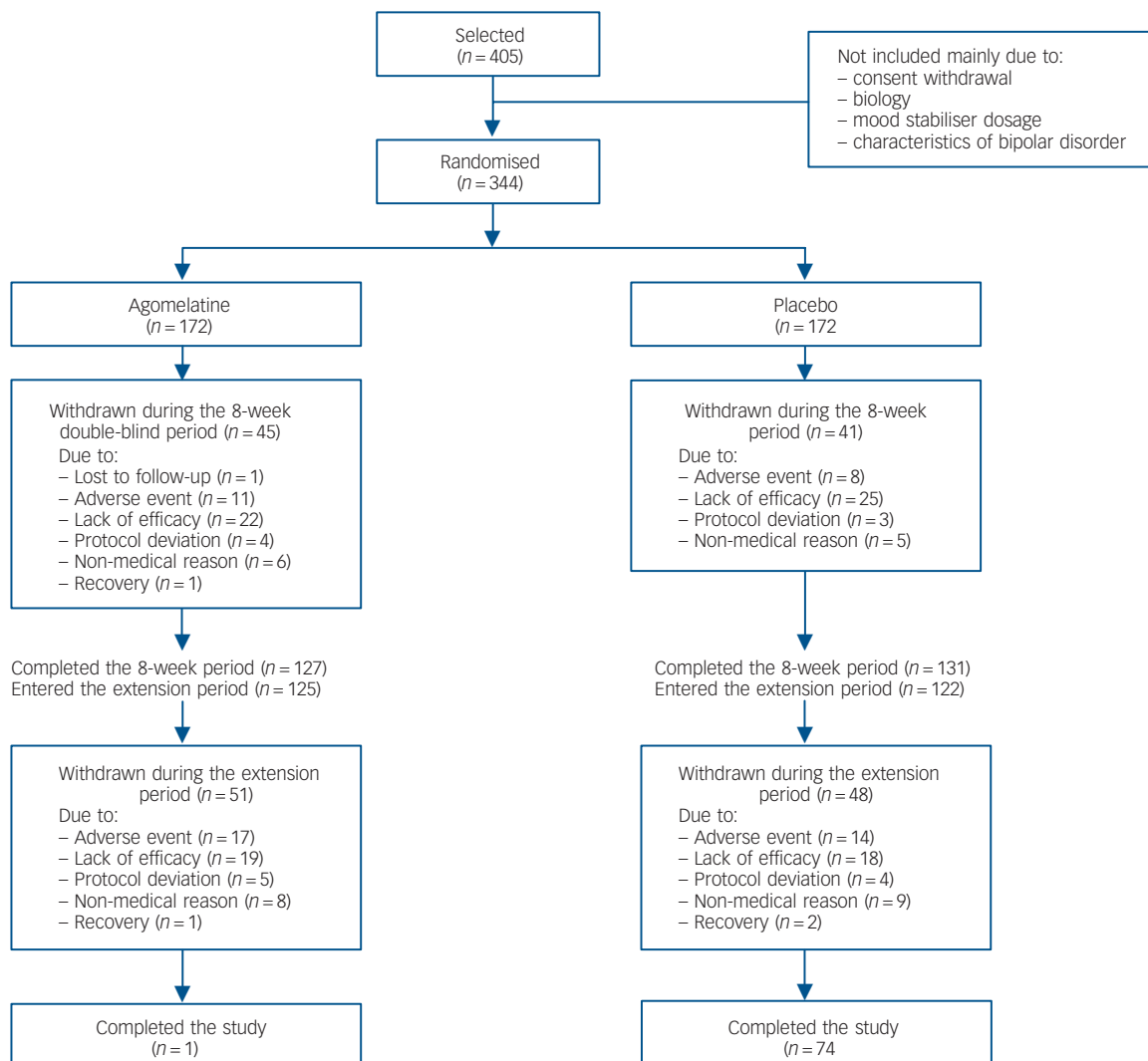


Fig. 1 Disposition of patients.

change scores from baseline to end-point for this subsample that entered the extension phase. Similarly, at the end of the extension period, MADRS total score mean changes using last observation carried forward (LOCF) for the full analysis set from baseline were also not different between the two groups (Table 3). The percentage of responders (61.9 % v. 55.0%, $P=0.195$ and remitters (57.7% v. 52.6%, $P=0.345$) on the MADRS scale at the last post-baseline assessment were numerically higher in the AGO-MS group than in the PBO-MS group, but neither comparison reached conventional levels of statistical significance.

Other secondary efficacy measures

There were no significant differences between the groups on CGI-BP-M depression, mania or general scores at week 8 or month 12. Similarly, no significant differences in change scores on the HRSD-17, Reverse Vegetative Symptoms Scale, or HRSA, LSEQ and QLESQ were observed between the groups at week 8.

Withdrawals

During the 8-week acute treatment period, 86 randomised patients (25.0%) withdrew from the study, 47 as a result of lack of efficacy (22 patients in the AGO-MS group; 25 patients in the PBO-MS group) (Fig.1). Of the 247 patients continuing into

the double-blind extension period of the study (125 patients in the AGO-MS group and 122 in the PBO-MS group), a total of 99 were prematurely withdrawn in the two groups; the commonest single reason was lack of efficacy (19 patients in the AGO-MS group; 18 patients in the PBO-MS group) (Fig. 1).

Post hoc analysis

Since the placebo response was very high (61% of patients in the PBO-MS met criteria for response on the MADRS total score), we conducted a *post hoc* exploratory analyses to examine and understand the impact of placebo response on the results of the trial.

A substantial number of centres had all patients (100%) randomised to PBO-MS meeting the criteria for response at 8 weeks. Therefore, we analysed the data after excluding centres with different rates of placebo response. For these analyses, we included data only from those centres ($n = 54$) that had randomised at least one patient per treatment group. We then examined the differences on the change from baseline to last post-baseline value at week 8 for MADRS total score between agomelatine and placebo after exclusion of data from centres that had placebo response rates of 100%, $\geq 90\%$, $\geq 80\%$, etc...0%. Changes in MADRS scores for agomelatine v. placebo groups for these

| | AGO-MS group (n = 172) | PBO-MS group (n = 172) |
|--|---------------------------|---------------------------|
| Age, years: mean (s.d.) | 45.6 (13.3) | 44.7 (12.0) |
| Male/female, % | 39/61 | 39/61 |
| <i>Bipolar I disorder</i> | | |
| Duration, years: mean (s.d.) | 17.7 (11.3) | 15.8 (11.1) |
| Number of manic episodes, ^a mean (s.d.) | 2.5 (2.6) | 2.7 (2.7) |
| Number of mixed episodes, ^a mean (s.d.) | 0.6 (1.2) | 0.9 (2.0) |
| <i>Major depressive episode</i> | | |
| DSM-IV severity, % | | |
| Mild | 2.3 | 0.6 |
| Moderate | 59.3 | 55.8 |
| Severe without psychotic feature | 38.4 | 43.6 |
| Melancholic features, % | 64.5 | 75.0 |
| Current major depressive episode duration, months: mean (s.d.) | 3.2 (2.4) | 3.2 (2.3) |
| Number of previous depressive episodes, mean (s.d.) | 5.2 (5.6) | 4.6 (4.1) |
| Previous psychotropic treatments, ^b % | 83.7 | 82 |
| Lorazepam, % | 24.42 | 20.59 |

AGO-MS, agomelatine as an add-on to a mood stabiliser; PBO-MS, placebo as an add-on to a mood stabiliser.
a. Within the previous 10 years.
b. Within the last 12 months, other than lithium and valproic acid.

| | Mean (s.d.) | |
|---|---------------------------|---------------------------|
| | AGO-MS group (n = 172) | PBO-MS group (n = 172) |
| Montgomery-Åsberg Depression Rating Scale, total score | 29.5 (5.5) | 30.6 (5.2) |
| Hamilton Rating Scale for Depression 17-item total score | 24.9 (3.8) | 25.1 (3.7) |
| Hamilton Rating Scale for Depression – Reverse Vegetative Symptom Scale, total score (8-item) | 4.9 (3.0) | 5.0 (3.1) |
| <i>Clinical Global Impressions scale for Bipolar Disorder – Modified</i> | | |
| Depression score | 4.6 (0.8) | 4.7 (0.8) |
| Mania score | 1.1 (0.3) | 1.1 (0.3) |
| Bipolar disorder score ^a | 4.4 (0.9) | 4.5 (0.9) |
| Hamilton Rating Scale for Anxiety, total score | 20.2 (7.1) | 20.3 (6.3) |
| Young Mania Rating Scale, total score | 2.7 (1.7) | 2.9 (1.8) |
| Quality of Life Enjoyment and Satisfaction Questionnaire, general activities score | 37.1 (14.7) | 37.2 (14.4) |

AGO-MS, agomelatine as an add-on to a mood stabiliser; PBO-MS, placebo as an add-on to a mood stabiliser.
a. Longitudinal severity of bipolar disorder during the previous year.

| MADRS total score | Mean (s.d.) | | | | |
|-------------------|-------------|-------------|--|-------------|--|
| | Baseline | Week 8 | Change over the acute treatment period | Month 12 | Change over the extension treatment period |
| AGO-MS group | 29.5 (5.4) | 14.1 (10.2) | – 15.4 (10.3) | 14.1 (12.8) | – 15.4 (12.7) |
| PBO-MS group | 30.6 (5.2) | 15.4 (12.1) | – 15.2 (11.8) | 15.7 (14.1) | – 14.9 (13.6) |

subgroups are displayed in Table 4. Agomelatine was significantly superior to placebo in all these analyses.

Conversely, we were interested in determining if placebo would beat agomelatine if all data were excluded from centres with a particular responder rate to agomelatine (i.e. 100%, $\geq 90\%$, $\geq 80\%$, etc....0%). Table 5 shows the MADRS change scores for these subgroups. Placebo was not superior to agomelatine in all these analyses except when data from all centres that had $\geq 30\%$ response were excluded. The number of remaining patients for analyses at this stage was very low.

Safety

The percentage of patients in the safety set who reported at least one emergent adverse event on treatment over 8 weeks was

numerically higher in the AGO-MS group than in the PBO-MS group (54.4% v. 46.2%) (mean difference: -8.14 (s.e. = 5.37), 95% CI -18.68 to 2.39, $P=0.131$). The most frequently affected system organ classes in the AGO-MS group were gastrointestinal disorders (16.4% of patients), nervous system disorders (15.2%), psychiatric disorders (12.3%) and infections and infestations (8.2%), and were similarly reported in the PBO-MS group (17.9%, 16.8%, 12.1%, 9.8%, respectively)

During the 12-month treatment period, the percentage of patients with at least one emergent adverse event showed no relevant difference between the AGO-MS and PBO-MS groups (69.6% v. 64.7%). The most frequent emergent adverse events were headache, nasopharyngitis, depression and somnolence (Table 6). Adverse events were generally less frequently reported in the AGO-MS group than in the PBO-MS group; only

Table 4 *Post hoc* analysis in centres with at least one patient in each group according to different placebo response rates: Montgomery–Åsberg Depression Rating Scale (MADRS) changes in agomelatine and placebo groups, impact of centres with different placebo response rates

| Placebo responders rate less than: | Centres conserved, <i>n</i> | AGO-MS group, <i>n</i> | PBO-MS group, <i>n</i> | AGO-MS group, adjusted mean change | PBO-MS group, adjusted mean change | Difference between adjusted treatment groups means (95% CI) | <i>P</i> |
|------------------------------------|-----------------------------|------------------------|------------------------|------------------------------------|------------------------------------|---|----------|
| 100% | 34 | 120 | 125 | −15.43 | −12.26 | −3.17 (−5.83 to −0.51) | 0.01 |
| 90% | 34 | 120 | 125 | −15.43 | −12.26 | −3.17 (−5.83 to −0.51) | 0.01 |
| 80% | 33 | 116 | 119 | −15.49 | −11.91 | −3.59 (−6.33 to −0.84) | 0.01 |
| 70% | 31 | 108 | 111 | −15.43 | −11.37 | −4.06 (−6.94 to −1.17) | 0.006 |
| 60% | 25 | 74 | 77 | −13.96 | −8.95 | −5.01 (−8.56 to −1.46) | 0.005 |
| 50% | 24 | 70 | 72 | −13.89 | −8.52 | −5.37 (−9.11 to −1.64) | 0.005 |
| 40% | 17 | 57 | 58 | −13.08 | −7.72 | −5.36 (−9.63 to −1.09) | 0.01 |
| 30% | 8 | 22 | 24 | −12.75 | −2.73 | −10.02 (−18.37 to −1.67) | 0.01 |
| 20% | 7 | 10 | 15 | −15.36 | 2.02 | −17.38 (−26.66 to −8.10) | 0.008 |
| 10% | 7 | 10 | 15 | −15.36 | 2.02 | −17.38 (−26.66 to −8.10) | 0.008 |
| 0% | 7 | 10 | 15 | −15.36 | 2.02 | −17.38 (−26.66 to −8.10) | 0.008 |

AGO-MS, agomelatine as an add-on to a mood stabiliser; PBO-MS, placebo as an add-on to a mood stabiliser.

Table 5 *Post hoc* analysis in centres with at least one patient in each group according to different agomelatine response rates: Montgomery–Åsberg Depression Rating Scale (MADRS) changes in agomelatine and placebo groups, impact of centres with different agomelatine response rates

| Placebo responders rate less than: | Centres conserved, <i>n</i> | AGO-MS group, <i>n</i> | PBO-MS group, <i>n</i> | AGO-MS group, adjusted mean change | PBO-MS group, adjusted mean change | Difference between adjusted treatment groups means (95% CI) | <i>P</i> |
|------------------------------------|-----------------------------|------------------------|------------------------|------------------------------------|------------------------------------|---|----------|
| 100% | 37 | 130 | 132 | −14.68 | −14.65 | −0.03 (−2.59 to 2.54) | 0.98 |
| 90% | 37 | 130 | 132 | −14.68 | −14.65 | −0.03 (−2.59 to 2.54) | 0.98 |
| 80% | 37 | 130 | 132 | −14.68 | −14.65 | −0.03 (−2.59 to 2.54) | 0.98 |
| 70% | 28 | 85 | 61 | −12.23 | −13.26 | 1.04 (−2.21 to 4.28) | 0.53 |
| 60% | 21 | 57 | 61 | −10.47 | −13.17 | 2.70 (−1.18 to 6.59) | 0.17 |
| 50% | 21 | 57 | 61 | −10.47 | −13.17 | 2.70 (−1.18 to 6.59) | 0.17 |
| 40% | 12 | 37 | 43 | −8.38 | −10.96 | 2.58 (−2.13 to 7.28) | 0.27 |
| 30% | 10 | 20 | 23 | −5.67 | −12.11 | 6.43 (1.64 to 11.23) | 0.01 |
| 20% | 10 | 20 | 23 | −5.67 | −12.11 | 6.43 (1.64 to 11.23) | 0.01 |
| 10% | 9 | 15 | 19 | −4.79 | −11.25 | 6.46 (1.37 to 11.55) | 0.01 |
| 0% | 9 | 15 | 19 | −4.79 | −11.25 | 6.46 (1.37 to 11.55) | 0.01 |

AGO-MS, agomelatine as an add-on to a mood stabiliser; PBO-MS, placebo as an add-on to a mood stabiliser.

nasopharyngitis, and somnolence were more frequently reported in the AGO-MS group than in the PBO-MS group (6.4% *v.* 4.0%; 5.8% *v.* 4.0%, respectively).

Manic or hypomanic symptoms

Over the 8-week period, the percentage of patients who experienced manic or hypomanic symptoms was not different between the treatment groups: 4.1% (seven patients: two hypomania, two mania, two elevated mood and one mixed episode) in the AGO-MS group and 3.5% (six patients: three hypomania, two mania, one mood swings) in the PBO-MS group. These symptoms were considered to be treatment related in all patients receiving AGO-MS, and in four of six patients receiving PBO-MS. The mean YMRS total score was stable over the acute period in both treatment groups (change from baseline: −0.38 (s.d.=3.67) in the AGO-MS group and −0.51 (s.d.=3.77) in the PBO-MS group). Over the extension period, 13 additional patients (7.6%) in the AGO-MS group and 7 (4.1%) in the PBO-MS group experienced manic or hypomanic symptoms. They were treatment related in all but one patient receiving AGO-MS (one hypomania), and in three of seven patients receiving PBO-MS. Among these symptoms, emergent hypomania was more frequent in the agomelatine group (7/13) than in the

Table 6 Most frequently reported emergent adverse events^a during the 12-month double-blind treatment period (at least 5% of the patients in any group)

| Adverse events | AGO-MS group (<i>n</i> = 171) | PBO-MS group (<i>n</i> = 173) |
|-----------------|--------------------------------|--------------------------------|
| Headache | 8.8 | 11.0 |
| Nasopharyngitis | 6.4 | 4.0 |
| Depression | 5.8 | 7.5 |
| Somnolence | 5.8 | 4.0 |
| Hypomania | 5.3 | 2.9 |
| Nausea | 4.7 | 6.9 |
| Insomnia | 4.1 | 6.4 |
| Dizziness | 4.1 | 5.8 |
| Diarrhoea | 4.1 | 5.2 |

a. Expressed as percent of number of affected patients to number of exposed patients in the considered treatment group.

placebo group (2/7). The same number of manic episodes (three) was reported in both groups. The mean YMRS total score was stable over the extension period (AGO-MS: 0.49 (s.d.=5.07); PBO-MS group: 0.25 (s.d.=4.80)).

Other safety events

One death occurred in the PBO-MS group after 35 days. This death, the result of an upper respiratory tract infection, was considered to be unrelated to the study treatment by the investigator. In both treatment groups, emergent non-fatal serious adverse events were mainly related to psychiatric disorders (including (hypo)manic symptoms) and did not differ between patients in the AGO-MS ($n=12$, 7.0%) and PBO-MS ($n=10$, 5.8%) groups. Among these events, suicide attempts were less frequent in the AGO-MS group (two patients, 1.2%) than in the PBO-MS group (five patients, 2.9%).

During the 12-month treatment period, no clinically relevant changes or differences between groups over time were detected for serious (non-fatal) or non-serious emergent adverse events leading to treatment withdrawal. Thus, 9 patients, in the AGO-MS group (5.3%) and 8 patients in the PBO-MS group (4.6%) withdrew because of emergent serious adverse event, whereas 28 patients in the AGO-MS group (16.4%) and 25 patients in the PBO-MS group (14.5%) discontinued because of non-serious adverse events.

During the study, no differences between groups over time were detected for biochemistry or haematological parameters, or physical examination including vital signs. No ECG abnormality was recorded. Two patients ($n=1$ in the AGO-MS group, $n=1$ in the PBO-MS group) had elevations in liver enzyme values more than three times the upper limit of the reference range. Both patients completely recovered.

Discussion

This randomised double-blind placebo-controlled study in patients with bipolar I disorder with current major depressive episode failed to show any beneficial effect of AGO-MS compared with PBO-MS on the primary outcome in the intent-to-treat full analysis sample. The MADRS score changes observed over the acute 8-week period were relatively large (about -15.0) in both treatment groups, and were maintained over the 10-month period. Response (approximately 61%) and remission rates (approximately 53%) on the MADRS scale for both treatment groups were also similar over the acute period. There were similar improvements in both groups on secondary efficacy measures in the full analysis set. Over the double-blind extension period, in the AGO-MS group, numerically but not significantly higher percentages of patients met criteria for response (61.9% *v.* 55.0%) and remission (57.7% *v.* 52.6%) compared with the PBO-MS group.

Magnitude of improvement in depression

The magnitude of reduction in depressive symptoms observed in the AGO-MS group in the present study is consistent with the effects noted in the preliminary open study²⁵ but, unexpectedly, a similar magnitude of improvement was also observed in the PBO-MS group. An improvement of 15 points on the MADRS in the PBO-MS group is larger than that observed in previous studies with PBO-MS. In the four large-scale double-blind trials that reported change scores on MADRS or HRSD in the PBO-MS groups, the reductions in depressive symptom scores were 8.06,¹² 11.03,³⁵ 12.9¹³ and 13.5.³⁶ The 15-point improvement observed in the PBO-MS group was larger than expected when compared with previous studies and translated to 61% of patients meeting criteria for response in the PBO-MS group. This is also substantially higher than the response rates observed in previous studies (34.9% in Nemeroff *et al*,¹² 31.7% in van der Loos *et al*,³⁵ 27.3% in Sachs *et al*¹³ and 42% in Loebel *et al*³⁶). Given

the challenges experienced in improving depressive symptoms in patients with bipolar depression in real-world clinical practice, such large response rates to PBO-MS in clinical trials are surprising. This finding raises the possibility that higher response rates in the PBO-MS group in the current study may have reduced the power of the study to detect an antidepressant effect of agomelatine.

Placebo response rates and strategies to improve assay sensitivity

High response to placebo has become as significant an issue in bipolar depression trials as in unipolar trials, where the effect was noted longer ago.³⁷ In monotherapy trials, the response to placebo was 26% in the lamotrigine trial³⁸ and it has steadily increased since then to 55.8% in the recent EMBOLDEN I study.³⁹ Entry score severity and inflation have been cited as reasons for increased placebo response. In order to address entry score inflation, a cut-off score on the HRSD was used for entry and the improvement in depression was assessed as the change score on MADRS for determination of efficacy. This strategy has not been found to diminish placebo response either in this study or in previous trials.^{40,41} Previous studies suggest that a score of 20 on the HRSD 17-item scale corresponds to a score of 28 on the MADRS.⁴² The mean HRSD score in this study was 25 but the mean MADRS score was only 30, which suggests a potential HRSD score inflation indicating that some patients who were less ill than required by the study protocol may have been recruited into the study.

In a meta-analysis that examined placebo response rates in major depressive disorder, Iovieno & Papakostas⁴³ observed that adjunctive studies with placebo response rates $>40\%$ were very unlikely to report drug-placebo differences. The present study accords with this conclusion. Previous work has highlighted the remarkable variation in drug-placebo differences by study site (of which there were 67 in the present study).¹⁶ One way to generate an assay-sensitive subgroup from the full analysis set is to exclude from a secondary analysis sites with improbably high response rates. Merlo-Pich *et al* have suggested this strategy for proof of concept and showed that it reduced the probability of trial failure from around 50% to around 10%.¹⁵

The objective of clinical trials should be to test new medications in representative clinical populations, which means in populations where the placebo response rates are neither high nor low. Recruitment of such populations has become an increasing problem for trials in psychiatry generally and, therefore, it is important to use secondary analyses to understand the phenomenon of high placebo response. In the present study, there was a substantial number of centres recruiting only a single patient ($n=8/67$) and others with 100% response rates to PBO-MS ($n=25/67$). Thus, in order to understand the impact of high placebo response on the outcome of this study, we conducted *post hoc* analyses examining only those centres that randomised at least one patient to each condition and excluding sequentially all patients from centres that had placebo response rates of 100%, $\geq 90\%$, $\geq 80\%$etc. Exclusion of patients (both PBO-MS and AGO-MS) from centres that had 100% placebo response yielded results suggesting significantly greater improvements in patients allocated to AGO-MS ($P=0.02$). Similarly, AGO-MS was significantly superior to PBO-MS when all patients were excluded from centres that had placebo response rates $\geq 90\%$, $\geq 80\%$0% (Table 4). Conversely, when data from centres that had different agomelatine responder rates were excluded, placebo did not beat agomelatine until all centres that had $\geq 30\%$ response to agomelatine were excluded. At $<30\%$,

the data from only 10 out of 67 centres were conserved with a total of only 43 patients. Hence, this analysis is not likely meaningful.

Safety and tolerability

Our findings provide additional data in confirmation of the tolerability and safety profiles of agomelatine 25–50 mg seen in the patients with major depressive disorder and generalised anxiety disorder.^{19,22} No unexpected adverse event was reported. The AGO-MS hepatic side-effects profile was similar to PBO-MS. The rate of emergent adverse effects over long-term treatment was also similar. The occurrence of mania in patients with bipolar disorder with antidepressant treatment, even if they are treated with a mood stabiliser, is a relatively old clinical observation⁴⁴ and a major concern.⁴⁵ Notably, AGO-MS was not associated with a high level of emergence of mania or hypomania symptoms over the study period.

Limitations

This study was conducted in 67 centres in 15 countries, which may have contributed to the large placebo response observed in the study. Such high placebo responses are not consistent with clinical practice in patients with bipolar depression and this raises questions about the quality of centres and the type of patients enrolled into the study. Exclusion of patients from centres with high placebo response rates yielded results that support the efficacy of agomelatine. However, this was based on *post hoc* analysis and hence, this cannot be taken as firm evidence of the efficacy of agomelatine. Further, in this *post hoc* analysis, we excluded data from only those centres that had randomised at least one patient to placebo and one patient to agomelatine. One could debate what this minimum number should be and a sensitive analysis combining data-sets from different studies might provide a more precise answer to this question. Although this study used an adjunctive design, refractoriness to mood stabiliser therapy was not prospectively confirmed. It is conceivable that agomelatine may be more effective in patients with bipolar depression who are refractory to mood stabiliser monotherapy.

Implications

The role of antidepressants in acute treatment of bipolar depression continues to remain controversial. In this study, agomelatine was not superior to placebo in improving depressive symptoms based on the changes in primary efficacy measure in acute bipolar depression. In general, there is a paucity of trial data on both the short- and long-term use of antidepressants in patients with bipolar disorder, so there is a real need to maximise understanding of the data that does exist. *Post hoc* analysis excluding patients from centres with a high placebo response suggested efficacy for agomelatine. We believe this procedure to be highly informative, compared with the publication of a mean response rate. The failure in this case to demonstrate benefit in the full analysis set underlines the challenge for improving the quality of patient recruitment to minimise placebo response. Failing that, one way to increase the assay sensitivity might be to set *a priori* criteria for excluding centres with certain rates of placebo response. A sensitivity analysis combining data from a number of bipolar depression studies might provide a better answer to what the ‘cut-off’ should be. Given that the average placebo response rates have not been higher than 62% in previous bipolar depression studies, a more stringent cut-off of 70% or greater might be appropriate if this is supported by a sensitivity analysis. Given the paucity of treatments, this may be particularly important for the clinical development of treatments for bipolar depression.

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