Agomelatine Prevents Relapse in Generalized Anxiety Disorder: A 6-Month Randomized, Double-Blind, Placebo-Controlled Discontinuation Study

Dan J. Stein, MD, PhD; Antti Ahokas, MD; Cristina Albarran, PharmD; Valérie Olivier, PharmD, PhD; and Christer Allgulander, MD

ABSTRACT

Objective: This study evaluated the efficacy and tolerability of agomelatine in the prevention of relapse in patients with generalized anxiety disorder (GAD).

Method: Patients with GAD (Hamilton Anxiety Rating Scale [HARS] ≥ 22, with items 1 and 2 ≥ 2, item 1 + 2 ≥ 5; Montgomery-Asberg Depression Rating Scale [MADRS] ≤ 16; and < 20% decrease in HARS total score between screening and baseline) who responded to a 16-week course of agomelatine 25–50 mg/d treatment were randomly assigned to receive continuation treatment with agomelatine (n = 113) or placebo (n = 114) for 26 weeks. The main outcome measure was time to relapse during this maintenance period. The estimated risk of relapse was calculated using the Kaplan-Meier method, and groups were compared using a log-rank test stratified for country. The study was undertaken in 31 clinical centers in Canada, Denmark, Estonia, Finland, Hungary, and Sweden from November 2007 to September 2009.

Results: During the 6-month maintenance period, the proportion of patients that relapsed during the double-blind period in the agomelatine group (22 patients, 19.5%) was lower than in the placebo group (35 patients, 30.7%). The risk of relapse over time was significantly lower for patients who continued treatment than for those switched to placebo ($P = .046$, log-rank test stratified for country). Agomelatine was also superior to placebo in preventing relapse in the subset of more severe patients with baseline HARS total score ≥ 25 and CGI-S score ≥ 5. The tolerability of agomelatine was good throughout the study, and there were no differences in discontinuation symptoms after withdrawal of agomelatine in comparison to maintenance on agomelatine.

Conclusions: The present study extends the positive findings of an earlier short-term study of agomelatine in GAD, demonstrating that agomelatine is effective and well-tolerated in the longer-term treatment of this chronic disorder.

Trial Registration: www.isrctn.org identifier: ISRCTN38094599

J Clin Psychiatry 2012;73(7):1002–1008
© Copyright 2012 Physicians Postgraduate Press, Inc.

Submitted: *October 28, 2011; accepted January 23, 2012 (doi:10.4088/JCP.11m07493).*
Corresponding author: *Dan J. Stein, MD, PhD, Groote Schuur Hospital UCT Department of Psychiatry, J-Block, Anzio Rd, Cape Town 7925, South Africa (dan.stein@uct.ac.za)*

Generalized anxiety disorder (GAD) is a chronic disorder characterized by excessive anxiety and uncontrollable worry and is associated with comorbidity (including major depression and other anxiety disorders) and morbidity (including psychosocial impairment and economic costs).[1]

Agomelatine is an antidepressant that was recently approved by the European Medicines Agency and that has both a serotonergic and a melatonergic mechanism of action.[2] The overall efficacy of agomelatine in the treatment of depression is associated with a good tolerability profile, including the absence of discontinuation symptoms on withdrawal.[3] Agomelatine is also effective in treating the anxiety symptoms associated with depression.[4,5] The efficacy and tolerability of agomelatine 25–50 mg/d in treating GAD patients have been demonstrated in a placebo-controlled phase II study.[6] Given that GAD is a chronic disorder, pharmacotherapy is often prescribed over the longer term. Relapse prevention trials in GAD have been reported for paroxetine,[7] escitalopram,[8] venlafaxine,[9,10] duloxetine,[11] and pregabalin.[12]

The present study was performed in nondepressed GAD patients to evaluate the longer-term efficacy and tolerability of agomelatine. After an initial response to agomelatine, time to relapse was assessed in patients randomized to treatment with agomelatine versus placebo during a 6-month maintenance period. A secondary objective of the study was to provide additional tolerability and safety data on long-term use of agomelatine in GAD patients and to confirm the absence of discontinuation symptoms.

METHOD

This was a multicenter, double-blind, randomized, placebo-controlled, parallel-group study conducted in 31 centers in 6 countries from November 2007 to September 2009. The countries were Canada (6 sites; 89 patients), Denmark (5 sites; 86 patients), Estonia (5 sites; 79 patients), Finland (6 sites; 125 patients), Hungary (5 sites; 50 patients), and Sweden (4 sites; 48 patients). Patients were recruited by advertisement (64.8%), self-referral (17.6%), or referral by a psychiatrist (5.2%), a psychologist (0.4%), general practitioner, or other specialist (12%). The study, undertaken in accordance with the principles of Good Clinical Practice (CPMP/ICH/135/95) and the Declaration of Helsinki, was approved by ethics committees and included only patients who gave informed written consent. The trial was registered on www.isrctn.org (identifier: ISRCTN38094599).

Study Design

This study began with a 16-week open-label treatment period that was followed by a 26-week, randomized, double-blind,

© Copyright 2012 Physicians Postgraduate Press, Inc. © Copyright 2012 Physicians Postgraduate Press, Inc.

placebo-controlled maintenance treatment period. Patients received agomelatine 25 mg/d during the first 4 weeks, then agomelatine was continued to the end of the open-label period (week 16) at a dose either maintained at 25 mg/d or increased to 50 mg/d in patients with insufficient improvement. This decision was determined centrally using an interactive voice response system (IRS), with criteria blind for both investigators and patients.

At week 16, all patients who had improved sufficiently according to investigator judgment were eligible to continue in the study. However, only patients who met criteria for a clinical response (Hamilton Anxiety Rating Scale [HARS][13] score ≤ 10 at week 16 and HARS score at week 16 minus HARS score at week 12 ≤ 4) were randomized to agomelatine versus placebo. These criteria were assessed centrally using IRS and were blind to investigators and patients.

At week 42, agomelatine-treated patients were rerandomized either to receive either placebo or to continue agomelatine (same dose) during 1 week to evaluate discontinuation symptoms on the 43-item Discontinuation Emergent Signs and Symptoms checklist (DESS).

Allocation to Treatment

After the open-label period, eligible patients were assigned to agomelatine or placebo treatment in a 1:1 ratio according to a balanced (nonadaptive) randomization with stratification by center. During the study, all patients took 2 tablets orally daily in the evening. The dosage schedule and the appearance and taste of study treatment were the same for all patients.

Patients

Male or female outpatients with a primary clinical diagnosis of GAD according to *DSM-IV-TR* criteria, confirmed by the Mini International Neuropsychiatric Interview (MINI),[14] were eligible.

Patients aged at least 18 years were required to have a screening 14-item HARS total score ≥ 22, with HARS item 1 ≥ 2 and item 2 ≥ 2, with the sum of HARS item 1 and item 2 ≥ 5; a Montgomery-Asberg Depression Rating Scale[15] (MADRS) total score ≤ 16; and a decrease of < 20% in HARS total score between screening and baseline.

Patients were required to be physically healthy or to have stabilized somatic illnesses. Patients with any of the following disorders from *DSM-IV-TR*, identified with the MINI, were excluded: panic disorder, posttraumatic stress disorder, agoraphobia, social phobia, obsessive-compulsive disorder, or psychiatric disorder other than GAD (within 6 months prior to the selection visit).

Patients were excluded when there was evidence of ongoing alcohol or drug abuse or any personality disorder that might compromise the study, if they were at risk of suicide, had a score > 3 on item 10 of MADRS, or reported a suicide attempt within the past year.

Patients with a current GAD episode resistant to at least 2 different previous antianxiety treatments during the past 12 months were also excluded.

Clinical Points

- Patients with GAD maintained on agomelatine treatment of 25–50 mg/d for 6 months had a reduced risk of relapse compared to patients switched to placebo.
- This evidence supports the view that, in clinical practice, agomelatine will have an efficacy at least equivalent to other available treatments.

Patients were excluded if they had received any of the following recent/concomitant therapies: psychotherapy of any type started within 30 days prior to the selection visit and during the study or anxiolytics or antipsychotics taken within 1 week prior to the selection visit. Washout times were 5 weeks for fluoxetine; 4 weeks for clomipramine and imipramine; 2 weeks for paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, duloxetine, and venlafaxine; and 1 week for mirtazapine. Benzodiazepines had to be stopped 2 weeks prior to screening in case of intermittent use and at least 6 months before screening visit in case of daily use. Other hypnotics/anxiolytics had to be discontinued at least 1 week prior to selection.

Assessments

Efficacy and tolerability parameters were assessed at inclusion and after 2, 4, 8, 12, and 16 weeks of open-label treatment; 4 weeks after week 16; and then every 4 weeks (2 weeks for the 2 last visits) until week 42.

The HARS was rated at each visit up to week 42 or in case of premature withdrawal.

The primary endpoint of efficacy was relapse occurring within 6 months from randomization and defined either by a HARS total score ≥ 15 or by clinical judgment of a lack of efficacy. The main outcome measure was the time to relapse during the maintenance period (time between randomization and relapse date).

Secondary efficacy parameters included HARS total score, HARS psychic and somatic anxiety subscore, and Clinical Global Impressions-Severity of Illness (CGI-S) and Global Improvement (CGI-I) scores.[16] The CGI-S was assessed at each visit up to week 42 or in case of premature withdrawal. During the open-label period, the CGI-I was compared between weeks 0 and 2; during the maintenance period, it was compared to the value at week 16.

The Hospital Anxiety and Depression scale (HAD)[17] was completed by the patient at screening and at weeks 0, 16, and 42 or in the case of premature withdrawal. The Sheehan Disability Scale (SDS)[18] was rated by the patient at weeks 0, 2, 16, and 42 or in the case of withdrawal. The Leeds Sleep Evaluation Questionnaire (LSEQ)[19] was completed by the patient at weeks 2, 16, and 42 or in the case of withdrawal.

The tolerability and safety evaluations were based on emerging adverse events (AEs) spontaneously reported by the patient or elicited by the investigator from week 0, vital

© Copyright 2012 Physicians Postgraduate Press, Inc.
© Copyright 2012 Physicians Postgraduate Press, Inc.

signs (blood pressure, heart rate, and weight), biochemistry and hematology parameters, and 12-lead electrocardiogram abnormalities. Liver enzyme values were monitored until return to normal values if > 3 times the upper limit of the reference range for aspartate aminotransferase/alanine aminotransferase (AST/ALT) and > 2 times the upper limit of the reference range for total bilirubin.

The DESS[20] was completed at weeks 42 and 43 for patients who had completed the 26-week double-blind maintenance treatment period.

Rater Training

Investigators were all experienced clinicians and were trained before and during the study on the diagnosis and the assessment of the main efficacy measure of the study (HARS) to ensure interrater consistency prior to and during the trial.

Statistical Analysis

The time to relapse was compared for agomelatine and placebo groups using Kaplan-Meier estimations and a log-rank test stratified for country. The hazard ratio (HR) of relapse was estimated with a Cox model associated with the likelihood ratio test, with adjustment for country.

The same analysis strategy was used in the subset of patients with HARS total score ≥ 25 and CGI-S ≥ 5 at inclusion.

Type I error was set at 5%. Descriptive statistics were provided for secondary efficacy parameters and for emergent AEs during the double-blind treatment period.

RESULTS

Patient Characteristics

Of the 477 patients entering the open-label period, 329 (69.0%) completed the open-label period, and 227 patients (47.6%) were randomized to maintenance treatment with agomelatine (113 patients) or placebo (114 patients). There were no significant demographic or clinical differences between the 2 groups (Table 1). Among the 113 agomelatine-treated patients, 33 (29.2%) received 50 mg/d.

The median duration of GAD symptoms was 8 years. At inclusion, 5.7% of patients had previously experienced an anxiety disorder other than GAD, and 12.8% had previously experienced a major depressive episode.

The mean ± SD HARS total score was 28.0 ± 3.7 at inclusion and was consistent with the mean ± SD CGI-S score of 4.8 ± 0.7, indicating markedly ill patients on average. The mean ± SD HAD anxiety score at inclusion was 14.4 ± 2.8.

On the SDS, on average, patients reported mean ± SD symptom-related impairments at work (6.3 ± 1.9), in social life (6.3 ± 1.9), and in family life (6.0 ± 2.0).

Among the 449 included patients continuing in the study after week 4, 195 (43.4%) had their agomelatine dose increased to 50 mg/d.

During the 16-week open-label period, 148 patients (31.0%) withdrew from the study, mostly for nonmedical reasons (10.7%) and lack of efficacy (10.1%).

Table 1. Demographic and Clinical Characteristics of Patients With Generalized Anxiety Disorder (GAD) During Open-Label Treatment and at Randomization to Double-Blind Treatment

	Open-Label Period	Double-Blind Period	
	Agomelatine	Agomelatine	Placebo
Characteristic	(N = 477)	(n = 113)	(n = 114)
Age, mean ± SD, y	44.8 ± 14.6	45.9 ± 14.0	47.0 ± 15.1
Male/female, %/%	36.9/63.1	37.2/62.8	38.6/61.4
Duration of GAD, median, y	8.0	7.7	8.1
Other anxiety disorder, %	5.7	4.4	4.4
Major depressive disorder, %	12.8	13.3	14.0

Of the 328 patients (68.8% of the included patients) who continued the study at week 16, 100 patients were not randomized (blinded response criteria were not fulfilled), and 1 patient was excluded from the statistical analysis because he did not take any study drug after week 16. Of these 100 patients, 38 received 25 mg/d of agomelatine, and 62 received 50 mg/d.

Mean ± SD HARS total score of these 100 patients at week 16 was 14.5 ± .3.2, which decreased to 8.1 ± 4.5 at week 42 (n = 53) (13.3 ± .7.5 at the last postbaseline assessment [n = 100]).

Efficacy Parameters During the Open-Label Period

The mean ± SD HARS total score and the mean ± SD CGI-S score progressively decreased from 28.0 ± 3.8 at inclusion to 9.7 ± 5.9 at week 16 (11.6 ± 7.6 at last assessment) and from 4.8 ± 0.7 at inclusion to 2.4 ± 1.1 at week 16 (2.7 ± 1.2 at last assessment), respectively.

Of the 474 patients with at least one postbaseline assessment, 323 (68.1%) and 346 (73.0%) patients were rated as responders on the HARS and CGI-I, respectively, at last postbaseline assessment.

The mean ± SD HAD anxiety and depression scores decreased from inclusion (14.4 ± 2.8 and 7.9 ± 3.6, respectively) to the last assessment (8.4 ± 4.3 and 5.0 ± 3.8, respectively).

The mean ± SD of the 3 SDS scores decreased from inclusion to the last assessment (work: from 6.3 ± 1.9 to 3.6 ± 2.5; social life: from 6.3 ± 1.9 to 3.6 ± 2.6; family life and home responsibilities: from 6.0 ± 2.0 to 3.4 ± 2.5).

Efficacy Parameters During the Double-Blind 26-Week Period

In the intention-to-treat population, the proportion of patients who relapsed during the double-blind period in the agomelatine group (22 patients, 19.5%) was lower than in the placebo group (35 patients, 30.7%). The risk of relapse over 6 months was significantly lower with agomelatine than placebo ($P = .046$), and the risk of relapse over time was reduced by 41.8% for agomelatine-treated patients (HR = 0.582) (Figure 1, Table 2).

A definition of relapse based only on a HARS total score ≥ 15 showed a significant result in favor of agomelatine ($P = .025$, post hoc analysis) with an overall percentage of

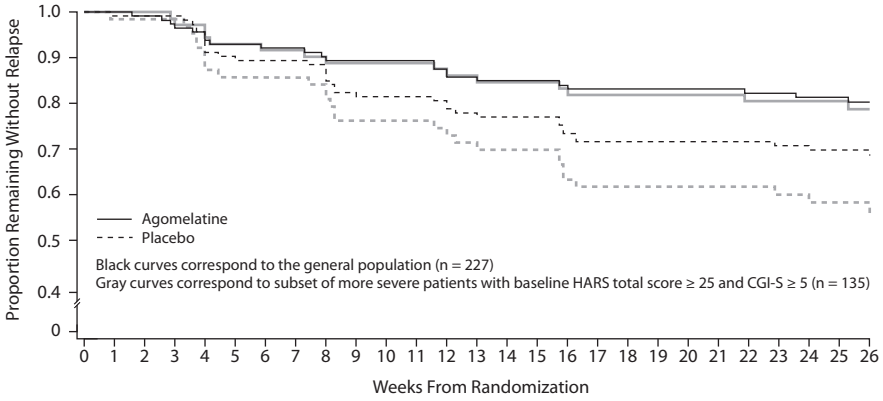
© Copyright 2012 Physicians Postgraduate Press, Inc. © Copyright 2012 Physicians Postgraduate Press, Inc.

Table 2. Primary Efficacy Measure: Time to Relapse During the 6-Month Double-Blind Period in Patients With Generalized Anxiety Disorder

Group	Patients, n	Relapses n	Relapses %	Estimated Risk of Relapse at 6 Months, E (SE) %[a]	Cox Model Hazard Ratio (agomelatine vs placebo), E (95% CI)[b]	Log-Rank Test *P* Value
Total population						
Agomelatine 25–50 mg/d	113	22	19.5	19.7 (3.8)	0.582 (0.341–0.995)	.046
Placebo	114	35	30.7	31.7 (4.5)		
Patients with baseline HARS total score ≥ 25 and CGI-S score ≥ 5						
Agomelatine 25–50 mg/d	72	15	20.8	21.2 (4.9)	0.407 (0.210–0.788)	.006
Placebo	63	27	42.9	44.0 (6.4)		

[a]Estimate (SE) of the percentage of patients with a relapse (Kaplan-Meier method).
[b]Log-rank test stratified for country, and Cox model adjusted for country.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, E = estimate, HARS = Hamilton Anxiety Rating Scale.

Figure 1. Primary Efficacy Result: Time to Relapse for the Patients With Generalized Anxiety Disorder Treated With Agomelatine (n = 113) and Placebo (n = 114) Over the 6-Month Double-Blind Treatment Period.[a,b,c]



[a]Kaplan-Meier survival estimation.
[b]The black curves illustrate that the estimated risk of relapse during the 6-month double-blind period in the agomelatine group (19.7%) was significantly lower than that in the placebo group (31.7%, dashed line) (stratified log-rank test $P = .046$) and the adjusted Cox proportional hazard model showed that the risk of relapse over time was reduced by 41.8% for agomelatine-treated patients (Cox model adjusted for country, hazard ratio = 0.582; 95% CI, 0.341–0.995).
[c]The gray curves illustrate that the estimated risk of relapse of more severely ill GAD patients who relapse over the 6-month period was significantly lower with agomelatine compared to placebo (dashed line) (log-rank test $P = .006$). A strong reduction of the risk of relapse, by 59.3%, was observed over time with agomelatine, as compared to placebo (Cox model, hazard ratio = 0.407; 95% CI, 0.210–0.788).

patients who had a relapse lower in the agomelatine group (n = 20, 17.7%) than in the placebo group (n = 35, 30.7%).

Agomelatine was superior to placebo in preventing relapse in the subset of severely ill patients with baseline HARS total score ≥ 25 and CGI-S score ≥ 5 (59.5% of the 227 patients; agomelatine: 72 patients, placebo: 63 patients). Fifteen severely ill patients relapsed in the agomelatine group (20.8%) versus 27 patients (42.9%) in the placebo group. The survival analysis showed a statistically significant difference in favor of agomelatine ($P = .006$) over 6 months, and the risk of relapse was reduced by 59.3% in patients treated with agomelatine versus placebo (HR: 0.407) (Figure 1, Table 2).

The mean ± SD HARS total score decreased over time in the agomelatine group (from 5.9 ± 2.7 at week 16 to 4.3 ± 3.5 at week 42) and in the placebo group (from 6.0 ± 2.6 at week 16 to 5.2 ± 3.7 at week 42). The mean ± SD HARS last post-randomization score remained stable in the agomelatine group (mean ± SD change of 1.6 ± 7.7), whereas it increased in the placebo group (mean± SD change of 3.6 ± 8.4) (Table 3).

The mean ± SD CGI-S score remained stable, although it was lower in the agomelatine group (vs placebo) at the last assessment (Table 3).

In the intention-to-treat population, the last HAD anxiety and depression scores remained stable in both treatment groups, although they were lower in the agomelatine group (vs placebo) at the last assessment. A similar pattern was observed in the agomelatine group for the 3 SDS scores and the LSEQ scores (Table 3).

Tolerability

During the maintenance treatment period, 77 patients (33.9%) experienced at least 1 emergent AE. In both groups, the majority of the emergent AEs were mild to moderate (93.3%), and the percentage of patients with at least

© Copyright 2012 Physicians Postgraduate Press, Inc. © Copyright 2012 Physicians Postgraduate Press, Inc.

Table 3. Secondary Efficacy Measures for Patients With Generalized Anxiety Disorder[a]

	Start of the Open-Label Period Agomelatine (n = 477)	Start of the Double-Blind Period (week 16)		End of the Double-Blind Period (week 42)		Last Postrandomization Value	
		Agomelatine (n = 113)	Placebo (n = 114)	Agomelatine (n = 89)	Placebo (n = 75)	Agomelatine (n = 113)	Placebo (n = 114)
HARS							
Total	28.0 ± 3.7	5.9 ± 2.7	6.0 ± 2.6	4.3 ± 3.5	5.2 ± 3.7	7.6 ± 8.0	9.6 ± 7.8
Psychic anxiety	14.8 ± 2.4	3.4 ± 2.0	3.4 ± 1.8	2.6 ± 2.4	3.2 ± 2.8	4.5 ± 4.8	5.7 ± 4.8
Somatic anxiety	13.2 ± 3.0	2.6 ± 1.7	2.6 ± 1.7	1.7 ± 1.6	2.0 ± 1.7	3.0 ± 3.7	3.9 ± 3.5
CGI							
Severity of illness	4.8 ± 0.7	1.8 ± 0.7	1.8 ± 0.8	1.5 ± 0.8	1.6 ± 0.8	2.0 ± 1.4	2.4 ± 1.4
HAD							
Anxiety	14.4 ± 2.8	6.1 ± 3.4	6.0 ± 3.0	4.9 ± 3.4	5.2 ± 3.1	6.4 ± 4.6	7.2 ± 4.4
Depression	7.9 ± 3.6	3.5 ± 2.8	3.0 ± 3.0	2.4 ± 2.2	2.7 ± 2.6	3.5 ± 3.3	3.9 ± 3.2
LSEQ							
Getting off to sleep	33.9 ± 15.5	28.8 ± 14.8	28.3 ± 14.4	27.3 ± 14.6	34.3 ± 14.2	32.1 ± 18.3	40.5 ± 18.7
Quality of sleep	38.4 ± 18.1	27.1 ± 19.2	26.8 ± 18.3	26.4 ± 18.3	29.0 ± 17.9	32.7 ± 22.5	37.2 ± 23.9
Sleep awakening	44.1 ± 17.0	35.2 ± 20.1	33.8 ± 18.4	32.1 ± 19.1	31.8 ± 18.4	36.5 ± 21.2	39.2 ± 21.5
Integrity of behavior	45.0 ± 16.2	32.2 ± 17.8	32.2 ± 16.5	29.7 ± 18.7	32.3 ± 18.1	34.9 ± 21.5	41.1 ± 21.6
SDS							
Work	6.3 ± 1.9	2.1 ± 1.6	2.0 ± 1.7	1.5 ± 1.7	1.9 ± 1.6	2.4 ± 2.5	2.7 ± 2.2
Social life	6.3 ± 1.9	2.3 ± 2.0	2.1 ± 1.9	1.7 ± 1.7	2.0 ± 2.1	2.5 ± 2.4	3.1 ± 2.6
Family life and home responsibilities	6.0 ± 2.0	2.2 ± 1.8	2.0 ± 1.8	1.7 ± 1.9	1.8 ± 1.9	2.5 ± 2.5	2.7 ± 2.5

[a]All data presented as mean ± SD.
Abbreviations: CGI = Clinical Global Impressions scale, HAD = Hospital Anxiety and Depression scale, HARS = Hamilton Anxiety Rating Scale, LSEQ = Leeds Sleep Evaluation Questionnaire, SDS = Sheehan Disability Scale.

Table 4. Most Frequently Reported Emergent Adverse Events in Patients With Generalized Anxiety Disorder[a]

Adverse Event, % (n)	Agomelatine (n = 113)	Placebo (n = 114)
Headache	10.6 (12)	2.6 (3)
Nasopharyngitis	5.3 (6)	5.3 (6)
Nausea	4.4 (5)	0 (0)
Upper respiratory tract infection	3.5 (4)	2.6 (3)
Gastroenteritis	3.5 (4)	1.8 (2)
Insomnia	2.7 (3)	1.8 (2)
Dizziness	2.7 (3)	0 (0)

[a]Adverse events are expressed as the ratio of number of affected patients to number of exposed patients by treatment group during the double-blind treatment period (categories with at least 3 affected patients in 1 treatment group).

1 emergent AE was significantly higher in the agomelatine group (n = 46, 40.7%) than in the placebo group (n = 31, 27.2%) ($P = .032$). The most common emergent AEs were the same in both groups, but higher proportions of patients reporting at least 1 emergent AE with agomelatine were seen for headache, nausea, gastroenteritis, and dizziness (Table 4). No death occurred. Two cases of treatment termination due to AEs were reported in the placebo group (1.8%).

During the entire agomelatine treatment period, 272 of 476 patients (57.1%) reported at least 1 emergent AE. The most frequent emergent AEs with agomelatine were similar to those reported during the double-blind treatment period and included headache (11.3%), nasopharyngitis (9.9%), dizziness (8%), nausea (6.5%), dry mouth (5.7%), somnolence (5.0%), and fatigue (4.4%). Seventeen patients (3.6%) had at least 1 emergent potentially clinically significant abnormal (PCSA) liver enzyme value (10 patients taking agomelatine 25 mg/d, 3 taking agomelatine 50 mg/d, and 5 taking placebo; 1 patient who received agomelatine 25 mg/d during the open-label phase had emergent PCSA values when receiving placebo during the double-blind phase). All values returned to baseline levels, with the exception of 3 total bilirubin values in patients taking placebo.

There were no clinically relevant mean changes from baseline or differences between treatment groups in other biochemistry and hematology parameters.

There were no discontinuation symptoms in patients switched to placebo compared with patients maintained on agomelatine during weeks 42 to 43. The mean ± SD number of discontinuation-emergent symptoms at week 43 was similar for patients maintained on agomelatine (0.9 ± 1.6) or switched to placebo (0.9 ± 1.9).

DISCUSSION

Patients with GAD who responded to open-label treatment with agomelatine 25–50 mg/d and who were maintained on treatment for 6 months had a reduced risk of relapse compared to patients switched to placebo. The risk of a relapse was about 1.6-fold lower on continued maintenance treatment with agomelatine than on placebo. The lower risk of relapse was particularly marked in those patients with higher symptom severity at baseline. The effect of agomelatine treatment was stable over time (HARS and HAD scores), and the maintenance of efficacy was supported by SDS scores in work, social, and family life domains.

These data on long-term efficacy extend previous work showing the short-term therapeutic benefit of agomelatine in GAD[6] and are consistent with work showing the efficacy of agomelatine for anxiety symptoms in depression.[5]

© Copyright 2012 Physicians Postgraduate Press, Inc.
© Copyright 2012 Physicians Postgraduate Press, Inc.

The rate of relapse in patients treated with agomelatine (19.5%) and placebo (30.7%) is partially consistent with the findings of previous relapse prevention studies in GAD. In such work, there has been a 10%–20% relapse rate on medication and a 40%–55% relapse rate on placebo.[7,8,11] The lower placebo relapse rate seen here very likely reflects the low rate of adverse effects during the trial and during discontinuation (improving the blind) and some methodological features (eg, longer open-label treatment, blinding of dose increases).[21,22]

For most approved antidepressants, there are case reports or warnings from manufacturers of reactions occurring in response to either abrupt discontinuation or medication tapering.[23] Thus, one of the problems associated with a study design that randomizes patients from active treatment to placebo is the risk that possible discontinuation symptoms might be misinterpreted as relapses. In the present study, there were low rates of early relapse in the placebo group, with gradual accumulation of relapses over time, also as seen in a previous study of agomelatine focused on the prevention of relapse in major depression.[24] This result confirms the absence of a discontinuation syndrome with agomelatine[3] and ensures that the efficacy of maintenance therapy is not overestimated. The absence of discontinuation symptoms was also verified after withdrawal of agomelatine at 42 weeks of treatment.

It is notable that, in those patients with the highest symptom severity at baseline, the relapse rate for patients who continued treatment with agomelatine was maintained at 21%, whereas it reached 43% with placebo. Those findings not only underline the efficacy of agomelatine in reducing relapse in GAD patients regardless of illness severity but they also illustrate the increased risk of relapse in more seriously ill patients after medication discontinuation. In this subset of patients, the relapse rate with placebo was in the range of that found in previous GAD relapse prevention studies.

The randomization rate appears low (47.8%) compared to that seen with paroxetine (86.8%)[7] and escitalopram (76.4%).[8] The most likely explanation lies in some advances in our trial design. First, the quite long duration of the open-label period allows having more stabilized responders, therefore mimicking the natural course of treatment. Similarly, in 2 relapse prevention studies with duloxetine and venlafaxine performed in GAD patients with a 6-month open-label period, the randomization rates were 48.4%[11] and 50.7%,[10] respectively. Secondly, the randomization criteria here are different from those used previously and may have led to a more representative, ie, sufficiently improved, and homogeneous sample of GAD patients. Thirdly, the blinding of randomization criteria reduces the rate of randomization as it circumvents the classical bias of inflated enrolment.[21,22] This design augments validity, insofar as it removes clinical trial biases.

Previous studies have demonstrated that long-term treatment with agomelatine is well tolerated, and this is confirmed in the current study. In the open-label period, the overall incidence and pattern of AEs were similar to those previously seen with agomelatine in GAD[6] and were consistent with those seen in depression,[5] as well as in the overall safety assessment of the drug.[25] During the entire double-blind period, the number of patients with at least 1 emergent AE was higher in the agomelatine group (vs placebo), but no AE led to agomelatine discontinuation (vs 2 cases of treatment termination with placebo). There were 14 (12.4%) and 11 (9.6%) cases of treatment-emerging AEs in the agomelatine and placebo groups, respectively, a rate that is very low compared to the selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors.[7,8] The profile of emergent AEs in the maintenance period in patients treated with agomelatine is similar to that reported in the major depressive disorder (MDD) relapse prevention study,[24] with a slightly lower rate here (40.7% vs 51.5%).

A number of limitations should be emphasized. First, this study was conducted by experienced academic clinical trial centers, using a highly homogenous patient population with little comorbidity. The findings may not be generalizable to other settings and to more heterogenous GAD populations. Second, tolerability and safety evaluations were based on spontaneously reported emergent AEs and not using a specific instrument (eg, the UKU Side Effects Rating Scale). Although heterogeneity in patients' reports across centers and countries is theoretically possible, the methodology allows a rigorous comparison with the previously collected data on agomelatine in MDD. In both the GAD and MDD programs, the pattern of adverse effects has been similar across centers and countries.

These data indicate that agomelatine is a promising option for the longer-term treatment of GAD. The data supplement earlier work demonstrating the efficacy and tolerability of agomelatine in the short-term treatment of GAD as well as in the short- and longer-term treatment of major depression, which is the most frequent comorbid condition in GAD. It can reasonably be predicted that, in clinical practice, agomelatine will have efficacy at least equivalent to other available treatments.

Drug names: citalopram (Celexa and others), clomipramine (Anafranil and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), imipramine (Tofranil and others), mirtazapine (Remeron and others), paroxetine (Paxil, Pexeva, and others), pregabalin (Lyrica), sertraline (Zoloft and others), venlafaxine (Effexor and others).

Author affiliations: Department of Psychiatry, Groote Schuur Hospital, Cape Town, South Africa (Dr Stein); Mehilainen Clinic, Helsinki, Finland (Dr Ahokas); Institut de Recherches Internationales Servier (IRIS), Suresnes, France (Drs Albarran and Olivier); and Department of Clinical Neuroscience, Section of Psychiatry, Karolinska Institutet, Karolinska, University Hospital, Huddinge, Sweden (Dr Allgulander).

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.

Agomelatine Study Group participants: The following members served as national coordinators or principal investigators and participated in Study CL3-20098-05 0 with the authors of this report: (from Canada) M.Van Ameringen, MD, McMaster University Medical Centre, Hamilton; D. Bakish, MD, Privater, Ottawa; P. Chokka, MD, Grey Nuns Hospital, Edmonton; M. J. Filteau, MD, Privater, Clinique Marie-Fitzbach, Quebec; K. Kjernisted, MD, Copeman Neuroscience Centre, Vancouver; R. Matte, MD, Sherbrooke; (from Demark) B. Bahr, MD, Privater,

© Copyright 2012 Physicians Postgraduate Press, Inc.

© Copyright 2012 Physicians Postgraduate Press, Inc.

Copenhagen; K. Behnke, MD, Frederiksberg; E. Knutsen, MD, Privater, Aarhus; S. Rasmussen, MD, Privater, Hillerod; J. Sogaard, MD, Privater, Copenhagen; (from Estonia) A. Lehtmets, MD, West Tallinn Central Hospital, Tallinn; T. Eller, MD, Tartu University Hospital, Tartu; R. Jents, MD, Viljandi Hospital Foundation, Viljandi Maakond; A. Puusild, MD, Parnu Hospital, Parnu; U. Vohma, MD, North Estonia Medical Centre Foundation, Tallinn; (from Finland) A. Ahokas, MD, Laakarikeskus Mehilainen Psychiatric, Helsinki; R. Jokinen, MD, Länsi-Suomen Erikoislääkäripalvelut, Turku; J. Penttinen, MD, Salon Psykiatripalvelu Psychiatric, Salo; M. Pirila, MD, Privater, Tampere; R. Riihikangas, MD, Seinajoen Laakaritalo, Seinajoki; M. Timonen, MD, Diapolis Oy, Oulu; (from Hungary) I. Bitter, MD, Semmelweis University Clinic of Psychiatry and Psychotherapy, Budapest; C. Banki, MD, Santha Kalman Mental Healthcare Center and Hospital 1st Department of Psychiatry, Nagykallo; K. Hideg, MD, Varoskapu Outpatient Clinic, Budapest; E. Szadoczky, MD, ClinExpert Outpatient Clinic, Budapest; Z. Torok, MD, Forras Outpatient Clinic, Budapest; (from Sweden) K. Wahlstedt, MD, Privater, Uppsala; P. Bosson, MD, Hjarnhalsan Psychiatry, Lund; C. Engstrom Lehman, MD, Privater, Sundsvall; I. Sjodin, MD, Universitetssjukhuset i Linkoping, Linkoping.

Potential conflicts of interest: **Dr Stein** has received research grants and/or consultancy honoraria from Abbott, AstraZeneca, Eli Lilly, GlaxoSmithKline, Jazz, Johnson & Johnson, Lundbeck, Orion, Pfizer, Pharmacia, Roche, Servier, Solvay, Sumitomo, Takeda, Tikvah, and Wyeth. **Dr Ahokas** has received research grants and/or consultancy honoraria from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Lundbeck, Orion, Otsuka, Sanofi-Aventis, Servier, and Wyeth. **Drs Albarran** and **Olivier** are employees of Servier. **Dr Allgulander** is an employee of Karolinska Institutet, the School of Medicine, Stockholm, Sweden; a speaker for Servier, Eli Lilly, AstraZeneca, and Pfizer; and an advisory board member of Pfizer Sweden.

Funding support: This study was sponsored by Servier (Suresnes, France).

Previous presentation: Presented at the 19th European Congress of Psychiatry; March 12–15, 2011; Vienna, Austria.

REFERENCES

1. Hoffman DL, Dukes EM, Wittchen HU. Human and economic burden of generalized anxiety disorder. *Depress Anxiety*. 2008;25(1):72–90.
2. de Bodinat C, Guardiola-Lemaitre B, Mocaër E, et al. Agomelatine, the first melatonergic antidepressant: discovery, characterization and development. *Nat Rev Drug Discov*. 2010;9(8):628–642.
3. Montgomery SA, Kennedy SH, Burrows GD, et al. Absence of discontinuation symptoms with agomelatine and occurrence of discontinuation symptoms with paroxetine: a randomized, double-blind, placebo-controlled discontinuation study. *Int Clin Psychopharmacol*. 2004;19(5):271–280.
4. Kasper S, Hajak G, Wulff K, et al. Efficacy of the novel antidepressant agomelatine on the circadian rest-activity cycle and depressive and anxiety symptoms in patients with major depressive disorder: a randomized, double-blind comparison with sertraline. *J Clin Psychiatry*. 2010;71(2):109–120.
5. Kennedy SH, Rizvi SJ. Agomelatine in the treatment of major depressive disorder: potential for clinical effectiveness. *CNS Drugs*. 2010;24(6): 479–499.
6. Stein DJ, Ahokas AA, de Bodinat C. Efficacy of agomelatine in generalized anxiety disorder: a randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol*. 2008;28(5):561–566.
7. Stocchi F, Nordera G, Jokinen RH, et al; Paroxetine Generalized Anxiety Disorder Study Team. Efficacy and tolerability of paroxetine for the long-term treatment of generalized anxiety disorder. *J Clin Psychiatry*. 2003;64(3):250–258.
8. Allgulander C, Florea I, Huusom AK. Prevention of relapse in generalized anxiety disorder by escitalopram treatment. *Int J Neuropsychopharmacol*. 2006;9(5):495–505.
9. Montgomery SA, Mahé V, Haudiquet V, et al. Effectiveness of venlafaxine, extended release formulation, in the short-term and long-term treatment of generalized anxiety disorder: results of a survival analysis. *J Clin Psychopharmacol*. 2002;22(6):561–567.
10. Rickels K, Etemad B, Khalid-Khan S, et al. Time to relapse after 6 and 12 months' treatment of generalized anxiety disorder with venlafaxine extended release. *Arch Gen Psychiatry*. 2010;67(12):1274–1281.
11. Davidson JR, Wittchen HU, Llorca PM, et al. Duloxetine treatment for relapse prevention in adults with generalized anxiety disorder: a double-blind placebo-controlled trial. *Eur Neuropsychopharmacol*. 2008;18(9): 673–681.
12. Feltner D, Wittchen HU, Kavoussi R, et al. Long-term efficacy of pregabalin in generalized anxiety disorder. *Int Clin Psychopharmacol*. 2008;23(1):18–28.
13. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol*. 1959;32(1):50–55.
14. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for *DSM-IV* and *ICD-10*. *J Clin Psychiatry*. 1998;59(suppl 20):22–33, quiz 34–57.
15. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382–389.
16. Guy W. *ECDEU Assessment Manual for Psychopharmacology*. US Department of Health, Education and Welfare publication (ADM) 76-338. Rockville, MD: National Institute of Mental Health, 1976; 217–222.
17. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67(6):361–370.
18. Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. *Int Clin Psychopharmacol*. 1996;11(suppl 3):89–95.
19. Parrott AC, Hindmarch I. The Leeds Sleep Evaluation Questionnaire in psychopharmacological investigations—a review. *Psychopharmacology (Berl)*. 1980;71(2):173–179.
20. Rosenbaum JF, Fava M, Hoog SL, et al. Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. *Biol Psychiatry*. 1998;44(2):77–87.
21. Fava M, Evins AE, Dorer DJ, et al. The problem of the placebo response in clinical trials for psychiatric disorders: culprits, possible remedies, and a novel study design approach. *Psychother Psychosom*. 2003;72(3): 115–127.
22. Kobak KA, Kane JM, Thase ME, et al. Why do clinical trials fail? the problem of measurement error in clinical trials: time to test new paradigms? *J Clin Psychopharmacol*. 2007;27(1):1–5.
23. Warner CH, Bobo W, Warner C, et al. Antidepressant discontinuation syndrome. *Am Fam Physician*. 2006;74(3):449–456.
24. Goodwin GM, Emsley R, Rembry S, et al; Agomelatine Study Group. Agomelatine prevents relapse in patients with major depressive disorder without evidence of a discontinuation syndrome: a 24-week randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2009;70(8): 1128–1137.
25. EPAR. European Public Assessment Report - Valdoxan. EMEA/H/C/915 ed 2009.

© Copyright 2012 Physicians Postgraduate Press, Inc. © Copyright 2012 Physicians Postgraduate Press, Inc.