Improvement in Subjective Sleep in Major Depressive Disorder With a Novel Antidepressant, Agomelatine: Randomized, Double-Blind Comparison With Venlafaxine

Patrick Lemoine, M.D., Ph.D.;
Christian Guilleminault, M.D., Biol.D.; and Enric Alvarez, M.D.

Objective: Patients with major depressive disorder (MDD) experience sleep disturbances that may be worsened by some antidepressant drugs early in treatment. The aim of this study was to assess the subjective quality of sleep of patients receiving agomelatine, a new antidepressant with melatonergic MT_1 and MT_2 receptor agonist and 5-HT_{2C} antagonist properties, compared with that of patients receiving venlafaxine, a serotonin-norepinephrine reuptake inhibitor.

Method: This double-blind, randomized study involved 332 patients with MDD (DSM-IV criteria), lasted 6 weeks, and compared the effects of agomelatine 25–50 mg/day and venlafaxine 75–150 mg/day, with a possible dose adjustment at 2 weeks. Subjective sleep was assessed with the Leeds Sleep Evaluation Questionnaire (LSEQ), and the main efficacy criterion was the "getting to sleep" score. Antidepressant efficacy was assessed with the 17-item Hamilton Rating Scale for Depression (HAM-D) and the Clinical Global Impressions (CGI) global improvement scale. The study was performed between November 2002 and June 2004.

Results: After 6 weeks, the antidepressant efficacy of agomelatine was similar to that of venlafaxine. The LSEQ "getting to sleep" score was significantly better with agomelatine (70.5 ± 16.8 mm) than with venlafaxine (64.1 ± 18.2 mm); the between-treatment difference at the last visit was 6.36 mm ($p = .001$), and the difference was already significant at week 1. Secondary sleep items, including LSEQ quality of sleep ($p = .021$), sleep awakenings ($p = .040$), integrity of behavior ($p = .024$), and sum of HAM-D items 4, 5, and 6 (insomnia score) ($p = .044$), were also significantly improved compared to venlafaxine, as was the CGI global improvement score ($p = .016$). Incidence of adverse events was 52.1% with agomelatine and 57.1% with venlafaxine, and withdrawals due to adverse events were more common with venlafaxine than with agomelatine (13.2% vs. 4.2%).

Conclusion: Agomelatine showed similar antidepressant efficacy with earlier and greater efficacy in improving subjective sleep than venlafaxine in MDD patients.

(J Clin Psychiatry 2007;68:1723–1732)

Received Dec. 29, 2006; accepted Sept. 7, 2007. From Clinique Lyon-Lumière, Lyon Bron, France (Dr. Lemoine); Stanford University Sleep Medicine Program, Stanford, Calif. (Dr. Guilleminault); and the Department of Psychiatry, Hospital de la Sta Creu I Sant Pau, Barcelona, Spain (Dr. Alvarez).

This study was sponsored by Servier (Courbevoie, France).

Drs. Lemoine and Alvarez were responsible for the drug company data collection and organization in France and Spain, respectively. Dr. Guilleminault was consultant for the study sleep protocols and analyses.

The authors thank all the investigators in France and Spain who contributed to the study by including patients.

The authors and the Association de Recherche en Psychiatrie received honoraria from Servier in conjunction with this study.

Corresponding author and reprints: Patrick Lemoine, M.D., Ph.D., Clinique Lyon-Lumière, 33 bis rue du 8 mai, 69330 Meyzieu, Lyon Bron, France (e-mail: patrick.lemoine99@free.fr).

The lifetime prevalence of major depressive disorder has been estimated at 16% among those aged ≥ 18 years in the United States,[1] and similar high estimates have been obtained in Europe.[2] Of those with an episode within the past 12 months, 87.4% reported role impairment described as at least moderate, and the impairment was severe or very severe in 59.3%.[1] The proportion of depressed patients who receive treatment has increased substantially in recent years, partly owing to the introduction of better-tolerated treatments such as selective serotonin reuptake inhibitors (SSRIs).[3] However, a recent survey indicated that only 57.3% of patients received any form of treatment, and the treatment was judged to be adequate in less than half of these cases.[1] Therefore, there is a continuing need for more effective, better-tolerated, and easier-to-prescribe agents.

Almost all patients with major depressive disorder experience quantitative or qualitative sleep disturbance, and numerous studies have pointed to a close link between the regulation of sleep and the regulation of mood, both in those with affective illness[4] and in the nonclinical population.[5] Depressed patients show altered circadian rhythms[6] and distinctive disturbances of sleep structure.[7] Insomnia often appears before the onset of mood disorder symptoms[8] and may persist into clinical remission.[4] The presence of insomnia is a risk factor for the future development of depression and an increased risk of relapse or recurrence.[9–11] Furthermore, when associated with chronic

illness such as depression, sleep disturbance can have as great an impact on health-related quality of life as the chronic illness itself.[12] Sleep disturbance generally improves with effective antidepressant treatment, although some agents, including SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs), may be sleep-disturbing, particularly early in treatment,[13–15] to the extent that a sedative/hypnotic compound, often a benzodiazepine, is commonly coprescribed.[16,17] However, combining a positive effect on mood and sleep-inducing properties, especially early in treatment, remains a desirable therapeutic goal that is not always currently achieved[13,15]; development of new antidepressants is therefore needed to target this goal. Therefore, assessment of subjective sleep, i.e., patients' own impressions of their sleep, using validated instruments is an important element for the clinical treatment of depression. Both subjective and objective measurements of sleep are recommended by European guidelines to demonstrate therapeutic efficacy on sleep (Clinical Investigation of Hypnotic Medicinal Products, Directive 75/318/EEC as amended[18]).

Agomelatine is a novel antidepressant with a distinctive mode of action. It is a potent agonist at melatonergic MT_1 and MT_2 receptors and an antagonist at serotonergic 5-HT_{2C} receptors. Animal studies indicate that interaction with both types of receptors contributes to the antidepressant action of agomelatine.[19–21] In addition, agomelatine has been shown to resynchronize altered circadian rhythms both in an animal model of depression[22] and in humans.[23,24] Clinically, agomelatine at a dose of 25–50 mg/day has shown significant antidepressant efficacy, relative to placebo, in patients with major depressive disorder.[25,26] On the basis of its pharmacologic profile, it was expected that agomelatine would have an effect on sleep disturbances in depressed patients besides its antidepressant action. In a recent study in depressed patients, correction of circadian disturbances by agomelatine 25 mg/day was detected using polysomnography.[27] In this study, treatment with agomelatine induced increases in slow-wave sleep and normalization throughout the night.[27,28] The primary goal of the present study was to compare the effects of agomelatine on subjective sleep variables with those of a well-established antidepressant, the SNRI venlafaxine, in patients with major depressive disorder.

METHOD

Study Design

This randomized, double-blind, parallel-group study was performed in France (41 centers) and Spain (15 centers) between November 2002 and June 2004. The study was performed in outpatients with major depressive disorder. After a brief (< 7 days) washout period without study treatment, patients were randomly assigned to receive agomelatine 25 mg/day or venlafaxine 75 mg/day for a 6-week treatment period. Patients took 2 capsules daily, 1 in the morning and 1 in the evening. Agomelatine-treated patients took the placebo capsule in the morning and the agomelatine 25 mg capsule in the evening; venlafaxine-treated patients took a capsule of venlafaxine 37.5 mg in the morning and evening. In patients with insufficient response at week 2, based on a predetermined cutoff on the 17-item Hamilton Rating Scale for Depression (HAM-D)[29] and global improvement score of the Clinical Global Impressions scale (CGI),[30] the doses were increased to 1 capsule of agomelatine 50 mg in the evening and 1 placebo capsule in the morning and to venlafaxine 150 mg (75 mg b.i.d.). All capsules were identical in appearance. Randomization was performed centrally; was nonadaptive, balanced, and stratified on the center; and used permutation blocks of fixed size. After inclusion of a patient, an interactive voice response system (IVRS) allocated a therapeutic unit number. Dose adjustment, if any, was performed centrally and blindly. The criteria for dose adjustment were determined before commencement of the study and were not revealed to investigators or patients. A new therapeutic unit number corresponding to an increased or unchanged dose was allocated at week 2, and investigators and patients were blind to any change.

Patients

Male and female outpatients aged 18 to 65 years who had major depressive disorder by DSM-IV criteria[31] of moderate or severe intensity, with a HAM-D score ≥ 20; did not have psychotic features or catatonic symptoms; and were not starting postpartum were recruited. Patients were excluded if they had a high risk of suicide or previous suicide attempt within 6 months, bipolar disorder, anxiety symptoms such as panic attacks, obsessive-compulsive disorders, posttraumatic stress disorders, drug abuse or dependency, previous depression resistant to antidepressants, and treatment with electroconvulsive therapy within 3 months or formal psychotherapy within 1 month. Patients who screened positive on clinical screening evaluation for sleep disorders, including obstructive sleep apnea and restless legs syndrome, were excluded, as were patients with recent or planned transmeridian air travel (time change of ≥ 3 hours) or phototherapy within 2 weeks. Patients with neurologic disorders (dementia, seizure, stroke), obesity with functional impairment, serious or not stabilized organic disorders (neoplasia, cardiovascular, pulmonary, uncontrolled type 1 or type 2 diabetes) were also excluded. Other antidepressants, hypnotics, anxiolytics, and neuroleptic agents were prohibited during the study and for a variable period before inclusion, depending on half-life. Urinary screening for benzodiazepines was performed before inclusion.

The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki, 1964 (amended in Edinburgh, 2000). The study protocol and

amendments were approved by independent ethics committees in both countries. All patients gave written informed consent.

Efficacy Measurements

The effects of study medication on subjective sleep were assessed with the following self-rating instruments, which were completed by the patients during study visits.

Leeds Sleep Evaluation Questionnaire. The main assessment of changes in subjective sleep with treatment was performed using the Leeds Sleep Evaluation Questionnaire (LSEQ),[32] a standardized instrument designed to quantify subjective assessments of the effects of drugs on sleep and early morning behavior. The questionnaire consists of 10 items, each quantified by a 100-mm visual analog scale (VAS) and grouped into 4 scores evaluating the ease of getting to sleep (made up of 3 VAS component items), the perceived quality of sleep (2 VAS items), the ease of awakening (2 VAS items), and the integrity of behavior following wakefulness (3 VAS items assessing whether patients feel more alert and less clumsy after getting up). The 4 scores were analyzed separately.

The LSEQ questions assess the changes experienced during treatment relative to the patient's condition before receiving the study treatment; therefore, there is no evaluation at baseline. For clarity, the scores for each item were subtracted from 100 mm, so that higher numerical scores indicate an improvement in sleep with treatment. The LSEQ "getting to sleep" score was the primary efficacy criterion of the study.

Visual analog scales for "daytime sleepiness" and "feeling well." These 2 scales were completed at each visit from inclusion to week 6.

Pittsburgh Sleep Quality Index questionnaire. The Pittsburgh Sleep Quality Index questionnaire[33] was completed by patients at inclusion in order to check the comparability of the treatment groups regarding sleep status.

Sleep diary. Patients completed a sleep diary every morning from selection to the week 3 visit, recording the times of light off, the sleep onset latency, and the number of nocturnal awakenings, as well as the wake-up time and time when getting up.

Efficacy on depressive symptoms. The efficacy of study medication on depression was assessed by the investigator during patient visits using the HAM-D 17-item scale and the global improvement score of the CGI. Responders were defined as showing a decrease of ≥ 50% in HAM-D score relative to baseline.

Safety Evaluation

Adverse events presented or reported by the patients, and any abnormal value judged to be clinically relevant by the investigator, were recorded at each visit. Heart rate and blood pressure were recorded at selection and at each visit. Blood samples were taken at selection and between week 4 and week 6. Body mass index (BMI), calculated from body weight, was recorded at week 0 and week 6, and a 12-lead electrocardiogram was performed at selection and at the last visit.

Statistical Analysis

The primary efficacy criterion was the "getting to sleep" score of the LSEQ. The score at the end of the treatment period (last value) was analyzed on an intention-to-treat (ITT) basis, using last-observation-carried-forward methodology to account for missing data. The difference between treatments for the last observation was analyzed using a 2-sided Student t test for independent samples applied to raw data. The time course of changes in the "getting to sleep" score was analyzed using a mixed model with treatment, time, time × treatment, and time^2 × treatment as factors, followed by the study of differences between treatments at each study visit using a 2-sided Student t test applied to raw data (without adjustment for the type I error risk). All other efficacy measures were analyzed as secondary criteria. A first analysis checked that the HAM-D scores obtained at the last postbaseline value (after 6 weeks of treatment) were not significantly different between the 2 treatment groups. The comparison between agomelatine and venlafaxine on subjective sleep was performed only if absence of significant difference was shown.

All efficacy criteria were analyzed in the full analysis set (FAS), defined, in accordance with the ITT principle, as all patients randomly assigned according to IVRS who took at least 1 dose of study medication. HAM-D, CGI, and LSEQ data were also analyzed in the subgroup of severely depressed patients (defined as HAM-D score ≥ 25 at baseline).

The number of patients was estimated to allow the conclusion of no difference in terms of antidepressant efficacy.

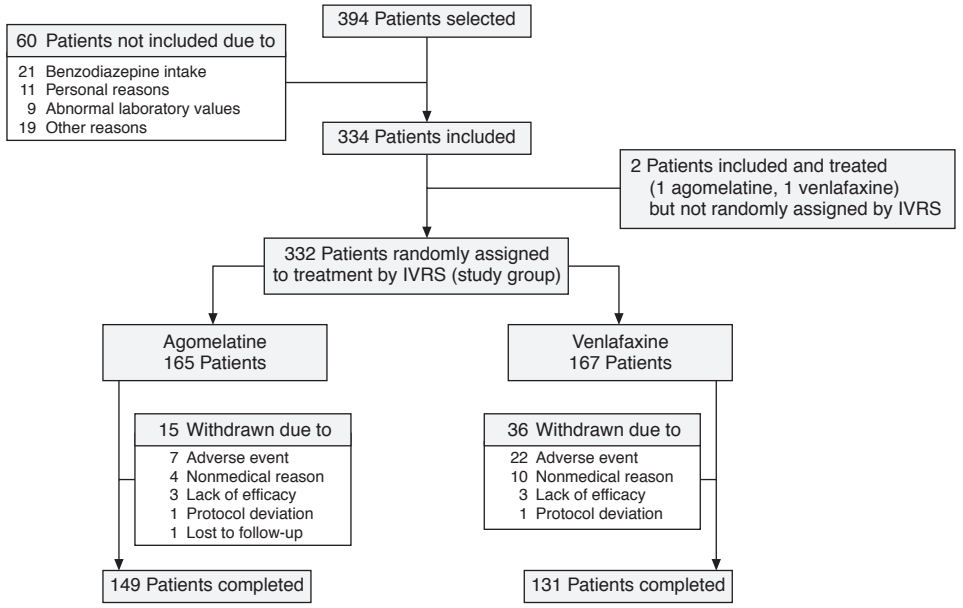
RESULTS

Patients

Three hundred ninety-four patients were screened, and 332 patients (study group) were randomly assigned to receive agomelatine (165) or venlafaxine (167). The study group (236 women: 75.2% of the agomelatine group, 67.1% for venlafaxine) had a mean age of 40.1 years (range, 18–60 years). All patients randomly assigned to treatment met DSM-IV criteria for major depressive disorder: 56.0% had a recurrent episode, and the mean number of recurrences (including the current one) was 2.2 ± 1.9. The median duration of the current episode was 2.8 months.

Two hundred eight patients (62.7%) had received psychotropic treatments within 1 year prior to entry into the study. The treatments were psycholeptics for 47.6% of patients (including anxiolytics [41%], hypnotics and

Figure 1. Flow of Participants Through the Study



Abbreviation: IVRS = interactive voice response system.

sedatives [16.9%]) and psychoanaleptics for 39.2% of patients, with usage of SSRIs in 31.6% and other antidepressants in 9%. There was no relevant difference between the 2 treatment groups at baseline.

The disposition of patients throughout the study is summarized in Figure 1, and the baseline demographic and clinical characteristics of the randomized patients are summarized in Table 1. A total of 51 patients were withdrawn (agomelatine 15, venlafaxine 36), and 1 patient (treated with agomelatine) was lost to follow-up. Forty patients (12.0%) had a dose increase after the week 2 visit (agomelatine 23 [13.9%], venlafaxine 17 [10.2%]). Seven patients were erroneously coprescribed benzodiazepines (agomelatine 3, venlafaxine 4). The severely depressed subgroup (HAM-D score ≥ 25 at baseline) comprised 213 patients (64% of the study group: agomelatine 103 [62.4%], venlafaxine 110 [65.9%]).

Compliance with treatment during the week 0 to week 6 period, estimated from the number of capsules returned by the patient, was 98.3 ± 6.9% in the agomelatine group and 91.9 ± 18.6% in the venlafaxine group.

Efficacy on Depressive Symptoms

Study group. In the FAS, between week 0 and the last value, the mean HAM-D total score decreased from 25.9 ± 3.2 to 9.9 ± 6.6 in the agomelatine group and from 26.0 ± 3.3 to 11.0 ± 7.4 in the venlafaxine group. The time course of improvement in HAM-D score was similar for both treatments, and there was no significant difference between groups at any visit (Figure 2). Rates of response at endpoint (≥ 50% reduction in HAM-D score from baseline) were similar in both groups: 76.4% with agomelatine and 70.6% with venlafaxine (95% confidence interval [CI] = –15.35 to 3.73). Changes from baseline to last observation in HAM-D score excluding items relating to sleep (items 4, 5, and 6) were also similar for agomelatine (from 21.3 ± 3.0 to 8.5 ± 5.6) and venlafaxine (from 21.4 ± 2.9 to 9.2 ± 6.3).

The mean CGI global improvement score decreased between the week 1 and week 6 visits from 3.2 ± 0.8 to 1.6 ± 0.7 in the agomelatine group and from 3.6 ± 0.9 to 1.6 ± 0.8 in the venlafaxine group. Exploratory analyses showed an improvement of scores in favor of agomelatine that was significant both at week 1 (difference 0.39, 95% CI = 0.20 to 0.58, $p < .0001$) and at the last observation (difference 0.32, 95% CI = 0.06 to 0.58, $p = .016$).

Severely depressed subgroup. In the subgroup of severely depressed patients, the mean HAM-D total score decreased between the week 0 and week 6 visits from 28.0 ± 2.2 to 11.2 ± 7.0 in the agomelatine group and from 27.8 ± 2.5 to 11.2 ± 6.9 in the venlafaxine group. There was no significant difference between groups at any visit. Between the week 1 and week 6 visits, the mean CGI score decreased similarly in the agomelatine group (from 3.3 ± 0.8 to 1.5 ± 0.7) and in the venlafaxine group (from 3.6 ± 0.9 to 1.6 ± 0.8).

Efficacy on Subjective Sleep

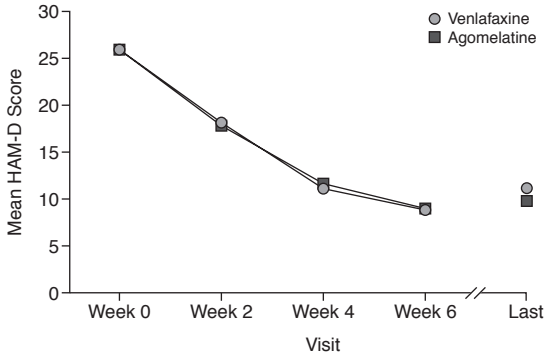
Study group. In an ITT analysis, the LSEQ "getting to sleep" score (the primary efficacy criterion) was signifi-

Table 1. Baseline Demographic and Clinical Characteristics of Patients Randomly Assigned to Agomelatine or Venlafaxine

Characteristic	Agomelatine (N = 165)	Venlafaxine (N = 167)
Age, y		
Mean ± SD	40.7 ± 10.7	39.6 ± 10.3
Range	18–59	18–60
Gender, N (%)		
Male	41 (24.8)	55 (32.9)
Female	124 (75.2)	112 (67.1)
No. of previous depressive episodes (including current episode), mean ± SD	2.3 ± 1.9	2.2 ± 1.8
Previous psychotropic treatments within 1 year, N (%)	106 (64.2)	102 (61.1)
Present depressive episode, N (%)		
Single episode	70 (42.4)	76 (45.5)
Recurrent episode	95 (57.6)	91 (54.5)
HAM-D total score, mean ± SD	25.9 ± 3.2	26.0 ± 3.3
Pittsburgh Sleep Quality Index,[a] mean ± SD	12.0 ± 3.3	12.5 ± 3.2
VAS daytime sleepiness (mm), mean ± SD	53.1 ± 29.5	46.9 ± 28.2
VAS feeling well (mm), mean ± SD	24.4 ± 20.1	24.6 ± 17.3
HAM-D insomnia items score (items 4 + 5 + 6), mean ± SD	4.6 ± 1.2	4.6 ± 1.4

[a]Assessed at selection.
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, VAS = visual analog scale.

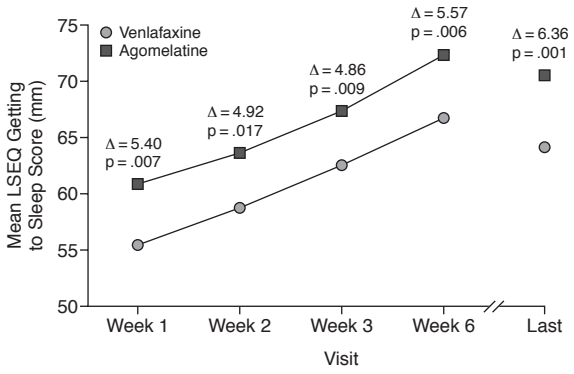
Figure 2. Hamilton Rating Scale for Depression (HAM-D) Total Scores by Study Visit, in Patients With Available Data in the Study Group



cantly higher (indicating improved sleep) at the last value with agomelatine (70.5 ± 16.8 mm) than with venlafaxine (64.1 ± 18.2 mm; between-group difference 6.36 mm, p = .001) (Figure 3). Using the mixed-model analysis, the treatment effect was significantly greater for agomelatine (p = .013). Analysis of data from each study visit indicated that the difference in the LSEQ "getting to sleep" score between treatments was significant at week 1 and continued through to week 6 (Figure 3).

When the 3 component items of the LSEQ "getting to sleep" score were considered separately, scores obtained with agomelatine were significantly better for the getting

Figure 3. Time Course of the Leeds Sleep Evaluation Questionnaire (LSEQ) "Getting to Sleep" Scores in the Study Group[a]



[a]LSEQ scores reflect differences in sleep during drug treatment compared with the before-treatment state, and higher values indicate improved sleep. p Values are by 2-sided Student t test.

to sleep "easier/harder" and "quicker/slower" items from week 1 throughout the 6-week treatment period (Table 2). However, there was no significant difference between treatments for the "felt more/less drowsy" item. All the other LSEQ items (quality of sleep, ease of awakening, and integrity of behavior scores), analyzed on an ITT basis, also showed significantly greater improvements at the end of the treatment period with agomelatine compared with venlafaxine (Table 3).

The HAM-D insomnia items score (sum of items 4, 5, and 6), analyzed on an ITT basis, decreased between baseline and the last value from 4.6 ± 1.2 to 1.4 ± 1.6 in the agomelatine group and from 4.6 ± 1.4 to 1.8 ± 1.7 in the venlafaxine group, with a significant agomelatine-positive between-treatment difference of 0.37 (95% CI = 0.01 to 0.72, p = .044). When HAM-D sleep items were considered individually, differences in favor of agomelatine were observed for items 4 (early insomnia) and 5 (middle insomnia), with statistically significant differences between treatments at the last value (0.18 [p < .05] and 0.17 [p < .05], respectively). Item 6 (early awakening) was improved similarly with agomelatine and venlafaxine (difference between treatments at last value = 0.02, 95% CI = –0.13 to 0.16).

The mean "daytime sleepiness" score, assessed by VAS, decreased over the 6-week period in both treatment groups, indicating that patients felt less sleepy during the day (Figure 4A). At week 1, the "daytime sleepiness" score was significantly lower in the agomelatine group (40.6 ± 24.8 mm) than in the venlafaxine group (49.3 ± 25.6 mm), with a difference between groups, adjusted for center and baseline, of 10.37 (p < .001). At later visits, the differences between treatment groups were not statistically significant.

© COPYRIGHT 2007 PHYSICIANS POSTGRADUATE PRESS, INC

Table 2. Individual Component Items of the Leeds Sleep Evaluation Questionnaire (LSEQ) Getting to Sleep Score at the Week 6 Visit, in the Study Groups (full analysis set)[a]

LSEQ Item	Week 6 Score (mm), Mean ± SD		Estimated Between-Group Difference (agomelatine – venlafaxine)		p Value
	Agomelatine (N = 165)	Venlafaxine (N = 167)	Mean (SE)	95% CI	
Getting to sleep "easier/harder"	78.7 ± 19.8	73.3 ± 20.3	5.40 (2.34)	0.79 to 10.00	.022
Getting to sleep "quicker/slower"	77.9 ± 17.4	72.3 ± 20.3	5.58 (2.35)	0.94 to 10.21	.019
Getting to sleep "felt more/less drowsy"	60.2 ± 25.7	54.3 ± 24.5	5.91 (3.14)	–0.28 to 12.09	.061

[a]LSEQ scores reflect differences in sleep during drug treatment relative to the before-treatment state; higher scores in the 3 items indicate that getting to sleep was easier, getting to sleep was quicker, and the patient felt more drowsy, respectively.

Table 3. Leeds Sleep Evaluation Questionnaire (LSEQ) Quality of Sleep, Sleep Awakening, and Integrity of Behavior Scores by Visit in the Study Groups[a]

Visit	Agomelatine, Mean ± SD Score (N)	Venlafaxine, Mean ± SD Score (N)	Estimated Between-Group Difference (agomelatine – venlafaxine)		p Value
			Mean (SE)	95% CI	
LSEQ quality of sleep score (mm)					
Week 1	61.2 ± 19.6 (154)	55.7 ± 19.8 (150)	5.51 (2.26)	1.06 to 9.96	.015
Week 2	62.2 ± 20.1 (158)	61.3 ± 21.4 (144)	0.89 (2.39)	–3.82 to 5.60	.710
Week 3	67.0 ± 20.7 (153)	64.9 ± 18.3 (137)	2.19 (2.31)	–2.35 to 6.73	.343
Week 6	76.3 ± 18.1 (132)	71.4 ± 19.8 (124)	4.85 (2.37)	0.19 to 9.51	.041
Last	72.5 ± 21.4 (164)	66.9 ± 22.3 (160)	5.63 (2.43)	0.85 to 10.41	.021
LSEQ sleep awakening score (mm)					
Week 1	57.4 ± 18.9 (153)	53.8 ± 18.2 (150)	3.69 (2.13)	–0.50 to 7.88	.084
Week 2	61.1 ± 18.0 (156)	55.5 ± 18.1 (143)	5.57 (2.09)	1.45 to 9.69	.008
Week 3	63.1 ± 20.5 (153)	57.5 ± 19.5 (136)	5.54 (2.36)	0.89 to 10.19	.020
Week 6	69.4 ± 19.4 (132)	64.3 ± 21.4 (125)	5.13 (2.54)	0.12 to 10.14	.045
Last	66.9 ± 20.5 (163)	62.0 ± 21.8 (160)	4.86 (2.35)	0.23 to 9.49	.040
LSEQ integrity of behavior score (mm)					
Week 1	58.6 ± 17.8 (157)	48.4 ± 18.5 (155)	10.25 (2.05)	6.21 to 14.29	< .0001
Week 2	57.8 ± 18.4 (159)	55.2 ± 19.2 (146)	2.60 (2.15)	–1.63 to 6.83	.227
Week 3	61.0 ± 19.2 (154)	59.5 ± 18.5 (137)	1.49 (2.21)	–2.87 to 5.85	.501
Week 6	68.8 ± 18.1 (135)	65.2 ± 18.9 (124)	3.61 (2.30)	–0.93 to 8.15	.118
Last	66.2 ± 20.1 (164)	61.0 ± 20.9 (160)	5.16 (2.28)	0.68 to 9.65	.024

[a]LSEQ scores reflect differences in sleep during drug treatment relative to the before-treatment state; higher scores indicate improved sleep.

"Feeling well" scores increased at week 1 to a significantly higher value with agomelatine (from 24.4 ± 20.1 mm at baseline to 44.7 ± 22.2 mm) than with venlafaxine (from 24.6 ± 17.3 mm at baseline to 36.8 ± 21.6 mm, p = .001) (Figure 4B); the difference was still significant at week 2 (p = .044), but was nonsignificant thereafter.

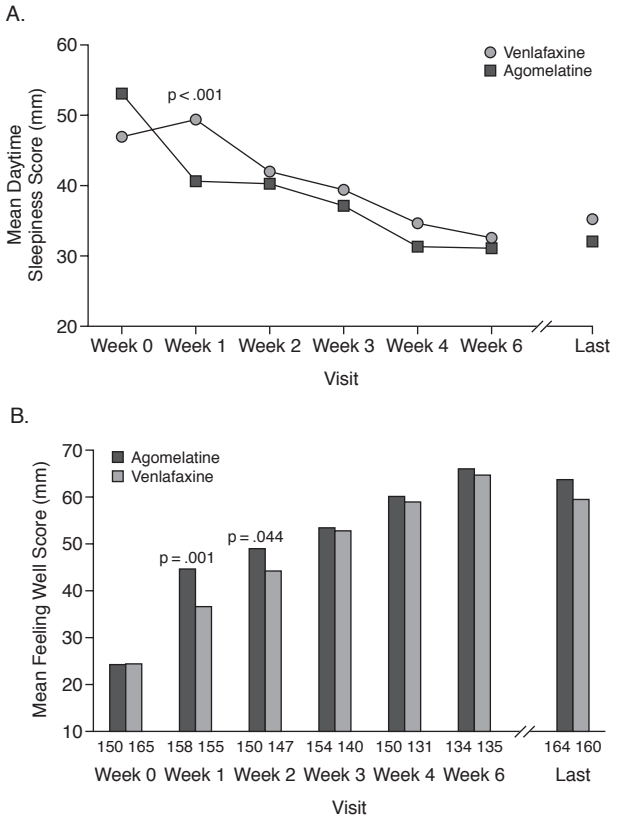
The sleep diary showed an improvement in the patients' sleep latency and number of awakenings in both treatment groups in the FAS, with no statistically significant differences between treatment groups.

Severely depressed subgroup. In the severely depressed subgroup, there was a significant between-group difference in the mean LSEQ "getting to sleep" score, with a last value of 71.1 ± 17.9 mm in the agomelatine group and 64.1 ± 19.6 mm in the venlafaxine group (between-group difference 6.94 mm, p = .008), analyzed on an ITT basis.

When the 3 component items of the LSEQ "getting to sleep" score were considered separately, there was a significant between-group difference in the mean LSEQ "easier/harder" score at the week 1, week 2, and week 6 visits and for the last value (77.9 ± 19.6 mm in the agomelatine group and 69.4 ± 22.7 mm in the venlafaxine group; between-treatment difference 8.47 mm, p = .004). There was also a significant difference in the mean "quicker/slower" score at the week 1 and week 6 visits and for the last value (75.5 ± 21.8 mm for agomelatine and 68.2 ± 23.0 mm for venlafaxine; between-treatment difference 7.25 mm, p = .020). By contrast, for the "felt more/less drowsy" score, there was no clear increase during the treatment period, and there was no significant difference between the treatment groups (60.0 ± 27.6 mm with agomelatine and 54.8 ± 24.5 mm with venlafaxine at the last value).

Regarding the other LSEQ items, there was a significant difference in the "quality of sleep" score between the agomelatine group and the venlafaxine group at the week 6 visit (between-treatment difference 6.57 mm, p = .036). The "ease of awakening" score was also significantly different in the agomelatine group compared with the venlafaxine group at week 2 (difference 7.03 mm, p = .007) and week 6 (difference 8.14 mm, p = .012) and for the last value (difference 6.81 mm, p = .027). The "integrity of behavior" score was significantly different in

Figure 4. Daytime Sleepiness (A) and Feeling Well (B) Scores by Study Visit, Assessed With Visual Analog Scales, in the Study Group[a]



[a]Higher daytime sleepiness scores indicate higher levels of daytime sleepiness; higher feeling well scores indicate feeling better. p Values are by 2-sided Student t test. Numbers of patients assessable at each visit are shown below the horizontal axis in part B.

the agomelatine group compared with the venlafaxine group at week 1 (difference 8.98 mm, $p < .001$) and at week 6 (difference 6.36 mm, $p = .027$).

Safety

The incidence of emergent adverse events (EAEs) was 52.1% with agomelatine and 57.1% with venlafaxine. Withdrawals due to adverse events were 3 times more common with venlafaxine (22 patients [13.2%]) than with agomelatine (7 patients [4.2%]).

The most frequent EAEs during the treatment period are summarized in Table 4. The total number of EAEs reported was 178 for agomelatine and 232 for venlafaxine. The following EAEs were notably more frequent in the venlafaxine group than with agomelatine: nausea (22.6% vs. 6.0%), dizziness (9.5% vs. 1.8%), and vomiting (4.8% vs. 1.2%). Tremor was reported in 4.2% of patients in the venlafaxine group but none in the agomelatine group; similarly, serotonin syndrome was observed in 3.0% of patients in the venlafaxine group but none in the

Table 4. Emergent Adverse Events (EAEs) During the 6-Week Treatment Period[a]

	Agomelatine (N = 166)			Venlafaxine (N = 168)		
	No. of	Patients Affected		No. of	Patients Affected	
Event	Events	N	%	Events	N	%
All	178	85	51.2	232	96	57.1
Headache	17	16	9.6	25	20	11.9
Nausea	11	10	6.0	39	38	22.6
Diarrhea	8	8	4.8	3	3	1.8
Somnolence	7	6	3.6	8	8	4.8
Constipation	6	6	3.6	7	7	4.2
Nasopharyngitis	6	6	3.6	6	6	3.6
Upper abdominal pain	5	5	3.0	7	7	4.2
Palpitations	5	5	3.0	5	5	3.0
Sweating	5	5	3.0	3	3	1.8
Dyspepsia	4	4	2.4	4	4	2.4
Influenza-like illness	4	4	2.4	0	0	0
Dizziness	4	3	1.8	16	16	9.5
Dry mouth	3	3	1.8	6	6	3.6
Vomiting	2	2	1.2	8	8	4.8
Insomnia	1	1	0.6	4	4	2.4
Tremor	0	0	0	7	7	4.2
Serotonin syndrome	0	0	0	5	5	3.0

[a]Occurring in ≥ 2% of patients in either group, arranged in order of frequency in the agomelatine group.

agomelatine group. Diarrhea occurred more frequently with agomelatine (4.8%) than with venlafaxine (1.8%). There was no relevant change in BMI in either treatment group, and most patients stayed in the same BMI class (normal, overweight, etc.) from baseline to the last post-baseline value (agomelatine 94.2%, venlafaxine 94.7%). No patient died during the study, and there were 2 suicide attempts (1 per group).

DISCUSSION

In this study, agomelatine showed similar antidepressant efficacy in patients with major depressive disorder to the SNRI venlafaxine over a 6-week treatment period. According to the LSEQ, agomelatine showed significantly greater efficacy than venlafaxine in the main efficacy criterion, the "getting to sleep" score analyzed on an ITT basis (in the FAS), at week 1 and at all other visits. At the end of the 6-week period, improvement with agomelatine was also significantly greater than with venlafaxine for other elements of the LSEQ (quality of sleep and ease of awakening). For quality of sleep and integrity of behavior following wakefulness, a significant difference between treatments was present as early as week 1. Significantly greater improvements in measures of daytime alertness and of feeling well were also observed with agomelatine compared with venlafaxine early during treatment (at week 1 and at weeks 1 and 2, respectively). An early improvement in sleep with treatment is desirable, since improvements in most depressive symptoms

are relatively slow with most current antidepressants, often taking at least 2 weeks to become significant and not reaching a maximum for 6 weeks.

The greater improvement in subjective sleep with agomelatine assessed by the LSEQ was also supported by positive results at last value for the sleep items of the HAM-D scale, with a significantly better improvement in scores of items 4 (early insomnia) and 5 (middle insomnia) compared to venlafaxine. Interestingly, scores on item 6 (early awakening), which is related more to depression, were improved similarly with agomelatine and venlafaxine, consistent with the similar antidepressant efficacy of the 2 treatments. The decrease in score on the CGI global improvement scale that was evident from week 1 may reflect an early improvement in the quality of sleep and daytime conditions. No statistically significant difference between treatments was observed in the sleep diary data, but sleep latency and number of awakenings tended to improve more (from week 1 for sleep latency) with agomelatine compared to venlafaxine, which is consistent with the significant early improvement in the "getting to sleep" score observed with the LSEQ. Nevertheless, the interpretation of the diary is difficult because many data omissions occurred, and the rating by the patient is often contaminated by the cognitive distortion well known in depressed patients. Furthermore, nocturnal awakenings as collected in the diary do not consider the microawakenings that occur frequently during the night in depressed patients and that are responsible for a poor quality of sleep.

The improvement in subjective sleep with agomelatine was accompanied by concomitant improvements in measures of daytime alertness. VAS assessments of daytime sleepiness and feeling well both improved markedly with agomelatine and were significantly better than with venlafaxine early in treatment. Improving sleep without causing daytime drowsiness is a desirable clinical goal that is not always achieved by antidepressant therapy. Some antidepressants, including most tricyclics, mirtazapine, and trazodone, are sedating, leading to an improvement in sleep but at the potential expense of daytime drowsiness.[17,34,35] Others, including SSRIs and SNRIs, tend to be sleep-disturbing, especially early in treatment, which can itself cause daytime drowsiness.[14,15,17]

Agomelatine treatment resulted in significant and progressive improvements in 2 of the 3 component items of the LSEQ "getting to sleep" score that related to the ease and speed of getting to sleep. There was no change and no significant difference between treatments in the component relating to feeling more or less drowsy when getting to sleep. This suggests that agomelatine improved getting to sleep without producing a hypnotic effect.

Agomelatine showed antidepressant efficacy similar to that of venlafaxine in terms of change in HAM-D total score and in HAM-D score excluding items related to sleep (items 4, 5, 6). These results show that the antidepressant efficacy of agomelatine is maintained also without the sleep items of the HAM-D. Agomelatine led to significantly better CGI global improvement results, with lower improvement scores at the last observation compared to venlafaxine, a medication known for its potent antidepressant effect.[36]

The flexible dosing regimen for venlafaxine used in the present study was in the middle of the recommended dose range for outpatients in European countries and did not include the maximum recommended dose of 225 mg. It is possible that some patients might have benefited from a higher venlafaxine dose. However, any such efficacy benefit might have been achieved at the expense of poorer tolerability, and the number of treatment withdrawals was already greater with venlafaxine than with agomelatine. In the severely depressed patients, agomelatine also showed antidepressant efficacy similar to that of venlafaxine. The beneficial effect on subjective sleep shown by agomelatine in the overall study group was also seen in this subgroup. Indeed, for most of the measures, the beneficial effects were more pronounced, relative to venlafaxine, in the severely depressed subgroup than in the total study group. These results may be related to the greater severity of sleep disturbances in this group of depressed patients, and they confirm the robustness of the results found in the study group. In addition, they are in line with the efficacy of agomelatine in more severely depressed populations seen in previous studies.[25,26,37]

In depressed patients, there may be discrepancy between subjective and objective sleep estimation. Specifically, changes in the severity of depression may influence patients' reporting of sleep.[38] However, given the similar changes in depression scores in the agomelatine and venlafaxine groups, it is unlikely that differential changes in depression severity could account for the observed differences in subjective sleep. Furthermore, agomelatine has demonstrated efficacy in improving polysomnographic sleep variables in patients with major depressive disorder in an open-label preliminary study.[27,28]

The benefits on subjective sleep with agomelatine, observed as early as the first week of treatment and demonstrated for up to 6 weeks, represent a substantial benefit for patients' quality of life. Long-term clinical trials are needed to determine whether over a longer period of treatment agomelatine is able to reduce residual insomnia symptoms, which are known to be a risk factor for relapse.

Although the overall mechanism of action of agomelatine is novel, it is consistent with current hypotheses of antidepressant action. The close relationship between regulation of sleep and mood has been well documented.[39] Agomelatine is a potent agonist at me-

latonergic receptors and an antagonist at the 5-HT_{2C} receptor. The interaction with these receptors contributes to agomelatine's efficacy in depression by resynchronizing disturbed circadian rhythms[23,24,40,41] and by increasing norepinephrine and dopamine in the frontal cortex.[19,42]

The safety profile of agomelatine compared favorably with that of venlafaxine. Fewer patients withdrew and there were fewer withdrawals due to adverse events in the agomelatine group. In particular, agomelatine treatment was associated with lower frequencies of nausea, vomiting, and dizziness.

The improvements in subjective sleep and daytime alertness detected as early as 1 week after treatment initiation with agomelatine are a beneficial characteristic of agomelatine, especially given the usually relatively slow onset of antidepressant efficacy with current agents and the scarcity of agents that improve sleep without causing daytime drowsiness. These original effects of agomelatine on sleep represent a novel contributing property in the class of antidepressant agents.

Drug names: mirtazapine (Remeron and others), venlafaxine (Effexor and others).

REFERENCES

1. Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 2003;289:3095–3105
2. Alonso J, Angermeyer MC, Bernert S, et al. Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. Acta Psychiatr Scand Suppl 2004; 420:21–27
3. Olfsson M, Marcus SC, Druss B, et al. National trends in the outpatient treatment of depression. JAMA 2002;287:203–209
4. Reynolds CF 3rd. Sleep and affective disorders: a minireview. Psychiatr Clin North Am 1987;10:583–591
5. Spoormaker VI, van den Bout J. Depression and anxiety complaints: relations with sleep disturbances. Eur Psychiatry 2005;20:243–245
6. Koenigsberg HW, Teicher MH, Mitropoulou V, et al. 24-h monitoring of plasma norepinephrine, MHPG, cortisol, growth hormone and prolactin in depression. J Psychiatr Res 2004;38:503–511
7. Staner L, Cornette F, Maurice D, et al. Sleep microstructure around sleep onset differentiates major depressive insomnia from primary insomnia. J Sleep Res 2003;12:319–330
8. Ohayon MM, Roth T. Place of chronic insomnia in the course of depressive and anxiety disorders. J Psychiatr Res 2003;37:9–15
9. Ford DE, Kamerow DB. Epidemiological study of sleep disturbances and psychiatric disorders: an opportunity for prevention? JAMA 1989; 262:1479–1484
10. Lustberg L, Reynolds CF. Depression and insomnia: questions of cause and effect. Sleep Med Rev 2000;4:253–262
11. Riemann D, Voderholzer U. Primary insomnia: a risk factor to develop depression? J Affect Dis 2003;76:255–259
12. Katz DA, McHorney CA. The relationship between insomnia and health-related quality of life in patients with chronic illness. J Fam Pract 2002;51:229–235
13. Jindal RD, Thase ME. Treatment of insomnia associated with clinical depression. Sleep Med Rev 2004;8:19–30
14. Mayers AG, Baldwin DS. Antidepressants and their effect on sleep. Hum Psychopharmacol 2005;20:533–559
15. Wilson S, Argyropoulos S. Antidepressants and sleep: a qualitative review of the literature. Drugs 2005;65:927–947
16. Rascati K. Drug utilization review of concomitant use of specific serotonin reuptake inhibitors or clomipramine with antianxiety/sleep medications. Clin Ther 1995;17:786–790
17. Winokur A, Gary KA, Rodner S, et al. Depression, sleep physiology, and antidepressant drugs. Depress Anxiety 2001;14:19–28
18. European Medicines Agency. Clinical Investigation of Hypnotic Medicinal Products, Directive 75/318/EEC as amended. September 1991. Available at: http://www.emea.europa.eu/pdfs/human/ewp/3cc27aen.pdf. Accessed September 27, 2007
19. Millan MJ, Gobert A, Lejeune F, et al. The novel melatonin agonist agomelatine (S20098) is an antagonist at 5-hydroxytryptamine$_{2C}$ receptors, blockade of which enhances the activity of frontocortical dopaminergic and adrenergic pathways. J Pharmacol Exp Ther 2003; 306:954–964
20. Papp M, Gruca P, Boyer P-A, et al. Effect of agomelatine in the chronic mild stress model of depression in the rat. Neuropsychopharmacology 2003;28:694–703
21. Bourin M, Mocaër E, Porsolt R. Antidepressant-like activity of S 20098 (agomelatine) in the forced swimming test in rodents: involvement of melatonin and serotonin receptors. J Psychiatry Neurosci 2004;29: 126–133
22. Fuchs E, Schmelting B, Mocaër E. Effects of the novel antidepressant agomelatine (S 20098) and fluoxetine in chronically stressed tree shrews, an animal model of depression [abstract]. Eur Neuropsychopharmacol 2006;16(suppl 4):S338
23. Kraüchi K, Cajochen C, Mori D, et al. Early evening melatonin and S-20098 advance circadian phase and nocturnal regulation of core body temperature. Am J Physiol 1997;272:R1178–R1188
24. Leproult R, Van Onderbergen A, L'hermite-Baleriaux M, et al. Phase-shifts of 24-h rhythms of hormonal release and body temperature following early evening administration of the melatonin agonist agomelatine in healthy older men. Clin Endocrinol (Oxf) 2005;63: 298-304
25. Loo H, Hale A, D'haenen H. Determination of the dose of agomelatine, a melatonergic agonist and selective 5-HT_{2C} antagonist, in the treatment of major depressive disorder: a placebo-controlled dose range study. Int J Clin Psychopharmacol 2002;17:239–247
26. Kennedy SH, Emsley R. Placebo-controlled trial of agomelatine in the treatment of major depressive disorder. Eur Neuropsychopharmacol 2006,16:93–100
27. Quera-Salva MA, Vanier B, Laredo J, et al. Major depressive disorder, sleep EEG and agomelatine: an open-label study. Int J Neuropsychopharmacol 2007;10:691–696
28. Lopes MC, Quera-Salva MA, Guilleminault C. Cyclic alternating pattern in the NREM sleep of patients within major depressive disorder: baseline results and change over time with a new antidepressant: agomelatine. Sleep Med 2005;6(suppl 2):87–88
29. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
30. Guy W. Clinical Global Impressions (CGI). ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:217–222
31. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 2004
32. Parrott AC, Hindmarch I. Factor analysis of a sleep evaluation questionnaire. Psychol Med 1978;8:325–329
33. Buysse DK, Reynolds CF, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193–213
34. Mouret J, Lemoine P, Minuit MP, et al. Effects of trazodone on the sleep of depressed subjects: a polygraphic study. Psychopharmacology (Berl) 1988;95(suppl):S37–S43
35. Rosenberg RP. Sleep maintenance insomnia: strengths and weakness of current pharmacologic therapies. Ann Clin Psychiatry 2006;18:49–56
36. Mann JJ. The medical management of depression. N Engl J Med 2005; 353:1819–1834
37. Pierre Olié J, Kasper S. Efficacy of agomelatine, a MT_1/MT_2 receptor agonist with 5-HT_{2C} antagonistic properties, in major depressive disorder [published online ahead of print May 4, 2007]. Int J Neuropsychopharmacol 2007;10(5):661–673. doi:10.1017/S1461145707007766
38. Tsuchiyama K, Nagayama H, Kudo K, et al. Discrepancy between subjective and objective sleep in patients with depression.

Psychiatry Clin Neurosci 2003;57:259–264
39. Boivin DB. Influence of sleep-wake and circadian rhythm disturbances in psychiatric disorders. J Psychiatry Neurosci 2000;25:446–458
40. Armstrong SM, McNulty OM, Guardiola-Lemaitre B, et al. Successful use of S20098 and melatonin in an animal model of delayed sleep-phase syndrome (DSPS). Pharmacol Biochem Behav 1993;46:45–49
41. Van Reeth O, Weibel L, Olivares E, et al. Melatonin or a melatonin agonist corrects age-related changes in circadian response to environmental stimulus. Am J Physiol Regul Integr Comp Physiol 2001;280: R1582–R1591
42. Millan MJ, Lejeune F, Gobert A. Reciprocal autoreceptor and heteroreceptor control of serotonergic, dopaminergic and noradrenergic transmission in the frontal cortex: relevance to the actions of antidepressant agents. J Psychopharmacol 2000;14:114–138

