The Efficacy of Agomelatine in Elderly Patients With Recurrent Major Depressive Disorder: A Placebo-Controlled Study

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ABSTRACT

Objective: The present placebo-controlled study evaluated the efficacy, tolerability, and safety of 8-week treatment with agomelatine (25–50 mg/d by mouth) in elderly patients with major depressive disorder (MDD).

Method: Elderly outpatients aged ≥ 65 years with a primary diagnosis of moderate to severe episode of recurrent MDD (*DSM-IV-TR*) were recruited in 27 clinical centers in Argentina, Finland, Mexico, Portugal, and Romania from November 2009 to October 2011. The primary outcome measure was the 17-item Hamilton Depression Rating Scale ($HDRS_{17}$) total score.

Results: A total of 222 elderly patients entered the study (151 in the agomelatine group, 71 in the placebo group), including 69 patients aged 75 years and older. Agomelatine improved depressive symptoms in the elderly population, as evaluated by the $HDRS_{17}$ total score, in terms of last postbaseline value (agomelatine-placebo difference: mean estimate [standard error] = 2.67 [1.06] points; $P = .013$) and response to treatment (agomelatine, 59.5%; placebo, 38.6%; $P = .004$). The agomelatine-placebo difference according to the Clinical Global Impressions-Severity of Illness scale (CGI-S) score was 0.48 (0.19). The agomelatine-placebo difference (estimate [standard error]) for remission on the $HDRS_{17}$ was 6.9% (4.7%) and did not achieve statistical significance ($P = .179$, post hoc analysis). Clinically relevant effects of agomelatine were confirmed on all end points in the subset of severely depressed patients ($HDRS_{17}$ total score ≥ 25 and CGI-S score ≥ 5 at baseline). Agomelatine was well tolerated by patients, with only minimal distinctions from placebo.

Conclusions: The present study provides the first evidence that an 8-week treatment with agomelatine 25–50 mg/d efficiently relieves depressive symptoms and is well tolerated in elderly depressed patients older than 65 years.

Trial Registration: Controlled-Trials.com identifier: ISRCTN57507360

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With an increasingly ageing population, there is a growing need to develop novel ways to treat depression in the elderly. Major depressive disorder (MDD) is one of the most common and disabling mental disorders among elderly patients. Prevalence rates range from 6.5% to 9% among elderly people seen in primary care[1] and are high in the very old population.[2,3] Acceptability of pharmacotherapy is a major concern in this population, especially for patients aged over 75 years, and adverse events frequently lead to premature treatment cessation, a major factor of depressive relapse.

Placebo-controlled trials in elderly depressed patients (ie, aged 60 years and over) have examined the antidepressant efficacy of duloxetine,[4,5] sertraline,[6–8] paroxetine,[9,10] venlafaxine,[11,12] citalopram,[13] escitalopram,[14] and Lu AA21004,[15] but only few results were considered clinically relevant. No efficacy in patients aged over 75 years has been clearly established yet. The meta-analyses of trials assessing the efficacy of second-generation antidepressants in elderly patients reported only a modest effect, and no efficacy was demonstrated in the pool of studies using age thresholds of 65 years or older.[16,17] To date, no class of available antidepressant has been found to have better efficacy than any other in the treatment of elderly patients with acute episodes of MDD, and no specific antidepressant is recommended. In clinical practice, the choice of treatment is usually made on a case-by-case basis, taking into account individual patient's characteristics (coexisting illnesses and medication) and the potential drugs' side effects.

The mechanism of action of the antidepressant agomelatine differs from that of other currently approved medications for MDD.[18] The overall antidepressant efficacy of this compound is associated with a good tolerability profile.[19] The rationale for assessing agomelatine in geriatric groups with MDD relies on 3 main points. First, given the widespread use of antidepressant medications in geriatric patients and the data indicating that the efficacy of these treatments is strikingly limited, the introduction of a medication treatment with a distinctive mechanism of action may be of interest. Second, elderly patients with MDD are often more prone to experiencing side effects and drug interactions, so they may benefit from a well-tolerated treatment. Third, the European Medical Agency considers that, for a compound with a novel mechanism of action, data on efficacy and safety obtained in younger patients may not generalize to patients aged over 65 years, given that the efficacy, safety, and tolerability can be altered by age.[20,21] The present postcommitment study was conducted in elderly patients (≥ 65 years old) with recurrent MDD, and, to follow the European Medical Agency demand, it included a one-third proportion of patients aged 75 years and older.

The primary objective of this study was to evaluate the efficacy of agomelatine (25–50 mg/d by mouth) compared with placebo in the 8-week treatment of elderly patients (≥ 65 years old) with recurrent MDD. The secondary objectives were to evaluate (1) the efficacy of

agomelatine in the subgroup of patients aged over 75 years and (2) the tolerability and safety of agomelatine compared with placebo.

- The 8-week treatment with agomelatine 25–50 mg/d is both effective and well tolerated in elderly depressed patients over 65 years of age.
- In clinical practice, agomelatine should be considered as an attractive option for treating major depressive disorder patients 65 years old and older with regard to its efficacy for depressive symptoms and social functioning, its benign adverse effect profile, and good tolerability by a medically complex population.

Clinical Points

METHOD

Subjects

The study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. Subjects signed informed consent prior to participating in the trial. The study was registered on Controlled-Trials.com (identifier: ISRCTN57507360).

Elderly outpatients (n = 222), aged at least 65 years, with a primary diagnosis of a moderate to severe episode of recurrent MDD according to *DSM-IV-TR*, were recruited in Argentina, Finland, Mexico, Portugal, and Romania (27 clinical centers) from November 2009 to October 2011.

The Mini-International Neuropsychiatric Interview[22] was used to identify a major depressive episode and potential comorbid disorders. Subjects must have had a 17-item Hamilton Depression Rating Scale ($HDRS_{17}$) total score ≥ 22, a score of ≥ 4 on item 1 of the Clinical Global Impressions-Severity of Illness scale (CGI-S),[23] a Hospital and Depression Anxiety Scale[24] depression subscore of ≥ 11, and a Mini-Mental State Examination (MMSE)[25] score ≥ 27, and they must have completed the Geriatric Depression Scale[26] and the Sheehan Disability Scale (SDS).[27] Subjects with a decrease of greater than 20% on the $HDRS_{17}$ between selection and inclusion were excluded. The ongoing episode of recurrent MDD must have lasted at least 4 weeks (and no more than 12 months) with or without melancholic features, without seasonal pattern, without psychotic features, and without catatonic features.

All patients had to be physically healthy or must have stabilized any significant illness on the basis of medical history, physical examination, 12-lead electrocardiogram (ECG), and clinical laboratory tests.

Patients were excluded if they had transaminase values ≥ 2 upper limit of normal (ULN), alkaline phosphatase level ≥ 3 ULN, and/or total bilirubin level ≥ 2 ULN.

Patients with any of the following disorders were excluded: (1) MDD single episode, bipolar I and II disorders, depression superimposed on dysthymic disorder, panic disorder, obsessive-compulsive disorder, posttraumatic stress disorder, acute stress disorder, schizoaffective depressive disorder or bipolar type, or any other psychotic disorder, including major depression with psychotic features; and (2) alcohol or drug abuse or dependence within the past 12 months. Patients at risk of suicide were excluded.

Patients were excluded if they had not responded for the current episode to an appropriate dose of 2 antidepressant drugs of different classes (used for at least 4 weeks). Patients with neurologic disorders or severe or uncontrolled organic disorders were excluded.

Patients were excluded if they had received any of the following therapies: insight-oriented and structured psychotherapy started within 3 months preceding inclusion, light therapy started within 2 weeks, oral antipsychotic drugs within 4 weeks, neuroleptics at low dose within 2 weeks, depot neuroleptics within 6 months, and electroconvulsive therapy or transcranial magnetic stimulation within the last 3 months. Washout times for medications were usually 1 week for antidepressants (2 weeks for nonselective monoamine oxidase inhibitors, 5 weeks for fluoxetine). Benzodiazepines, zolpidem, and zopiclone were authorized if started at least 4 weeks before inclusion and used at a stable dosage to week 8.

Measures

Randomization was unbalanced, with a 2 to 1 ratio, and stratified on the center and on the age of patients ([65–75[/ ≥ 75) by using an interactive response system. Treatments were identically labeled. At week 2, in case of insufficient improvement, the dosage of agomelatine could be increased to 50 mg daily, according to a predefined dose adjustment algorithm. Both investigators and subjects were blind to the up-titration.

The primary outcome measure was the $HDRS_{17}$ total score, rated at the selection visit and at weeks 0 (inclusion), 2, 4, 6, and 8). The primary outcome variable was the difference between groups on the $HDRS_{17}$ total score at end point.

Secondary outcome measures included the CGI-S; item 1 (severity of illness) was assessed at each visit from selection to week 8, and CGI-Improvement (CGI-I) was assessed at each visit from week 2 to week 8. The SDS was rated at selection and at weeks 2 and 8.

Safety measures included adverse events reporting at each visit, vital signs (heart rate and blood pressure at each visit; weight and body mass index at selection visit and at weeks 0, 4, and 8), 12-lead ECGs, and laboratory tests (biochemistry, hematology) at the selection visit and week 8.

If the patient withdrew prematurely, the measurements above were repeated at the time of withdrawal.

Statistical Analyses

The efficacy analyses were performed in the full analysis set (patients of the randomized set who took at least 1 dose of medication, with a value at baseline and at least 1 postbaseline value for the primary efficacy criterion). The primary analysis examined agomelatine-placebo differences on the last postbaseline value of the $HDRS_{17}$ total score over the 8-week period by using a 3-way analysis-of-covariance model on factor treatment, with center (random effects),

Table 1. Disposition of Patients Over 8 Weeks of Treatment

	Agomelatine, n	Placebo, n
Included (randomized)	151	71
Lost to follow-up	0	0
Withdrawn	26	21
Due to adverse event	12	5
Due to nonmedical reason	4	9
Due to lack of efficacy	9	7
Due to protocol deviation	1	0
Completed	125	50
Full analysis set	148	70
Sub–full analysis set aged ≥ 75 y	48	21
Sub–full analysis set of severely depressed patients with baseline $HDRS_{17}$ total score ≥ 25 and CGI-S score ≥ 5	97	41
Safety set	151	71
Safety subset aged ≥ 75 y	48	21

Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale.

Table 2. Baseline Patient Demographic and Clinical Characteristics

Characteristic	Agomelatine (n = 151)	Placebo (n = 71)
Age, mean (SD), y	71.9 (5.1)	71.7 (4.8)
Sex, %		
Male	30.5	35.2
Female	69.5	64.8
Illness severity (*DSM-IV*), %		
Moderate	47.0	49.3
Severe without psychotic features	52.9	50.7
Melancholic features, %	67.5	64.8
No. of depressive episodes, mean (SD)[a]	3.5 (2.2)	3.2 (2.3)
Duration of current MDE, mean (SD), mo	5.72 (3.35)	5.68 (3.28)
Previous psychotropic treatments, %	37.1	43.7
$HDRS_{17}$ total score, mean (SD)	26.8 (2.8)	26.7 (3.2)
CGI-S score, mean (SD)	4.9 (0.6)	4.9 (0.7)
Hospital and Depression Anxiety Scale, mean (SD)		
Depression score	14.8 (2.5)	14.7 (2.6)
Anxiety score	11.2 (3.5)	10.5 (3.6)
MMSE score, mean (SD)	29.2 (0.8)	29.1 (1.0)
Geriatric Depression Scale score, mean (SD)	11.3 (2.2)	11.3 (2.3)
Sheehan Disability Scale, mean (SD)		
Work	6.9 (1.7)	6.9 (2.1)
Social life	7.1 (1.7)	7.3 (1.8)
Family life	7.1 (1.7)	7.0 (2.1)

[a]Including the current one.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, MDE = major depressive episode, $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, MMSE = Mini-Mental State Examination.

classes of age ([65–75[; ≥ 75) (fixed effects), and baseline $HDRS_{17}$ total score as covariates and without interaction.

A sensitivity analysis of the method of handling missing values was performed in the full analysis set. Treatment groups were compared on the value at week 8 by using a mixed-effects for repeated-measures model (MMRM), including terms for the fixed effects of treatment, class of age, baseline $HDRS_{17}$ total score, visit, and interaction term of treatment and visit, and for the random effect of center. The analysis fitted an unstructured covariance matrix.

Additional analyses were conducted by using a χ^2 test to assess agomelatine-placebo differences in response to treatment (at least 50% decrease from baseline $HDRS_{17}$ score) and remission ($HDRS_{17}$ score < 7), taking into account the last postbaseline value (post hoc analysis for remission).

The same primary analysis strategy was used in the planned subset of patients with both $HDRS_{17}$ score ≥ 25 and CGI-S score ≥ 5 at baseline. Treatment groups were compared in a descriptive way in the subset of patients ≥ 75 years of age. Treatment groups were compared in the subset of patients < 75 years old by using a 2-way analysis of covariance model on factor treatment, with center (random effects) and baseline $HDRS_{17}$ total score as covariates, and without interaction (post hoc analysis).

The agomelatine-placebo differences were studied in the full analysis set over the 8-week period for (1) the last postbaseline value of CGI-S score and last value of CGI-I score by using a 2-sided Student *t* test for independent samples, (2) the response to treatment according to the CGI-I (global improvement score = 1 or 2), using a χ^2 test on the last value, and (3) SDS work, social life, and family life scores, taking into account the mean change from baseline to last postbaseline value using a 2-sided Student *t* test (post hoc analysis).

Treatment groups were compared in a descriptive way for patients aged ≥ 75 years.

The efficacy of agomelatine was compared to placebo in the full analysis set subset of patients having a score on $HDRS_{17}$ items 10 + 11 (psychic anxiety and somatic anxiety) ≥ 5 at inclusion (n = 119) by using a 3-way analysis of covariance model on factor treatment, with center (random effects), class of age (fixed effects), and baseline $HDRS_{17}$ total score as covariates (post hoc analysis).

For every safety measurement, descriptive statistics were provided by treatment group in the safety set (all included patients who took at least 1 dose of study medication) and in the safety subset of patients aged ≥ 75 years.

Statistical analysis was performed using SAS software, version 9.1.3 or 9.2 (SAS Inc; Cary, North Carolina). The type I error was set at 5% (2-sided tests).

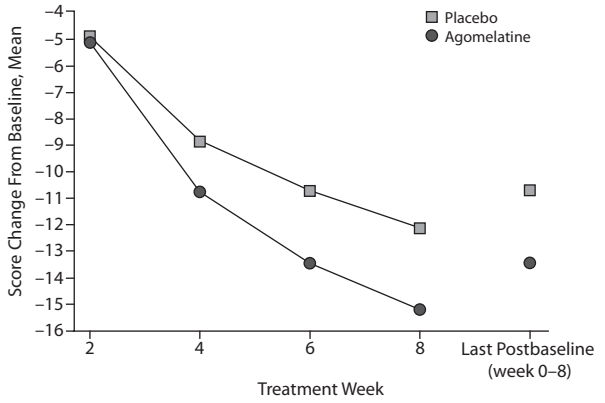
RESULTS

Patients

Two hundred twenty-two patients were randomized to receive either agomelatine (151 patients, including 48 patients aged ≥ 75 years) or placebo (71 patients, including 21 patients aged ≥ 75 years). A total of 175 patients completed the 8-week treatment period (78.8%). Reasons for withdrawal were mainly adverse events, lack of efficacy, and nonmedical reason (Table 1).

The mean (SD) age of patients was 71.8 (5.0) years; 31.1% (n = 69) were aged ≥ 75 years. Half of patients (n = 113, 50.9%) felt at least moderately anxious (Hospital and Depression Anxiety Scale anxiety subscore ≥ 11). At selection, patients had no relevant cognitive impairment (MMSE total mean [SD] score = 29.2 [0.9]). There were no clinically relevant differences between the groups for demographic and clinical characteristics (Table 2). In all, 32 of 151 patients (21.2%) taking agomelatine had a dose increase.

Figure 1. $HDRS_{17}$ Total Score Expressed as Mean Change From Baseline at Each Visit and at Last Postbaseline Value in the Group of Elderly Patients Receiving Agomelatine 25–50 mg/d or Placebo Over the 8-Week Study Period (full analysis set, n = 218)



Abbreviation: $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale.

Efficacy

Whole study population. The mean $HDRS_{17}$ total score decreased from baseline to week 8 in both groups. Agomelatine was associated with a statistically significant and clinically relevant decrease in symptoms at the last postbaseline value (main analysis: placebo minus agomelatine mean [SE] difference of 2.67 [1.06] points; $P = .013$) (Figure 1, Table 3). The MMRM sensitivity analysis provided results consistent with the main analysis: a placebo minus agomelatine mean (SE) difference in score of 2.76 (1.02) (95% CI, 0.75–4.78; $P = .007$) was observed at week 8. There was a significantly higher response rate on agomelatine versus placebo ($P = .004$), with a clinically relevant difference of 20.89% (Table 3). The remission rate according to $HDRS_{17}$ was 16.9% in patients in the agomelatine group and 10% in patients in the placebo group, with a difference (estimate [standard error]) of 6.9% (4.7%) that did not reach statistical significance ($P = .179$; post hoc analysis) (Table 3).

The differences of the mean CGI-S and CGI-I scores between agomelatine and placebo were statistically significant at the last value. The placebo minus agomelatine difference (estimate [standard error]) was 0.48 (0.19) for CGI-S ($P = .010$) and 0.36 (0.17) for CGI-I ($P = .034$) (Table 3). The percentage of responders according to CGI-I was significantly higher in the agomelatine group (71.0%) than in the placebo group (50.0%) ($P = .003$).

For the 3 SDS scores, patients reported significantly less symptom-related impairments with agomelatine than with placebo in work (mean [SD] change from baseline to last postbaseline value: −3.1 [2.6] in the agomelatine group vs −2.0 [2.9] in the placebo group; $P < .001$), in social life (−3.4 [2.8] in the agomelatine group vs −2.6 [2.8] in the placebo group; $P = .004$), and in family life (−3.2 [2.9] in the agomelatine group vs −2.1 [2.5] in the placebo group; $P = .002$).

Severely ill patients. In the subset of severely depressed patients, the placebo-agomelatine difference (estimate [standard error]) was 3.79 (1.37) points ($P = .007$) (Table 4). The response rate according to $HDRS_{17}$ was significantly higher in patients taking agomelatine than those taking placebo ($P = .002$), with a clinically relevant difference of 28.36%. The remission rate according to $HDRS_{17}$ was 17.5% in patients in the agomelatine group and 9.8% in patients in the placebo group, with an estimated (standard error) difference of 7.8% (6.0%) that did not achieve statistical significance ($P = .246$; post hoc analysis) (Table 4). The mean (SD) CGI-S scores after 8 weeks were 3.0 (1.2) for agomelatine (median = 3) and 3.7 (1.4) for placebo (median = 4). For CGI-I scores, a significant placebo minus agomelatine difference (estimate [standard error]) of 0.56 (0.20) was noted ($P = .006$) (Table 4). The percentage of responders according to CGI-I score was 76.3% in the agomelatine group and 48.8% in the placebo group.

In the subset of 119 severely anxious patients ($HDRS_{17}$ items 10 + 11 score ≥ 5 at baseline; 82 patients in the agomelatine group), the placebo-agomelatine difference was 4.14 (1.57) points (95% CI, 1.03–7.24; $P = .010$).

Patients aged < 75 years. In patients aged < 75 years, the mean (SD) $HDRS_{17}$ change from baseline to the last postbaseline assessment over the 8-week period was −14.0 (8.4) (median = −15) in the agomelatine group and −10.3 (7.3) (median = −9) in the placebo group. The placebo-agomelatine difference on the last postbaseline $HDRS_{17}$ value over the 8-week period was 3.74 (1.26) points ($P = .004$). The response rate according to $HDRS_{17}$ was higher in patients in the agomelatine group (60.0%) than in patients in the placebo group (34.7%), with a clinically relevant difference of 25.31% ($P = .004$). The remission rate according to $HDRS_{17}$ was higher in patients in the agomelatine group (23.0%) than in patients in the placebo group (6.12%), with a clinically relevant difference of 16.88% ($P = .011$; post hoc analysis).

The differences of the mean (SD) CGI-S and CGI-I scores between agomelatine and placebo were statistically significant at the last value. The placebo minus agomelatine difference was 0.66 (0.23) for CGI-S ($P = .004$) and 0.42 (0.19) for CGI-I ($P = .015$). The percentage of responders according to CGI-I was significantly higher in the agomelatine group (71.0%) than in the placebo group (49.0%) ($P = .009$).

For the 3 SDS scores, patients reported significantly less symptom-related impairments with agomelatine than with placebo in work (mean [SD] change from baseline to last postbaseline value: −3.2 [2.7] in the agomelatine group vs −2.2 [2.5] in the placebo group; $P = .002$), in social life (−3.7 [2.9] in the agomelatine group vs −2.3 [2.5] in the placebo group; $P = .002$), and in family life (−3.4 [2.8] in the agomelatine group vs −2.0 [2.0] in the placebo group; $P < .001$).

Patients aged ≥ 75 years. In the subset of patients aged ≥ 75 years, the mean (SD) $HDRS_{17}$ change from baseline to the last postbaseline assessment over the 8-week period was −12.2 (7.9) (median = −13.5) in the agomelatine group and −11.7 (9.0) (median = −12.0) in the placebo group. The percentage of responders was 58.3% in the agomelatine group (28/48) and 47.6% in the placebo group (10/21). The percentage of remitters was 4.2% in the agomelatine group (2/48) and 19.1% in the placebo group (4/21).

Table 3. Agomelatine-Placebo Differences in the Full Analysis Set (agomelatine: n = 148; placebo: n = 70) After 8 Weeks of Treatment

	Score, Mean (SD)		Difference Between Treatments		
Criterion	Baseline	Week 8	Estimate (SE)	95% CI (2-sided)	*P* Value (2-sided)
$HDRS_{17}$ total score					
Agomelatine, 25–50 mg/d	26.9 (2.8)	13.4 (7.5)[a]			
Placebo	26.8 (3.2)	16.1 (7.6)[a]	2.67 (1.06)[b]	0.57 to 4.76	.013
Response rate for $HDRS_{17}$					
Agomelatine, 25–50 mg/d	…	59.46[c]			
Placebo	…	38.57[c]	−20.89 (7.08)[d]	−34.77 to −7.01	.004
Remission rate for $HDRS_{17}$					
Agomelatine, 25–50 mg/d	…	16.89[e]			
Placebo	…	10.00[e]	−6.89 (4.73)[f]	−16.16 to 2.37	.179
CGI-S score					
Agomelatine, 25–50 mg/d	4.9 (0.6)	3.0 (1.3)[g]			
Placebo	4.9 (0.7)	3.5 (1.3)[g]	0.48 (0.19)[h]	0.12 to 0.85	.010
CGI-I score					
Agomelatine, 25–50 mg/d	…	2.2 (1.2)[g]			
Placebo	…	2.6 (1.2)[g]	0.36 (0.17)[h]	0.03 to 0.69	.034
SDS Work					
Agomelatine, 25–50 mg/d	6.9 (1.8)	−3.1 (2.6)[i]			
Placebo	6.9 (2.1)	−2.0 (2.9)[i]	1.18 (0.35)[h]	0.50 to 1.86	< .001
SDS Social life					
Agomelatine, 25–50 mg/d	7.1 (1.7)	−3.4 (2.8)[i]			
Placebo	7.3 (1.8)	−2.6 (2.8)[i]	1.05 (0.36)[h]	0.34 to 1.76	.004
SDS Family life					
Agomelatine, 25–50 mg/d	7.1 (1.7)	−3.2 (2.9)[i]			
Placebo	7.0 (2.1)	−2.1 (2.5)[i]	1.14 (0.36)[h]	0.42 to 1.85	.002

[a]Last postbaseline value for $HDRS_{17}$ total score.
[b]Difference between adjusted treatment group mean values (placebo minus agomelatine); 3-way analysis of covariance model on factor treatment, with center (random effects), class of age ([65–75[/≥ 75 years) (fixed effects), and baseline $HDRS_{17}$ total score as covariates.
[c]Percentage of patients at last postbaseline value for response rate by $HDRS_{17}$.
[d]Difference between adjusted treatment group percentages (placebo minus agomelatine); χ^2 test.
[e]Percentage of patients at last postbaseline value for remission rate according to $HDRS_{17}$.
[f]Difference between adjusted treatment group percentages (placebo minus agomelatine); χ^2 test.
[g]Last postbaseline value.
[h]Difference between adjusted treatment group mean values (placebo minus agomelatine) (2-sided Student *t* test).
[i]Change from baseline to last postbaseline value.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, SE = standard error, SDS = Sheehan Disability Scale.

The CGI-S mean (SD) scores at last postbaseline assessment showed no difference between the agomelatine (3.1 [1.2], median = 3.0) and placebo (3.2 [1.3], median = 3.0) groups. The CGI-I mean (SD) score was 2.3 (1.3) (median = 2.0) in the agomelatine group and 2.6 (1.3) (median = 2.0) in the placebo group. The percentage of responders according to CGI-I score was 70.8% in the agomelatine group and 52.4% in the placebo group

The SDS scores for work-related symptoms (mean [SD] change from baseline to last postbaseline value) were −2.8 (2.5) (median = −3) for patients taking agomelatine and −1.6 (3.7) (median = −1) for patients taking placebo. Mean (SD) changes on SDS score for family life–related symptoms were −2.7 (3.2) (median = −3) for patients taking agomelatine versus −2.1 (3.4) (median = −1) for those taking placebo. Mean (SD) changes on SDS social life score were −2.8 (2.6) for agomelatine and −3.2 (3.5) for placebo (median = −3 in both groups).

Tolerability

During the 8-week study period, in the safety set, the percentage of patients with at least 1 emergent adverse event was 52.3% in the agomelatine group versus 36.6% in the placebo group.

Somnolence, headache, dry mouth, and diarrhea were the most frequent emergent adverse events reported by patients in the agomelatine group. Among the emergent adverse events reported in at least 2% of patients, only 5 (somnolence, dry mouth, upper respiratory tract infection, constipation, pain in extremity) were reported more often by patients taking agomelatine than by those taking placebo (Table 5). The majority of adverse events were rated as mild or moderate. The percentage of patients who experienced at least 1 emergent adverse event rated as severe was 4.6% in the agomelatine group (7 patients) versus 8.5% in the placebo group (6 patients).

Adverse events leading to discontinuation were as frequent in the agomelatine group (7.9%) as in the placebo group (8.5%). Four patients (2.6%) in the agomelatine group and 4 in the placebo group (5.6%) reported serious adverse events (Table 6). Emergent adverse events related to study treatment were more frequent with agomelatine (28.5%) than with placebo (19.7%).

There were no clinically relevant between-group differences nor changes from baseline to the last value during treatment for the biochemical and hematologic parameters, the supine blood pressure, heart rate, weight, and body mass index. No clinically relevant ECG abnormalities were recorded.

Table 4. Agomelatine-Placebo Differences in Subset of Severely Depressed Patients[a] After 8 Weeks of Treatment

Variable	Agomelatine (n = 97)	Placebo (n = 41)
$HDRS_{17}$ total score, mean (SD)		
Baseline	28.0 (2.5)	28.5 (2.8)
Last postbaseline value	12.8 (7.5)	16.7 (8.2)
Estimate (SE)	3.79 (1.37)[b]	
95% CI (2-sided)	1.07 to 6.51	
P value (2-sided)	.007	
Response rate for $HDRS_{17}$, %		
Last postbaseline value	64.95	36.59
Estimate (SE)	−28.36 (8.95)[c]	
95% CI (2-sided)	−45.90 to −10.83	
P value (2-sided)	.002	
Remission rate for $HDRS_{17}$, %		
Last postbaseline value	17.53	9.76
Estimate (SE)	−7.77 (6.03)[c]	
95% CI (2-sided)	−19.59 to 4.05	
P value (2-sided)	.246	
CGI-I total score, mean (SD)		
Last value	2.0 (1.1)	2.6 (1.1)
Estimate (SE)	0.56 (0.20)[d]	
95% CI (2-sided)	0.16 to 0.97	
P value (2-sided)	.006	

[a]$HDRS_{17}$ total score at baseline ≥ 25 and CGI-S ≥ 5.
[b]Three-way analysis of covariance model on factor treatment, with center (random effects), class of age ([65–75[/≥ 75 years) (fixed effects), and baseline $HDRS_{17}$ total score as covariates.
[c]Placebo minus agomelatine (χ^2 test).
[d]Placebo minus agomelatine (2-sided Student *t* test).
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, SE = standard error.

Table 5. Most Frequently Reported Emergent Adverse Events During the Double-Blind, 8-Week Treatment Period (at least 2% of the patients in the agomelatine group)

Adverse Event[a]	Agomelatine (n = 151)	Placebo (n = 71)
Somnolence	6.0	1.4
Headache	5.3	5.6
Dry mouth	4.6	2.8
Diarrhea	4.6	0
Dizziness	3.3	5.6
Nasopharyngitis	3.3	4.2
Nausea	3.3	4.2
Upper respiratory tract infection	3.3	1.4
Constipation	2.6	1.4
Pain in extremity	2.6	0
Fatigue	2.0	4.2

[a]Expressed as percentage of number of affected patients to number of exposed patients in the considered treatment group.

Table 6. Safety Results by Treatment Group During the Study Period

Result	Agomelatine (n = 151), n (%)	Placebo (n = 71), n (%)
Death	0	0
Serious adverse event	4 (2.6)	4 (5.6)
Severe emergent adverse events	7 (4.6)	6 (8.5)
Treatment-related emergent adverse event	43 (28.5)	14 (19.7)
Emergent adverse event leading to withdrawal	12 (7.9)	6 (8.5)
Biological investigations: liver function test		
Emergent AST or ALT ≥ 3 ULN	2	0

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, ULN = upper limit of normal.

Proportions, description, and characteristics of emergent adverse events and laboratory parameters were similar in the safety subset of patients aged ≥ 75 years.

Two patients in agomelatine group (1 aged ≥ 75 years) with normal liver enzyme values at baseline had emergent, potentially clinically significant abnormal transaminases (> 3 ULN), probably related to treatment. All values normalized after agomelatine discontinuation.

DISCUSSION

The 8-week treatment with agomelatine 25–50 mg/d is both effective and well tolerated in elderly depressed patients over 65 years of age. The efficacy of agomelatine demonstrated on the primary criterion ($HDRS_{17}$ total score) is notable, with a placebo-agomelatine difference of 2.67 points, and is supported by consistent findings on CGI variables and clinical response (about 21% agomelatine-placebo difference). The remission rate after 8 weeks of treatment failed to achieve statistical significance in the whole study population, but it can be considered as promising in the subset of patients aged under 75 years. The benefit of the agomelatine treatment was maintained in the subgroup of severely ill patients, with a significant placebo-agomelatine difference that reached 3.5 points for the $HDRS_{17}$ and about 28% by clinical response to treatment. Those severely depressed patients are usually regarded as patients likely to be most impaired by their depression and most likely to be actively treated in ordinary practice. To our knowledge, only 6 placebo-controlled studies[4,6,8–10,15] have reported an antidepressant that was efficacious in patients aged over 60–65 years. A recent meta-analysis[17] showed a modest efficacy in patients depending on the age range, with heterogeneous results across studies. In this publication, no treatment effect was noted for patients aged over 65 years; the response to treatment was about 42% in the active treatment arm versus 39% in the placebo arm. In comparison, the response to agomelatine treatment according to $HDRS_{17}$ was notable in the whole study population (59.4% vs 38.5% in the placebo group) as well as in the subset of severely ill patients (64.9% vs 36.5% in the placebo group).

In the older patients, aged over 75 years, the response to treatment according to $HDRS_{17}$ remained stable (58.3%) and close to that observed in patients aged less than 75 years (60.0%), despite a higher response rate for placebo in patients ≥ 75 years (47.6%) than for patients < 75 years (34.7%). Such a finding is interesting, since there is a strong increase in antidepressant use in this rapidly growing segment of the elderly population, yet there is a difficulty in effectively treating this population.[13] Although preliminary, our results can be considered as a welcome addition of data, as, to date, the efficacy and safety of antidepressant medications in patients older than age 75 years remain scant.

To accurately treat depression in patients aged over 65 years, it is important that clinicians treat alteration in the functional status, which is often the clue of depression in an

older person.[28] Alterations in general, core family, and social functioning of elderly populations place additional burden on older adults. On the basis of SDS findings, agomelatine improves symptom-related functional impairments in patients aged over 65. Especially in elderly patients, functional impairment can contribute to diminished quality of life so that a positive impact on the functional status of elderly patients may be an interesting feature of agomelatine. To our knowledge, this study is the first to administer the SDS scale to a population of elderly patients, so this interpretation can be limited by the absence of validation of the SDS scale in the geriatric population.

As marked anxiety is a common comorbid symptom with depression in later life,[29] the placebo-agomelatine difference of about 4 points on $HDRS_{17}$ score, seen in severely anxious patients (with $HDRS_{17}$ items 10 + 11 score at baseline ≥ 5), can be considered as encouraging, although the finding has the limitation of resulting from a post hoc analysis.

One paramount consideration in the choice of an antidepressant for the elderly population is its safety and tolerability. Some side effects considered minor in younger patients may carry more significant risk in the elderly.[21] The satisfactory profile of adverse events seen with agomelatine 25–50 mg/d in adult patients ≤ 65[18,19] is preserved here in the elderly population. Agomelatine is well tolerated by patients, with only minimal distinctions from placebo, and patients exhibited a favorable safety profile, including those areas of special concern among elderly patients (eg, cardiovascular safety). Overall, 7.95% of agomelatine-treated patients discontinued due to adverse events, a rate lower than discontinuation rates reported in a meta-analysis[30] of antidepressant tolerability in late-life depression. The rate of discontinuation due to adverse events also compares favorably with that observed among adult patients ≤ 65 years.[31] There is also no further specific concern with liver enzymes. Interestingly, agomelatine treatment is safe and well tolerated in patients aged over 75.

Collectively, these findings support agomelatine treatment as an attractive option for those elderly patients who have increasingly complex medication regimens and can be more sensitive to potential adverse effects of treatment and drug interactions. In addition to its efficacy, such tolerability and safety profiles most likely encourage good adherence to treatment.

Some limitations deserve mention when interpreting the present findings. First, a number of exclusion criteria have been used, so the findings reported in our sample of included patients may not be generalized to such patients presenting those additional criteria (eg, severe or uncontrolled organic diseases). However, the current exclusion criteria are usually used in clinical trials, which make our results comparable to the existing literature. Second, an unbalanced randomization ratio of 2:1 has been used to limit the number of patients exposed to placebo and to improve recruitment. Although classically used,[32] it may diminish sensitivity of the trial, notably in subsets. Alternatively, there may be a gain in terms of information about treatment response.[33]

Few treatments are available for treating depression in the elderly population, yet their efficacies are (1) controversial in populations aged over 60 years and (2) not demonstrated in the older old population. The introduction of an additional treatment with a compound having a distinct mechanism of action may represent an important contribution in the field. The present findings suggest that agomelatine should be considered as an attractive option for this population older than 65 years because of its efficacy for symptoms and social functioning, benign adverse effect profile, and good tolerability by a medically complex population.

Drug names: citalopram (Celexa and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), venlafaxine (Effexor and others), zolpidem (Ambien, Edluar, and others).

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Author contributions: All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The authors were involved in the design and conduct of the study, the preparation, writing, and approval of the manuscript.

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