Agomelatine in Generalized Anxiety Disorder: An Active Comparator and Placebo-Controlled Study

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ABSTRACT

Background: Agomelatine was efficacious in reducing symptoms in a short-term placebo-controlled trial in generalized anxiety disorder (GAD) and in preventing relapse in a longer term placebo-controlled study. An additional short-term placebo-controlled study is required by regulatory agencies to confirm the efficacy of agomelatine in GAD.

Method: This 12-week, placebo-controlled, double-blind, randomized, parallel group, international, multicenter study was designed to confirm the efficacy of agomelatine 25–50 mg/d in the treatment of patients with a primary *DSM-IV-TR* diagnosis of GAD. The primary outcome measure was the Hamilton Anxiety Rating Scale (HARS) total score. Assay sensitivity was evaluated by including an escitalopram (10–20 mg/d) group.

Settings: The study was undertaken in 45 clinical centers in Argentina, Czech Republic, Finland, South Korea, Poland, Russia, and Slovakia from April 2010 to July 2011.

Results: One hundred thirty-nine outpatients were included in the agomelatine group, 131 in the placebo group, and 142 in the escitalopram group. Agomelatine significantly reduced mean (SD) HARS total score (agomelatine-placebo difference: 4.71 [1.03], $P < .0001$) and had significant effects on secondary outcome measures, including psychic and somatic HARS subscales, response rate (estimate [standard error]) (agomelatine-placebo difference: 27.4% [5.9%], $P < .0001$), remission on the HARS (agomelatine-placebo difference: 16.8% [5.4%], $P = .002$), Clinical Global Impressions-Severity of Illness scale (CGI-S) ($P < .001$), functional impairment ($P < .0001$), and sleep quality ($P < .001$). Findings were confirmed in the subset of more severely ill patients (HARS total score ≥ 25 with or without CGI-S ≥ 5 at baseline). Agomelatine was well tolerated by patients, with no more adverse events than placebo. Escitalopram was similarly efficacious but was accompanied by a higher incidence of adverse events compared to placebo.

Conclusions: In clinical practice, agomelatine has at least similar efficacy to that of escitalopram for the short-term treatment of GAD and is well tolerated.

Trial Registration: Controlled-Trials.com identifier: ISRCTN03554974

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Generalized anxiety disorder (GAD) is a chronic disorder characterized by excessive anxiety, uncontrollable worry, and somatic anxiety symptoms. Generalized anxiety disorder is associated with comorbidity (including comorbidity of major depression and other anxiety disorders) and morbidity (including psychosocial impairment and economic costs).[1] With a lifetime prevalence of 3%–7% in the general population, GAD is the most common anxiety disorder in primary care practice.[1–5]

Several medications are available for the pharmacologic management of GAD[6–8]; these include benzodiazepines, monoaminergic reuptake inhibitors, some first-generation tricyclics, pregabalin,[9] antihistamines, and antipsychotics.[10] Nevertheless, many patients fail to respond to, cannot tolerate, or develop discontinuation symptoms after use of such medications.[11]

The mechanism of action of agomelatine differs from that of currently approved therapies for major depressive disorder (MDD) and GAD.[12] The antidepressant efficacy of this compound is associated with a good tolerability profile, including the absence of discontinuation symptoms upon withdrawal.[13] Agomelatine is effective in treating the anxiety symptoms associated with depression[14,15]; its efficacy and tolerability in treating GAD patients have been demonstrated in a placebo-controlled phase II study[16]; and its ability to prevent relapse in GAD has been established.[17]

There is a need for additional data to confirm the efficacy of agomelatine in GAD and to determine the relationship between GAD severity and outcome. The primary objective of this study was to confirm the superiority of agomelatine (25–50 mg/d orally) compared to placebo in reducing symptoms after a 12-week treatment in nondepressed outpatients diagnosed with GAD. Assay sensitivity was evaluated by including escitalopram (10–20 mg/d orally) as an active treatment arm. Escitalopram was chosen as active control given its demonstrated efficacy in the treatment of GAD.[18–21] The secondary objectives were to describe the clinical benefit of agomelatine, such as response to treatment and remission rates and the ability of agomelatine to improve social functioning and sleep patterns, and to evaluate the tolerability and safety of agomelatine.

METHOD

Patients

The study (Controlled-Trials.com identifier: ISRCTN03554974) was conducted in accordance with the principles of Good Clinical Practice[22] and the Declaration of Helsinki.[23]

A total of 412 physically healthy male and female outpatients, aged 18–65 years, who had a primary diagnosis of GAD according to *DSM-IV-TR* criteria and had signed informed consent, were

Clinical Points

- This 12-week, placebo-controlled, double-blind, randomized, international, multicenter study confirms the efficacy and the good tolerability of agomelatine in the treatment of patients with a primary diagnosis of generalized anxiety disorder.
- Agomelatine had similar efficacy to escitalopram but was better tolerated.

recruited in Finland (7 centers), Russia (8 centers), Poland (9 centers), Czech Republic (5 centers), Slovakia (5 centers), Argentina (6 centers), and South Korea (5 centers).

The Mini-International Neuropsychiatric Interview (MINI)[24] was used to diagnose GAD and any potential comorbid disorders. Patients were required to have a Hamilton Anxiety Rating Scale (HARS)[25] total score of ≥ 22, a score of ≥ 2 on both HARS items 1 and 2, a score of > 5 on HARS items 1 + 2, a Hospital Anxiety and Depression Scale (HAD)[26] anxiety subscore > depression subscore, and a Montgomery-Asberg Depression Rating Scale (MADRS)[27] score of ≤ 16 at selection and inclusion. Patients with a decrease of greater than 20% on the HARS total score between selection and inclusion were excluded. Patients with all types of current anxiety disorders (within 6 months prior to the selection visit) other than GAD, such as panic disorder, posttraumatic stress disorder, acute stress disorder, agoraphobia, social phobia, or obsessive-compulsive disorder according to *DSM-IV-TR* criteria and confirmed by MINI, other psychiatric disorders including MDD, dysthymia, drug or alcohol abuse dependence, attention-deficit/hyperactivity disorder, and severe personality disorders, a history of bipolar or psychotic disorder, neurologic disorders, and suicide risk, as judged by the clinician, a score > 3 on item 10 of the MADRS, or who had made a suicide attempt within the past year, were excluded. Patients with severe or uncontrolled general medical disorders, or pregnancy, were excluded.

Patients receiving psychotropic agents or other treatments likely to interfere with the central nervous system or with the study evaluation, and patients having recently begun psychotherapy, were excluded. Menopause hormone replacement therapy or β-blockers were permitted (at stable dose for 3 months before the baseline evaluation and during the study).

Design and Measures

Patients were randomized to receive agomelatine, escitalopram, or placebo in the evening for 12 weeks. Randomization was balanced and stratified by center and was done using an interactive response system. Treatments were identically labeled. On the basis of insufficient improvement, daily dosage of agomelatine or escitalopram could be increased at week 4 (agomelatine: from 25 mg to 50 mg; escitalopram: from 10 mg to 20 mg) in blinded fashion according to a predefined dose adjustment algorithm (blind for investigators and patients). After the 12-week treatment period (or in case of premature withdrawal and according to investigator's opinion), the dose of escitalopram was gradually reduced during a double-blind tapering period of 1 week to avoid possible withdrawal reactions, whereas the dose of agomelatine remained unchanged, as this antidepressant is not associated with discontinuation symptoms on abrupt withdrawal.[13] Patients were followed up for 1 week after discontinuation. During the 12-week period, visits were scheduled at weeks 0 (inclusion visit), 2, 4, 8, and 12 (last visit).

The primary outcome measure was the HARS total score, which was rated at the selection and inclusion visits and at weeks 2, 4, 8, and 12. Secondary outcome measures included scores on the Clinical Global Impressions (CGI) scale[28]; the CGI-Severity of Illness (CGI-S) was assessed at each visit following selection, and CGI-Improvement (CGI-I) was assessed from week 2. The HARS psychic and somatic anxiety subscores were also secondary outcome measures. The HAD anxiety and depression subscores were rated at weeks 0, 8, and 12. The Leeds Sleep Evaluation Questionnaire (LSEQ)[29] was administered from week 2 to week 12, and the Sheehan Disability Scale (SDS)[30] was rated at weeks 0, 8, and 12. All efficacy measures were performed at the end of the study in case of premature withdrawal.

Safety measures included adverse events reporting at each visit; vital signs (heart rate, blood pressure) and 12-lead electrocardiograms (ECGs) at weeks 0 and 12; weight and body mass index (BMI) at weeks 0, 4, and 12; and standard laboratory tests (biochemistry, hematology) at weeks 4 and 12 (or in case of premature withdrawal).

Training

Given the breath of centers and diverse cultures that participated in this study, a specific training program was designed for this study. Investigators at all sites were trained in administering the diagnostic instruments and the outcome measures. Presentations were done at an international investigator's meeting on *DSM-IV-TR* criteria for GAD and on the MINI. Videos of clinical cases were used to establish interrater reliability on symptom measures. Training sessions on symptom severity measures were repeated during the recruitment period.

Statistical Analyses

The efficacy analyses were performed in the full analysis set (all randomized patients having taken at least 1 dose of study medication and having a value at baseline and at least 1 postbaseline value for the primary efficacy criterion over the 12-week period). The primary analysis assessed the agomelatine-placebo difference on the change from baseline to last postbaseline value of the HARS total score over the 12-week period, using a 2-way analysis of covariance model on treatment and center (random effect), with baseline HARS total score as covariate.

The escitalopram-placebo difference was assessed using the same model for purposes of assay sensitivity.

Table 1. Disposition of Patients

Variable	Agomelatine, n	Placebo, n	Escitalopram, n
Included (randomized)	139	131	142
Lost to follow-up	…	…	1
Withdrawn	23	35	25
Due to adverse event	3	4	11
Due to nonmedical reason	4	7	7
Due to lack of efficacy	14	22	6
Due to protocol deviation	1	1	1
Due to remission	1	1	…
Completed	116	96	116
Full analysis set (FAS)	139	131	139
Sub-FAS with HARS total score ≥ 25 at week 0	121	112	122
Sub-FAS with HARS total score ≥ 25 and CGI-S ≥ 5 at week 0	77	74	74
Safety set	139	131	141

Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HARS = Hamilton Anxiety Rating Scale.

Table 2. Baseline Patient Demographic and Clinical Characteristics: Randomized Set[a]

Characteristic	Agomelatine (n = 139)	Placebo (n = 131)	Escitalopram (n = 142)
Age, y	43.6 (12.5)	43.0 (12.2)	41.19 (12.5)
Male gender, n	35	37	45
Female gender, n (%)	104 (74.8)	94 (71.8)	97(68.3)
Duration of GAD,[b] median, y	3.0	3.1	3.0
Previous psychotropic treatments,[c] n (%)	58 (41.7)	64 (48.9)	66 (46.5)
HARS total score	28.6 (4.0)	28.2 (3.4)	28.6 (3.9)
HARS psychic anxiety score	15.1 (2.2)	15.2 (2.1)	15.3 (2.4)
HARS somatic anxiety score	13.5 (3.4)	13.0 (2.7)	13.3 (3.0)
CGI-S score	4.7 (0.7)	4.7 (0.6)	4.6 (0.6)
HAD anxiety score	14.8 (2.3)	14.8 (2.4)	14.8 (2.6)
HAD depression score	6.6 (3.3)	6.5 (3.4)	6.8 (3.5)
MADRS total score	12.0 (2.4)	12.3 (2.4)	12.2 (2.5)
SDS work	6.1 (2.0)	6.5 (1.8)	6.4 (1.8)
SDS social life	6.5 (1.8)	6.3 (2.1)	6.6 (1.9)
SDS family life	6.2 (1.9)	6.1 (1.8)	6.2 (1.7)

[a]Values are presented as mean (SD) unless stated otherwise.
[b]Duration since first anxious symptoms with functional impact.
[c]At least 1 previous psychotropic treatment during the last 12 months. During the study, no psychotropic treatment was allowed; at inclusion, all patients tested negative for urine benzodiazepines.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, GAD = generalized anxiety disorder, HAD = Hospital Anxiety and Depression Scale, HARS = Hamilton Anxiety Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, SDS = Sheehan Disability Scale.

As prespecified, this analysis was repeated in the subsets of patients with HARS total score ≥ 25 and patients with both HARS total score ≥ 25 and CGI-S score ≥ 5 at baseline.

Secondary analyses assessed in the full analysis set the agomelatine-placebo difference and the escitalopram-placebo difference in response to treatment (at least 50% decrease from baseline HARS total score) and remission (HARS total score ≤ 7) on the last postbaseline value using a χ^2 test (post hoc analysis for remission).

The drug-placebo differences were studied in the full analysis set over the 12-week period for HARS psychic and somatic anxiety scores (unplanned analyses); CGI-S and CGI-I scores; HAD anxiety and depression subscores; SDS work, social life, and family life scores; and LSEQ scores (unplanned analyses) on the last value and using a Student *t* test for independent samples or a χ^2 test, depending on the nature of the criterion.

For every safety measurement, descriptive statistics were provided by treatment group in the *safety set*, defined as all included patients having taken at least 1 dose of study medication.

Statistical analysis was performed using SAS software, version 9.1.3 (SAS Institute; Cary, North Carolina). The type I error was set at 5%.

RESULTS

Patients

Four hundred twelve patients were randomly assigned to receive agomelatine (139 patients), placebo (131 patients), or escitalopram (142 patients). A total of 83 patients did not complete the trial (79.6% completers). Reasons for withdrawal were mainly lack of efficacy, adverse events, and nonmedical reasons (Table 1).

The patients' mean (SD) age was 42.6 (12.4) years, and a greater proportion of patients were female. There were no clinically relevant differences between the treatment groups for demographic criteria and clinical characteristics (Table 2).

In all, 20 of 129 patients (15.5%) in the agomelatine group and 10 of 122 patients (8.2%) in the escitalopram group were given an increase in dose.

Primary Efficacy Criterion

Full analysis set. The mean HARS total score decreased from baseline to week 12 in all groups. Agomelatine and escitalopram were associated with a statistically significant and clinically relevant decrease in estimate (standard error [SE]) HARS total score at endpoint (difference vs placebo of 4.71 [1.03] for agomelatine and 4.77 [1.03] for escitalopram after adjustment for center and baseline, $P < .0001$) (Table 3).

This result was confirmed by a sensitivity analysis without any adjustment, with a statistically significant difference (estimate [SE]) versus placebo in favor of both agomelatine (difference of 4.61 [1.11], $P < .0001$) and escitalopram (difference of 4.67 [1.11], $P < .0001$).

A clinically relevant difference versus placebo was seen for agomelatine, with a delta (agomelatine–placebo) response rate (as defined by the HARS) of 27.4% ($P < .0001$). A similar difference from placebo was observed for escitalopram (Δ response rate = 29.5%, $P < .0001$). The advantage of agomelatine and escitalopram over placebo was also seen for remission rate at the last value (Table 3).

Severely anxious patients. For patients with HARS total score at baseline ≥ 25 (n = 355), the superiority of agomelatine versus placebo was established with an estimate (SE) difference in change in HARS total score of 5.05 (1.12) points ($P < .0001$). The escitalopram difference versus placebo in this subset was 4.95 (1.12) points ($P < .0001$) (Table 4).

Table 3. Hamilton Anxiety Rating Scale (HARS) Total Score,[a] Response to Treatment, and Remission Rates (last values)

		Difference vs Placebo			
	Value	Estimate	SE	95% CI[b]	*P* Value
HARS total score, mean (SD)					
Placebo (n = 131)	−10.6 (9.5)				
Agomelatine (n = 139)	−15.6 (9.4)	4.71	1.03	2.69 to 6.73	< .0001[c]
Escitalopram (n = 139)	−15.6 (8.2)	4.77	1.03	2.74 to 6.79	< .0001[c]
HARS response rate, %					
Placebo (n = 131)	36.6				
Agomelatine (n = 139)	64.0	27.39	5.86	15.91 to 38.86	< .0001[d]
Escitalopram (n = 139)	66.2	29.55	5.82	18.15 to 40.94	< .0001[d]
HARS remission rate, %[e]					
Placebo (n = 131)	19.9				
Agomelatine (n = 139)	36.7	16.84	5.37	6.32 to 27.37	.002[d]
Escitalopram (n = 139)	31.7	11.81	5.26	1.49 to 22.12	.027[d]

[a]Expressed as change from baseline at the last postbaseline value over 12 weeks of treatment.
[b]Two-sided.
[c]Analysis of covariance model on factor treatment (including the 3 treatment groups): adjustment for center (random effect) and HARS total score at week 0.
[d]χ^2 test.
[e]Unplanned analysis.
Abbreviation: SE = standard error.

Response rates were comparable for agomelatine (64.5%) and escitalopram (65.6%), and rates for both antidepressants were significantly higher than placebo (36.6%) (Table 4). Remission rates were 36.4% for agomelatine, 28.7% for escitalopram, and 20.5% for placebo (Table 4).

For patients with HARS total score ≥ 25 and CGI-S score ≥ 5 at baseline (n = 225), the estimate (SE) difference versus placebo on HARS total score was 5.61 (1.49) points ($P < .001$) for agomelatine and 4.08 (1.50) ($P = .007$) for escitalopram (Table 4). Response rates were significantly higher for both antidepressants as compared to placebo (agomelatine, 64.9%; escitalopram, 59.5%; and placebo, 35.1%) (Table 4). Remission rates were 37.7% for agomelatine, 18.9% for escitalopram and 20.3% for placebo; statistical significance was reached only when comparing the agomelatine and placebo groups ($P = .019$) (Table 4).

Secondary Efficacy Criteria in the Full Analysis Set

Psychic and somatic symptoms of GAD were significantly more improved on both agomelatine and escitalopram compared with placebo at endpoint ($P < .001$ for each subscore and for both comparisons; Table 5).

The agomelatine-placebo difference on the mean CGI-S score was statistically significant at the last value for agomelatine (0.60 [0.16], $P < .001$) and escitalopram (0.65 [0.16], $P < .0001$) (Table 5).

Hospital Anxiety and Depression Scale depression and anxiety subscores decreased during treatment with agomelatine and escitalopram (Table 5).

Results of the 3 SDS scores showed that agomelatine and escitalopram significantly separated from placebo in improving patients' functional impairment ($P < .0001$ in each case) (see Supplementary eTable 1 at PSYCHIATRIST.COM).

In only the agomelatine group, patients had an improvement in LSEQ ratings of getting off to sleep ($P = .002$), quality of sleep ($P < .001$), and integrity of behavior ($P = .049$) scores (Supplementary eTable 2).

Tolerability

In the safety set (n = 411), similar percentages of patients reported at least 1 emergent adverse event during the 13-week treatment period in the agomelatine (47.5%), escitalopram (48.2%), and placebo (44.3%) groups (Supplementary eTable 3). Headache, nasopharyngitis, and diarrhea were the most frequent emergent adverse events reported in the study. The relevant percentages of patients in the agomelatine and placebo groups were comparable for headache (7.2% and 7.6% in the agomelatine and placebo groups, respectively) and nasopharyngitis (4.3% and 5.3%, respectively) and lower in the placebo group for diarrhea (4.3% vs 1.5%). In the escitalopram group, the percentage of patients with nasopharyngitis was 5.7%, and headache and diarrhea were reported by 12.8% and 6.4% of patients, respectively. After diarrhea, the emergent adverse events somnolence and nausea were more frequently reported by patients in the agomelatine group (3.6% of patients for each) compared to placebo (2.3% of patients for somnolence and 0.8% for nausea). In the escitalopram group, nausea and somnolence were reported by 7.8% and 3.5% of patients, respectively (Supplementary eTable 3). The majority of emergent adverse events were rated as mild or moderate.

Few severe emergent adverse events were reported: 1 patient (0.7%) in the agomelatine group, 4 patients (3.1%) in the placebo group, and 6 patients (4.3%) in the escitalopram group.

Adverse events leading to treatment discontinuation were less frequent in the agomelatine group compared to escitalopram and placebo. Three patients (2.2%) receiving agomelatine had treatment-related emergent adverse events that led to a treatment withdrawal (vertigo, edema, gastrointestinal disorder). Four patients (3.1%) receiving placebo had treatment-related emergent adverse events that led to a treatment withdrawal (hyperhidrosis, insomnia, fatigue, somnolence). Ten patients (7.1%) receiving escitalopram had treatment-related emergent adverse events that led to a treatment withdrawal (dizziness, panic attack, nausea [2 patients], libido decrease, eczema, ocular hyperemia, headache, anxiety [2 patients]).

Five emergent serious adverse events (4 patients, 1.0%) were noted during the study. Emergent serious adverse events were reported in 1 patient in the agomelatine, 1 in the escitalopram, and 2 in the placebo groups (pregnancy in each active treatment group, bunion operation in the placebo group [1 patient], and vertigo and vomiting in the placebo group [1 patient]). None of the emergent serious adverse events were considered treatment related by the investigator.

There were no clinically relevant between-group differences, nor changes from baseline to the last value on treatment, in the biochemical and hematologic parameters during the study.

Four patients (2 in each active treatment group) had emergent potentially clinically significant abnormal transaminases

Table 4. Hamilton Anxiety Rating Scale (HARS) Total Score,[a] Response to Treatment, and Remission Rates: Subsets of Severely Anxious Patients at Baseline

Variable	(1) Agomelatine	(2) Placebo	(3) Escitalopram	(1) – (2) Estimate (SE)	(1) – (2) 95% CI[b]	(1) – (2) *P* Value	(2) – (3) Estimate (SE)	(2) – (3) 95% CI[b]	(2) – (3) *P* Value
HARS total ≥ 25	(n = 121)	(n = 112)	(n = 122)						
HARS total, mean (SD)									
Baseline	29.4 (3.7)	29.0 (2.9)	29.3 (3.6)						
Last value	13.1 (9.5)	18.0 (9.7)	13.2 (8.6)						
Change	−16.2 (9.3)	−11.0 (9.8)	−16.1 (8.0)	5.05 (1.12)	2.85 to 7.25	<.0001[c]	4.95 (1.12)	2.75 to 7.14	<.0001[c]
HARS response rate, %	64.46	36.61	65.57	27.86 (6.30)	15.51 to 40.20	<.0001[d]	28.97 (6.26)	16.69 to 41.24	<.0001[d]
HARS remission rate, %[e]	36.36	20.54	28.69	15.83 (5.80)	4.45 to 27.20	.008[d]	8.15 (5.60)	2.82 to 19.12	.149[d]
HARS total ≥ 25 and CGI-S ≥ 5	(n = 77)	(n = 74)	(n = 74)						
HARS total, mean (SD)									
Baseline	30.4 (3.8)	29.8 (2.9)	30.5 (3.9)						
Last value	13.5 (10.3)	18.4 (9.9)	15.1 (9.1)						
Change	−16.9 (10.1)	−11.3 (10.0)	−15.4 (8.8)	5.61 (1.49)	2.68 to 8.55	<.001[c]	4.08 (1.50)	1.11 to 7.04	.007[c]
HARS response rate, %	64.94	35.14	59.46	29.8 (7.77)	14.57 to 45.03	<.001[d]	24.32 (7.96)	8.72 to 39.93	.003[d]
HARS remission rate, %[e]	37.66	20.27	18.92	17.39 (7.23)	3.21 to 31.57	.019[d]	1.35 (6.52)	−14.14 to 11.44	.836[d]

[a]Baseline, last postbaseline value, and change from baseline to last postbaseline value over 12 weeks of treatment.
[b]Two-sided.
[c]Analysis of covariance model on factor treatment (including the 3 treatment groups): adjustment for center (random effect) and HARS total score at week 0.
[d]χ^2 test.
[e]Unplanned analysis.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, SE = standard error.

Table 5. Secondary Efficacy Criteria in the Full Analysis Set: Expressed as Baseline and Last Postbaseline Value Over 12 Weeks of Treatment

Measure	(1) Agomelatine (n = 139)	(2) Placebo (n = 131)	(3) Escitalopram (n = 139)	(1) – (2) Estimate (SE)	(1) – (2) 95% CI	(1) – (2) *P* Value[a]	(2) – (3) Estimate (SE)	(2) – (3) 95% CI	(2) – (3) *P* Value[a]
HARS psychic anxiety score, mean (SD)									
Baseline	15.1 (2.2)	15.2 (2.1)	15.3 (2.4)						
Last value	6.9 (5.5)	9.5 (5.1)	6.8 (4.7)	2.55 (0.64)	1.28 to 3.81	<.0001[b]	2.64 (0.59)	1.47 to 3.81	<.0001[b]
HARS somatic anxiety score, mean (SD)									
Baseline	13.5 (3.4)	13.0 (2.7)	13.3 (3.0)						
Last value	6.0 (4.4)	8.1 (4.9)	6.1 (4.5)	2.06 (0.57)	0.94 to 3.19	<.001[b]	2.03 (0.57)	0.9 to 3.16	<.001[b]
CGI-S score, mean (SD)									
Baseline	4.7 (0.7)	4.7 (0.6)	4.6 (0.6)						
Last value	2.7 (1.3)	3.3 (1.3)	2.7 (1.3)	0.60 (0.16)	0.28 to 0.91	<.001	0.65 (0.16)	0.33 to 0.96	<.0001
CGI-I score, mean (SD)									
Last value	2.1 (1.3)	2.7 (1.4)	2.1 (1.2)	0.60 (0.16)	0.29 to 0.92	<.001	0.65 (0.15)	0.35 to 0.96	<.0001
HAD depression score, mean (SD)									
Baseline	6.6 (3.3)	6.9 (3.3)	6.7 (3.5)						
Last value	4.7 (4.1)	5.6 (3.8)	4.1 (3.7)	0.90 (0.49)	−0.06 to 1.86	.067[b]	1.40 (0.47)	0.49 to 2.32	.003[b]
HAD anxiety score, mean (SD)									
Baseline	14.8 (2.3)	14.8 (2.4)	14.8 (2.6)						
Last value	7.8 (4.5)	10.3 (5.1)	7.3 (4.2)	2.48 (0.59)	1.31 to 3.65	<.0001[b]	2.98 (0.58)	1.85 to 4.11	<.0001[b]

[a]Two-sided Student *t* test for independent samples.
[b]Unplanned analysis.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, HAD = Hospital Anxiety and Depression Scale, HARS = Hamilton Anxiety Rating Scale, SE = standard error.

possibly related to treatment (agomelatine: potentially clinically significant abnormal values of alanine aminotransferase (ALT) were 4.1 upper limit of normal (ULN) and 3.4 ULN; escitalopram: potentially clinically significant abnormal values of ALT were 4.8 ULN and 3.2 ULN). All values normalized after study drug discontinuation.

There were neither clinically relevant between-group differences nor changes from baseline to the last postbaseline value in groups for the supine blood pressure, heart rate, weight, and BMI. No clinically relevant ECG abnormalities were recorded.

DISCUSSION

The results provide additional evidence that agomelatine 25–50 mg is efficacious and well tolerated in the short-term treatment of GAD. The efficacy of agomelatine is demonstrated on the primary outcome measure (HARS total score), with a placebo-agomelatine difference of

4.7 points, and is supported by consistent findings on secondary measures of clinical response, remission, sleep improvement, and decrease in associated disability. The positive data with escitalopram reinforce the finding with agomelatine and validate the study. The timeline of improvement on agomelatine is consistent with previous results.[16]

The benefit of agomelatine may be especially apparent in more severely anxious patients. Agomelatine was as efficacious in the subset of patients with HARS total score ≥ 25 and CGI-S ≥ 5 at baseline, with a 5.6 point difference versus placebo on the HARS and a substantial rate of response to treatment (about 65%) over the 12-week period. In this group of more severe patients, remission with agomelatine was achieved in about 4 of 10 patients (37.7%). In contrast, only 2 of 10 patients showed remission of symptoms in the placebo (20.3%) and escitalopram (18.9%) groups. Such data are consistent with prior basic work emphasizing agomelatine's unique mechanism of action and with previous clinical work indicating that agomelatine may be more effective than a number of other antidepressants in the treatment of anxious depression.[31]

The benefits of agomelatine on both psychic and somatic symptoms of GAD are also notable. Whereas some agents that are efficacious in GAD act primarily on psychic rather than somatic symptoms of the HARS, agomelatine appeared efficacious for both sets of symptoms, which is consistent with previous work in GAD trials with this antidepressant.[16,17] Although psychic symptoms of anxiety may be more specific to GAD, somatic symptoms appear to be a particularly important clinical predictor of the presence of anxiety disorder.[32] It is key for clinicians to screen for both psychic and somatic symptoms of GAD. Agents such as agomelatine, escitalopram, and venlafaxine, which reduce both sets of symptoms in GAD, may be particularly useful in clinical practice.

In addition to robustly reducing anxiety symptoms, agomelatine had a range of other positive effects, including improvement on all sleep criteria assessed by the LSEQ. Sleep disturbance is 1 of the key diagnostic criteria for GAD[33] and occurs in an estimated 50%–70% of patients with this condition.[34] Thus, improvement in the self-reported ratings of GAD patients on getting to sleep, perceived quality of sleep, and behavioral integrity in the morning may represent a particularly useful aspect of agomelatine efficacy. The benefit of escitalopram for the treatment of sleep problems in GAD patients has been reported[35] but did not appear in this study on the LSEQ.

The expected profile of adverse events was found for both agomelatine and escitalopram. Consistent with prior work on agomelatine in MDD and GAD patients,[12,16,17,36] agomelatine proved to be well tolerated, with only minimal distinctions from placebo apparent. This lack of differentiation of agomelatine from placebo not only validates the double-blind nature of the current trial but also suggests that agomelatine may have a unique position in the clinical pharmacotherapy of anxiety disorders.

Some limitations of the current study deserve mention. First, patients enrolled in GAD trials, like those in the registration trials for other agents, may not be representative of those seen in general psychiatric or medical practice, where there may be significant comorbidity with depression and other disorders.[37] Nevertheless, patients had severe GAD symptoms and high levels of associated disability (as shown by HARS, CGI-S, and SDS scores). Most trials in GAD patients exclude primary psychiatric comorbidities, which makes this patient sample comparable to many of those reported in the literature. Second, sleep symptoms were measured by self-report, rather than by an objective laboratory assessment. Further work is needed to confirm the interesting sleep findings reported here.

There are several pharmacologic treatment options for GAD, but each has limitations. For example, benzodiazepines carry a risk for abuse, dependence, and withdrawal, while tricyclics, selective serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors each have particular side-effect profiles that can have a negative impact on adherence. As there is a high prevalence of depression and anxiety, there is clearly a need in clinical practice for agents with unique mechanisms of action for those patients who cannot tolerate existing therapies due to side effects or for those patients who do not respond adequately. The present study is one of the few trials on GAD that has both a placebo and active comparator arm,[18,38–40] thus providing the sort of data that help inform clinicians of the relative utility of different antidepressants in the treatment of GAD. The data here reinforce early work indicating the efficacy and tolerability of agomelatine in the short- and long-term treatment of GAD and suggest that agomelatine may have a unique position in the clinical armamentarium for the management of this disorder.[16,17]

Drug names: escitalopram (Lexapro and others), pregabalin (Lyrica and others).

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Author contributions: The 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. Dr. Stein was the scientific consultant for this project.

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Supplementary Material

Article Title: Agomelatine in Generalized Anxiety Disorder: An Active Comparator and Placebo-Controlled Study

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List of Supplementary Material for the article

1. eTable 1 — SDS - Scores at baseline and last post-baseline assessment over 12 weeks of treatment
2. eTable 2 — LSEQ in the FAS at last assessment over 12 weeks of treatment
3. eTable 3 — Most frequently reported emergent adverse events* during the double-blind treatment period (at least 2% of the patients in any group)

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Supplementary eTable 1: SDS - Scores at baseline and last post-baseline assessment over 12 weeks of treatment (expressed as Mean ± SD)

		Agomelatine (N = 139)	Placebo (N = 131)	Escitalopram (N = 139)
Work				
	Baseline	6.1 ± 2.0	6.5 ± 1.8	6.4 ± 1.8
	Last value	2.7 ± 2.4	4.4 ± 2.8	2.8 ± 2.5
	E (SE)	1.69 (0.35)		1.55 (0.35)
	95% CI	[1.00 ; 2.38]		[0.87 ; 2.23]
	P value [(1)]	<0.0001		<0.0001
Social life				
	Baseline	6.5 ± 1.8	6.3 ± 2.1	6.6 ± 1.9
	Last value	2.8 ± 2.4	4.4 ± 2.8	3.1 ± 2.6
	E (SE)	1.55 (0.32)		1.28 (0.33)
	95% CI	[0.92 ; 2.18]		[0.63 ; 1.92]
	P value[(1)]	<0.0001		<0.001
Family life and home responsibilities				
	Baseline	6.2 ± 1.9	6.1 ± 1.8	6.3 ± 1.7
	Last value	2.9 ± 2.5	4.2 ± 2.7	2.9 ± 2.6
	E (SE)	1.35 (0.32)		1.35 (0.32)
	95% CI	[0.73 ; 1.98]		[0.70 ; 1.99]
	P value[(1)]	<0.0001		<0.0001

[(1)] *Two sided Student's T-test for independent samples*
E (SE): Estimate (Standard Error) of the difference between treatment group means: Placebo minus Agomelatine or Escitalopram - 95% CI: Two-sided 95% Confidence Interval of the estimate - P value: p-value of treatment effect

Supplementary eTable 2: LSEQ in the FAS at last assessment over 12 weeks of treatment

		Agomelatine (N = 139)	Placebo (N = 131)	Escitalopram (N = 139)
Getting off to sleep score				
Last value	Mean ± SD	35.1 ± 15.9	41.8 ± 19.6	39.6 ± 20.0
	E (SE)		6.73 (2.17)	2.23 (2.41)
	95% CI		[2.45; 11.00]	[-2.52; 6.98]
	p-value [(1)]		0.002	0.357
Quality of sleep score				
Last value	Mean ± SD	30.7 ± 18.9	40.1 ± 23.6	37.5 ± 23.6
	E (SE)		9.40 (2.60)	2.66 (2.87)
	95% CI		[4.29; 14.51]	[-3.00; 8.32]
	p-value [(1)]		<0.001	0.355
Awakening score				
Last value	Mean ± SD	38.8 ± 19.7	43.7 ± 21.6	42.5 ± 21.5
	E (SE)		4.92 (2.52)	1.15 (2.62)
	95% CI		[-0.04; 9.88]	[-4.02; 6.31]
	p-value [(1)]		0.052	0.662
Integrity of behaviour score				
Last value	Mean ± SD	38.4 ± 20.3	43.5 ± 22.5	40.1 ± 22.2
	E (SE)		5.15 (2.61)	3.43 (2.72)
	95% CI		[0.02; 10.28]	[-1.92; 8.79]
	p-value [(1)]		0.049	0.208

[(1)] Two-sided Student's t-test

E (SE): Estimate (Standard Error) of the difference between treatment group means: Placebo minus Agomelatine or Escitalopram - 95% CI: Two-sided 95% Confidence Interval of the estimate - P value: p-value of treatment effect

Supplementary eTable 3: Most frequently reported emergent adverse events* during the double-blind treatment period (at least 2% of the patients in any group). – Safety set

Adverse events	Agomelatine (N = 139)	Placebo (N=131)	Escitalopram (N = 141)
All	47.5	44.3	48.2
Headache	7.2	7.6	12.8
Nasopharyngitis	4.3	5.3	5.7
Diarrhoea	4.3	1.5	6.4
Nausea	3.6	0.8	7.8
Dizziness	2.2	3.1	5.7
Somnolence	3.6	2.3	3.5
Insomnia	2.2	0.8	3.5
Hyperhidrosis	-	1.5	3.5
Dry mouth	1.4	2.3	0.7
Dyspepsia	2.2	1.5	0.7
Tension headache	-	3.1	1.4
Vision blurred	1.4	2.3	0.7
Anxiety	0.7	-	2.8
Abdominal pain	2.9	-	-
Bronchitis	2.2	0.8	-
Gamma-glutamyltransferase increased	2.2	-	0.7
Hypercholesterolemia	2.2	-	-
Neck pain	-	2.3	-

* expressed as percent of affected patients among exposed patients in the considered treatment group