Agomelatine in the Treatment of Major Depressive Disorder: An 8-Week, Multicenter, Randomized, Placebo-Controlled Trial

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Objective: To evaluate the efficacy, safety, and tolerability of fixed-dose agomelatine 25 and 50 mg/d in the treatment of outpatients with moderate-to-severe major depressive disorder (MDD) compared to placebo.

Method: In this 8-week, multicenter, double-blind, parallel-group trial, patients with *DSM-IV*–defined MDD were randomly assigned (1:1:1) to receive a once-daily dose of agomelatine 25 mg, agomelatine 50 mg, or placebo. The primary efficacy measure was the change from baseline to week 8 in the clinician-rated 17-item Hamilton Depression Rating Scale ($HDRS_{17}$); other efficacy measures were the clinical remission and response rates (measured by $HDRS_{17}$), Clinical Global Impressions scales, Hospital Anxiety and Depression Scale (HADS) score, subjective measures on sleep, and the overall quality of life. The study was conducted between December 2006 and January 2008.

Results: Agomelatine 25 mg/d was more efficacious based on the $HDRS_{17}$ total score ($P = .01$) compared to placebo throughout the treatment period, whereas for agomelatine 50 mg/d, statistically significant reduction in $HDRS_{17}$ total score could be observed from weeks 2 to 6 but not at week 8 ($P = .144$). A higher proportion of patients receiving agomelatine 25 mg/d showed clinical response ($P = .013$), clinical remission ($P = .07$), and improvement according to the Clinical Global Impressions-Improvement scale ($P = .065$) compared to those receiving placebo. No statistically significant difference between patients receiving agomelatine 50 mg/d compared to placebo on clinical response ($P = .116$) or clinical remission ($P = .457$) was observed. HADS score, quality of sleep, and quality of life significantly improved with agomelatine 25 mg/d compared to placebo. Both agomelatine doses were safe and well tolerated, although clinically notable aminotransferase elevations were observed transiently in the agomelatine 50 mg/d group.

Conclusions: Agomelatine 25 mg/d was effective in the treatment of patients with moderate-to-severe MDD and was safe and well tolerated. Agomelatine 50 mg/d provided evidence for its antidepressant efficacy until week 6 and was also safe and well tolerated.

Trial Registration: clinicaltrials.gov Identifier: NCT00411242

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Major depressive disorder (MDD) is the most common mood disorder, and it imposes considerable economic and human suffering such as decreased quality of life (QoL), functional impairment, and increased mortality rate. By 2020, depressive disorders are expected to be the second highest cause of morbidity in the world.[1] The lifetime prevalence of MDD is approximately 16.6% in the United States.[2] Less than one-quarter of the patients are correctly identified and appropriately treated.[3] Patients who receive appropriate medications with available drugs are often inadequately treated, which is attributed to poor compliance and tolerability and lack of efficacy.

Episodes of MDD are often chronic and recurrent, with a relapse rate of 55%–90% for individuals who have experienced 1 or 2 prior depressive episodes. More than 80% of individuals who experience a second episode and are not treated will experience a third within 3 years.[4]

The current mainstays of pharmacologic treatments for depression include the use of selective serotonin reuptake inhibitors[5,6] and serotonin-norepinephrine reuptake inhibitors,[7] which provide reasonable treatment options. However, these therapies are not effective in all patients and are often associated with undesirable side effects such as weight gain and sexual dysfunction. The lack of efficacy and the adverse events (AEs) associated with the use of these antidepressants lead to high levels of treatment discontinuation.[8] Even with multiple consecutive treatments, only a small proportion of patients remain asymptomatic.[9] Thus, there continues to be a substantial unmet medical need for new antidepressants with greater response rates and improved tolerability.

Although this may be considered an oversimplified view of the neurobiology of MDD, dysfunction of the monoamine neurotransmitter circuits in the central nervous system, particularly those involving serotonin (5-HT) and norepinephrine, is considered to be involved in many symptoms observed in MDD.[10] More recent approaches to understanding the neurobiology of depression include investigations of the role of stress hormones, alterations in the hypothalamic-

pituitary-adrenal axis, changes in the circadian system (eg, sleep-wake rhythms), changes in neuropeptidergic mechanisms, and influence on neurogenesis in specific regions of the central nervous system.[10–14]

A promising approach for developing an innovative antidepressant is derived from the recognition that circadian rhythm dysregulation is an integral feature of mood disorders.[15–17] Among the circadian disturbances, sleep disturbances are the most common and are reported in up to 80% of patients experiencing depression.[18,19]

Agomelatine is an innovative antidepressant with a unique pharmacologic profile of MT_1 and MT_2 receptor agonism and 5-HT_{2C} receptor antagonism, which combines chronobiotic activities with neurotransmitter augmentation properties.[6] Agomelatine increases monoaminergic transmission (norepinephrine and dopamine) in the prefrontal cortex, which was shown to be associated with antidepressant-like effects in animals, presumably through 5-HT_{2C} antagonism.[20] The effect of agomelatine on slow-wave sleep[21,22] might be mediated by the 5-HT_{2C} antagonism and by the agonism of agomelatine on melatonin receptors, which contribute to the normalization of disturbed circadian rhythms and sleep disturbances.[23] This mechanism of action is considered to be responsible for its novel approach to the treatment of MDD.[20,24,25] Agomelatine has shown promising antidepressant and anxiolytic effects in clinical studies[26] as well as in preclinical models of depression.[27,28]

Agomelatine is associated with a low propensity to cause weight gain[29] and sexual dysfunction, a profile similar to that of bupropion, which might be explained through its enhancement of norepinephrine and dopamine release.[24,30] Agomelatine showed no discontinuation symptoms[31] and improvement in onset and quality of sleep associated with depression.[19] The overall efficacy of agomelatine is at least comparable to the efficacy of currently marketed antidepressants, and its AE profile is qualitatively superior.[32,33] The drug has been recently registered in the European Union for the treatment of patients with MDD.

This study was conducted to evaluate the efficacy, safety, and tolerability of fixed-dose agomelatine (25 mg and 50 mg once daily) for the treatment of outpatients with moderate-to-severe MDD compared to placebo.

METHOD

This 8-week, randomized, double-blind, fixed-dose, placebo-controlled, multicenter, parallel-group trial was conducted between December 2006 and January 2008 in the United States in accordance with Good Clinical Practice and Declaration of Helsinki 2002. The protocol was approved by the institutional review board affiliated with each center. The data presented here report the double-blind, placebo-controlled results of the study. All participants provided written informed consent.

Table 1. Inclusion and Exclusion Criteria

Inclusion criteria
Written informed consent provided prior to conducting any assessment
Male and female patients aged 18–70 y
Diagnosis of MDD, single or recurrent episode, according to *DSM-IV* criteria
IVR $HDRS_{17}$ total score ≥ 20[a]
Clinician-rated $HDRS_{17}$ total score ≥ 22[a]
CGI-S score ≥ 4[a]
Exclusion criteria
Improvement of more than 20% in $HDRS_{17}$ screening score at baseline (IVR or clinician rated)
History of
Bipolar disorder (I or II), schizophrenia, schizoaffective disorder, eating disorder, obsessive-compulsive disorder, any other current Axis I disorder according to *DSM-IV* criteria
Suicide attempts or suicidal tendencies within the past 6 mo prior to screening
Heart failure with left ventricular dysfunction
Viral hepatitis positive serologic findings and history of hepatic impairment
At screening
Substance or alcohol abuse within the last 3 mo, or dependence[b]
Systolic blood pressure ≥ 165 mm Hg or diastolic blood pressure ≥ 95 mm Hg[a]
Unstable angina pectoris[a]
Myocardial infarction and/or cerebrovascular accident or stroke[c]
Long QT syndrome or QTc > 450 ms (male) or > 470 ms (female)[c]
Positive urine drug screen[c]
Concomitant treatment
Use of any psychoactive medication after the screening visit
Use of preparations with known psychotropic potential (including but not limited to melatonin, St John's wort, omega fatty acids)
Treatment with other investigational drugs within the 30 d prior to screening
Psychotherapy of any type 30 d prior to screening and during the study
Electroconvulsive treatment, transcranial magnetic stimulation, vagal stimulation in the 3 mo prior to screening
Miscellaneous
Female patients of childbearing potential who are not using effective contraception, are lactating, or have a positive serum pregnancy test at screening or a positive urine pregnancy test at baseline
Any significant medical condition that could interfere with study participation and/or study assessments
Two or more documented failed treatment trials with a registered antidepressant during the current depressive episode[d]
Abnormal laboratory tests at screening judged by the investigator to be clinically significant
Patients who are judged by the investigator as unlikely to be able to complete or to be compliant with study procedures and shift workers

[a]At screening and baseline.
[b]Within the last 6 months.
[c]At screening.
[d]Period of at least 4 weeks during which the patient received an adequate dosage of the antidepressant.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, IVR = interactive voice response, MDD = major depressive disorder.

Selection of Study Population

Patients diagnosed with MDD according to *DSM-IV* criteria[34] were enrolled in the study. Inclusion and exclusion criteria are described in Table 1. After a prerandomization period of up to 14 days, 503 patients from 49 centers were randomly assigned (1:1:1) to receive agomelatine 25 mg/d, agomelatine 50 mg/d, or placebo for 8 weeks. Patients were

required to take their medication orally approximately 1 hour before bedtime.

Efficacy and Safety Variables

Scheduled assessment visits for the efficacy and safety analysis occurred at screening (weeks –2 to –1), at baseline, and throughout the double-blind treatment phase, with assessment visits at weeks 1, 2, 3, 4, 6, and 8 or early termination and week 9 (follow-up). The primary efficacy assessment was performed by measuring the change from baseline to week 8 in the total score of the clinician-rated 17-Item Hamilton Depression Rating Scale ($HDRS_{17}$).[35] The $HDRS_{17}$ was administered at each center by a certified rater.

Secondary efficacy and severity assessments included evaluation of the 7-point Clinical Global Impressions-Improvement scale (CGI-I),[36] measured by the proportion of patients who showed clinical improvement, wherein improvement was defined by a score of 1 or 2 (1 = very much improved; 2 = much improved) based on the CGI-I. Clinical response was measured by a reduction of at least 50% in the baseline clinician-rated total $HDRS_{17}$ score, whereas clinical remission was defined by a total score of ≤ 7 on the $HDRS_{17}$ at week 8. Furthermore, the change from baseline to week 8 in the $HDRS_{17}$ subscale scores (Maier, anxiety, retardation, and sleep) was assessed. For severity assessment, a 7-point Clinical Global Impressions-Severity of Illness scale (CGI-S) was used. Supportive post hoc analyses of the primary endpoint included the $HDRS_{17}$ score excluding the sleep items (early insomnia, middle insomnia, and early awakening items) and $HDRS_{17}$ item 1 (depressed mood); the latter was assessed by visit and at week 8.

Subjective sleep (onset and quality) was measured by the scores from the Leeds Sleep Evaluation Questionnaire (LSEQ),[37] a 10-item, self-assessed, visual-analog questionnaire. Patient self-rated outcome was measured by the change from baseline in the Hospital Anxiety and Depression Scale (HADS)[38] total score and depression and anxiety subscale scores at week 8. Functionality and QoL were measured by the change from baseline to week 8 in the total scores of the Sheehan Disability Scale (SDS),[39] which is a patient-rated scale that quantifies a patient's perception of disability in 3 areas of life—work, social, and family—and the QoL in Depression Scale (QLDS),[40] a self-reported depression-specific QoL questionnaire.

Adverse events, serious adverse events (SAEs), and pregnancies were monitored and recorded throughout the study. Safety assessments also included physical examination (performed at screening and week 8/early termination) and evaluation of vital signs, body mass index, laboratory variables, and electrocardiograms (assessed at screening, at baseline, and throughout the study). Adverse events data were obtained through an unstructured global approach, as opposed to a standardized checklist.

Clinical laboratory samples were analyzed by a central laboratory, and notable abnormalities were communicated to the investigators. In addition to the routine blood and urine collections, additional postbaseline liver function tests, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transferase (GGT), alkaline phosphatase, and bilirubin, were performed at weeks 2, 4, 6, and 8/early termination.

Statistics

Sample size and power calculation were generated according to the primary endpoint (change from baseline to week 8 in $HDRS_{17}$ total score) using 2-sided *t* tests. Assuming a minimum clinically meaningful treatment effect of 3.0 and a standard deviation of 8.0 on the primary efficacy variable, a total of 490 evaluable patients (163 per treatment arm) would have approximately 90% power to reject at least 1 null hypothesis of no differences in efficacy between an agomelatine dose group and placebo using the Hochberg procedure[41] with an overall α of 5%. The power for the individual comparisons of each agomelatine dosage group versus placebo would be 87% at the α level of 2.5%.

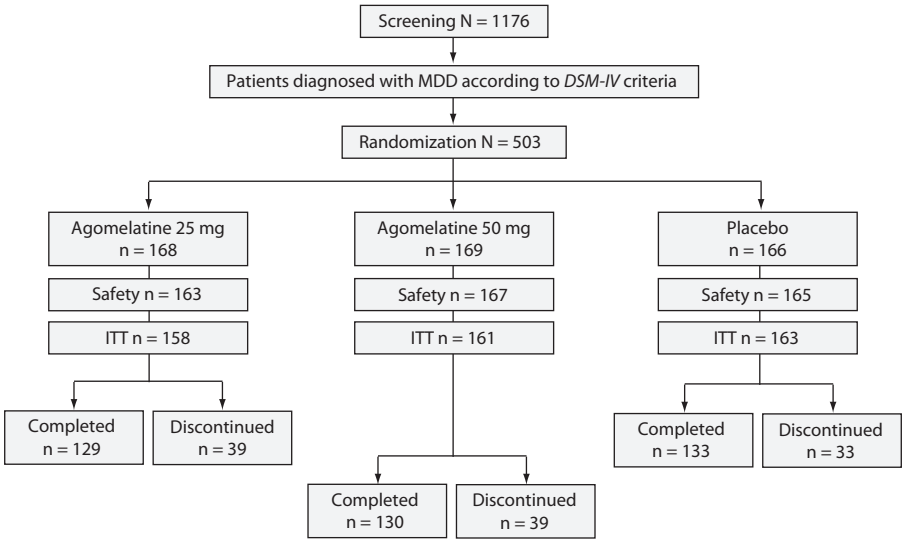
Multiplicity in the primary efficacy analysis was adjusted using the Hochberg procedure: If the larger *P* value was ≤ .05, both null hypotheses were rejected. If the larger *P* value was > .05, the corresponding null hypothesis was not rejected, and the procedure continued for the smaller *P* value. In relation to smaller *P* values, the corresponding null hypothesis was rejected if $P \leq .025$, and neither of the two null hypotheses were rejected if $P > .025$.

Efficacy analyses were performed on the intention-to-treat (ITT) population, defined as all randomized patients who received at least 1 dose of study drug and had at least 1 postbaseline assessment of $HDRS_{17}$ total score. However, 3 randomized patients were excluded from the ITT and safety populations of this study as they were subsequently randomized in a second ongoing agomelatine study.

Descriptive summary statistics were calculated for quantitative variables, whereas frequencies and proportions were given for qualitative variables. In addition, 2-sided 95% CIs and *P* values were calculated for differences between each agomelatine dose and placebo. For each of the 2 agomelatine doses, the following null hypothesis was tested: there is no difference between agomelatine dose group and placebo in the change from baseline to week 8 (last observation carried forward [LOCF]) in $HDRS_{17}$ total score. Tests of hypotheses were 2-sided and based on the contrasts between each of the 2 agomelatine doses and placebo within an analysis of covariance (ANCOVA) model, with treatment, pooled center, and baseline $HDRS_{17}$ total score as explanatory variables (fixed effects).

Similar analyses were conducted to examine the effects of treatment on the $HDRS_{17}$ subscale scores (Maier, anxiety, retardation, and sleep), on $HDRS_{17}$ item 1 (depressed mood), and on the $HDRS_{17}$ total score excluding the 3 sleep items. Proportions of patients with clinical improvement, response, and remission were analyzed by logistic regression

Figure 1. Disposition of Patients and Analysis Population



Abbreviations: ITT = intent-to-treat, MDD = major depressive disorder

with treatment and baseline $HDRS_{17}$ total score as explanatory variables. The ratings of the CGI-S at week 8 (LOCF) were analyzed by the Cochran-Mantel-Haenszel test blocking on pooled centers, using the mean score statistic of the ordinal response. Change from baseline in the HADS total and subscale scores, SDS, and QLDS total score at week 8 (LOCF) was analyzed using an ANCOVA model, in a manner similar to the analysis of the primary efficacy variable, with treatment and pooled center as fixed effects. In addition, the corresponding baseline scores were included in the model as explanatory variables. The LSEQ domain scores at week 8 (LOCF) were analyzed using an ANCOVA model with treatment, pooled center, and baseline $HDRS_{17}$ total score as explanatory variable (fixed effects).

To assess treatment group differences as a function of time as a discrete variable, a sensitivity analysis of the primary efficacy variable was performed using a mixed-effect model for repeated measures (MMRM) that included the terms for effects of treatment group, pooled center, baseline $HDRS_{17}$ total score, visit, and an interaction term for treatment group and visit. Additional sensitivity analyses included, among others, "by visit" and "observed cases" analyses (data not shown).

Table 2. Baseline Demographics, by Treatment Group (N = 503)[a]

Demographic Variable	Agomelatine 25 mg/d (n = 168)	Agomelatine 50 mg/d (n = 169)	Placebo (n = 166)
Age, n (%)			
< 45 y	84 (50.0)	83 (49.1)	86 (51.8)
45 to < 65 y	80 (47.6)	83 (49.1)	72 (43.4)
≥ 65 y	4 (2.4)	3 (1.8)	8 (4.8)
Age, mean (SD)	43.2 (11.82)	43.8 (11.96)	43.0 (13.11)
Gender, n (%)			
Female	114 (67.9)	108 (63.9)	107 (64.5)
Male	54 (32.1)	61 (36.1)	59 (35.5)
Race, n (%)			
Caucasian	124 (73.8)	131 (77.5)	123 (74.1)
Black	31 (18.5)	25 (14.8)	30 (18.1)
Asian	5 (3.0)	4 (2.4)	3 (1.8)
Other	8 (4.8)	9 (5.3)	10 (6.0)
No. of previous MDD episodes, mean (SD)[b]	5.6 (8.45)	5.7 (7.91)	4.9 (6.14)
$HDRS_{17}$ total score, mean (SD)[c]	26.8 (3.28)	26.8 (3.35)	26.4 (2.92)

[a]A total of 503 patients were randomized.
[b]Safety population. Agomelatine 25 mg/d, n = 163; agomelatine 50 mg/d, n = 161; placebo, n = 164.
[c]Intent-to-treat population. Agomelatine 25 mg/d, n = 158; agomelatine 50 mg/d, n = 161; placebo, n = 163.
Abbreviations: $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, MDD = major depressive disorder.

RESULTS

In the present study, 1,176 patients were screened, and a total of 503 patients were randomized. Of these 503 randomized patients, 76.9% of patients who were randomly assigned to agomelatine and 80.1% of patients who were randomly assigned to placebo completed the study (Figure 1). The main reasons for exclusion from the study were related to the category "other" (mostly comprising failure to meet the criterion for the interactive voice response $HDRS_{17}$) and unacceptable laboratory value(s), which resulted in screening failure for 49.9% and 27.6% of the screened patients, respectively.

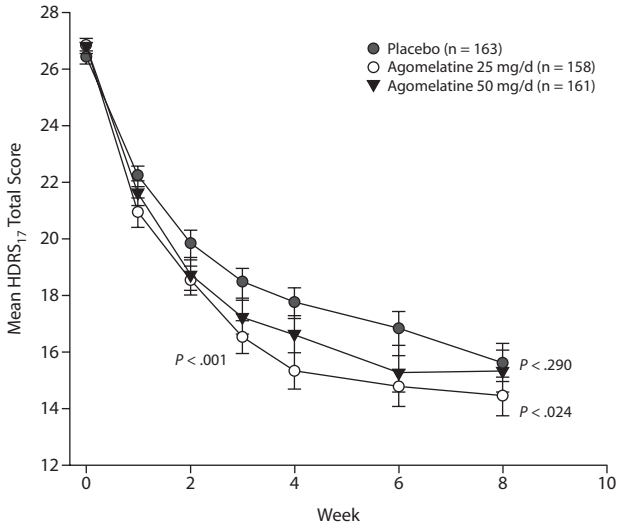
Treatment groups were well balanced with respect to baseline demographic characteristics (Table 2). The mean age of all patients was 43.3 years. The majority of patients were female (65.1%) and belonged to the Caucasian race (75.1%). The mean (± SD) baseline total score for $HDRS_{17}$

Table 3. Change From Baseline to Week 8 (LOCF) in the $HDRS_{17}$ Total Score—ITT Population (n = 482)

Treatment	Baseline Mean (SE)	Endpoint Mean (SE)	LS Mean Change (SE)	Treatment Group vs Placebo Difference in LS Mean Change		
				Mean (SE)	95% CI	*P* Value
Agomelatine 25 mg/d (n = 158)	26.8 (0.26)	15.0 (0.64)	11.8 (0.61)	2.2 (0.85)	0.5 to 3.9	.010
Agomelatine 50 mg/d (n = 161)	26.8 (0.26)	15.9 (0.65)	10.8 (0.61)	1.2 (0.85)	−0.4 to 2.9	.144
Placebo (n = 163)	26.4 (0.23)	17.1 (0.62)	9.6 (0.60)	…	…	…

Abbreviations: CI = confidence interval, $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, ITT = intent-to-treat, LOCF = last observation carried forward, LS = least squares, SE = standard error.

Figure 2. Mean 17-Item Hamilton Depression Rating Scale ($HDRS_{17}$) Total Score by Study Visit (MMRM)–ITT Population, Observed Cases[a]



[a]The *P* values (compared to placebo) for agomelatine 25 mg/d were .005 (week 1), .011 (week 2), < .001 (weeks 3, 4), .001 (week 6), and .024 (week 8) and for agomelatine 50 mg/d were .109 (week 1), .041 (week 2), .029 (week 3), .053 (week 4), .014 (week 6), and .290 (week 8).
Abbreviations: ITT = intent-to-treat, MMRM = mixed-effects model repeated measures.

was 26.6 (± 3.19) and indicated a moderate-to-severe grade of MDD. The mean number of previous MDD episodes was also balanced between the treatment groups (5.6 for agomelatine 25 mg, 5.7 for agomelatine 50 mg, 4.9 for placebo) (Table 2).

Primary Efficacy Results

In the ITT population (n = 482), the mean $HDRS_{17}$ total score decreased from baseline to endpoint (week 8, LOCF) in all treatment groups. The estimated treatment difference between the agomelatine 25 mg/d and placebo groups was 2.2, with 95% CIs (0.5 to 3.9) and a *P* value .010, whereas the difference between the agomelatine 50 mg/d and placebo groups was 1.2, with a 95% CI (−0.4 to 2.9) and a *P* value .144 (Table 3). Therefore, using the Hochberg procedure, the difference between the agomelatine 25 mg group and the placebo group was found to be statistically significant (smaller *P* value compared to α = .025), whereas the difference between the agomelatine 50 mg and the placebo group was not statistically significant (larger *P* value compared to α = .05).

The MMRM analysis of the $HDRS_{17}$ showed that the overall treatment difference in least squares (LS) mean change between agomelatine 25 mg/d and placebo was 2.2 ± 0.61 ($P < .001$). Statistically significant difference was found as early as week 1 ($P = .005$) and at all subsequent evaluations ($P = .024$ at week 8). The overall treatment difference with agomelatine 50 mg/d and placebo was 1.4 ± 0.60 ($P = .024$), and the treatment differences were significant at weeks 2 ($P = .041$), 3 ($P = .029$), and 6 ($P = .014$), but not at weeks 1, 4, and 8 ($P = .290$ at week 8) (Figure 2).

Secondary Efficacy Results

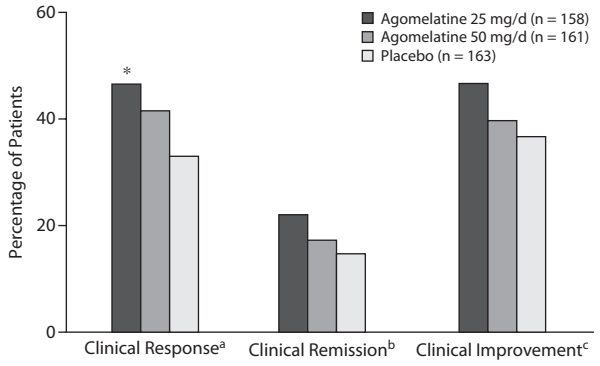
$HDRS_{17}$ subscale scores (Maier, anxiety, retardation, and sleep). The difference in LS mean change from baseline to week 8 (LOCF) achieved statistical significance between the agomelatine 25 mg/d group and the placebo group ($P = .013$) for the $HDRS_{17}$ Maier subscale score (items 1, 2, 7, 8, 9, and 10). The respective LS mean changes were 5.5 ± 0.32 and 4.4 ± 0.32 in the agomelatine 25 mg/d and the placebo groups, respectively. LS mean change at week 8 for agomelatine 50 mg/d was 5.0 ± 0.32 ($P = .158$). For the $HDRS_{17}$ anxiety subscale, the LS mean changes were 3.3 ± 0.21 for agomelatine 25 mg/d ($P = .277$), 3.1 ± 0.21 for agomelatine 50 mg/d ($P = .751$), and 3.0 ± 0.21 for placebo.

For the agomelatine 25 mg/d group in comparison to placebo, statistically significant differences in changes from baseline to week 8 (LOCF) of both $HDRS_{17}$ retardation (items 1, 7, 8, and 14; LS mean change = 0.7 ± 0.32, $P = .022$) and $HDRS_{17}$ sleep (items 4, 5, and 6; $P = .004$) subscale scores were observed. Patients in the agomelatine 25 mg/d and placebo groups had respective LS mean changes in the sleep subscale score of 2.6 ± 0.16 and 1.9 ± 0.16, with a mean difference of 0.7 ± 0.22. For both retardation (LS mean change = 0.5 ± 0.32) and the sleep subscale scores, no statistically significant differences between the agomelatine 50 mg/d group and the placebo group were observed.

Clinical response, remission, and improvement using CGI-I.

Clinical response. A higher proportion of patients showed clinical response in the agomelatine 25 mg/d and 50 mg/d groups (46.8% and 41.6%, respectively) compared

Figure 3. Proportion of Patients With Clinical Response, Clinical Remission, and Clinical Improvement at Week 8 of the Treatment Period



[a]At least 50% reduction in 17-Item Hamilton Depression Rating Scale total score.
[b]17-Item Hamilton Depression Rating Scale total score of ≤ 7.
[c]Clinical Global Impressions-Improvement scale (score 1 or 2, indicating improvement).
*P = .013 (compared to placebo).

to the placebo group (33.1%) at week 8 (LOCF) (Figure 3). The difference between the agomelatine 25 mg/d and placebo groups was statistically significant (P = .013). For the agomelatine 50 mg/d group, the difference compared to the placebo group was not statistically significant (P = .116).

Clinical remission. The proportion of patients who achieved clinical remission at week 8 (LOCF) was higher in the agomelatine 25 mg/d group when compared to the placebo group (Figure 3) without reaching statistical significance (22.2% and 14.7%, respectively; P = .070). In the agomelatine 50 mg/d group, the proportion of patients who achieved remission was also numerically higher compared to those in the placebo group, but the difference was not statistically significant (17.4% and 14.7%, respectively; P = .457).

Clinical improvement (CGI-I). A higher proportion of patients receiving agomelatine showed clinical improvement (Figure 3). The percentages of patients with CGI-I improvement at week 8 (LOCF) in the agomelatine 25 mg/d, agomelatine 50 mg/d, and placebo groups were 46.8%, 39.8%, and 36.8%, respectively (P = .065 for agomelatine 25 mg/d and P = .568 for agomelatine 50 mg/d, compared to placebo).

Clinical Global Impressions-Severity of Illness scale. The proportion of patients who were "normal, not at all ill" at week 8 (LOCF) was higher in the 2 agomelatine groups (10.1% for the agomelatine 25 mg/d group and 8.1% for the agomelatine 50 mg/d group) compared to the placebo group (5.5%). The proportion of patients who were "markedly ill" at week 8 was higher in the placebo group (20.9%) compared to the agomelatine 25 mg/d (11.4%) and agomelatine 50 mg/d (16.8%) groups. The difference in CGI-S rating at week 8 between the agomelatine 25 mg/d group and the placebo group achieved statistical significance (P = .010), whereas the difference between the agomelatine 50 mg/d group and the placebo group did not (P = .115).

Hospital Anxiety and Depression Scale. A reduction in HADS mean total score from baseline to week 8 (LOCF) was observed in all treatment groups. The difference in LS mean change was 2.6 and achieved statistical significance only between the agomelatine 25 mg/d group and the placebo group (P = .004) (Table 4). For the HADS depression and anxiety subscale scores, the treatment difference in LS mean change between agomelatine 25 mg/d and placebo was 1.3 for both subscales and was statistically significant (P = .010 for the depression subscale and P = .006 for the anxiety subscale).

Leeds Sleep Evaluation Questionnaire. Positive treatment differences, indicating greater improvement in both the 25 mg/d and 50 mg/d agomelatine groups compared to placebo, were observed for the LSEQ "getting to sleep" and "quality of sleep" domain scores at week 8 (LOCF) (Figure 4A and B). For both domain scores, statistically significant differences were reported for agomelatine 25 mg/d and 50 mg/d as compared to placebo.

Sheehan Disability Scale. The SDS mean total score decreased from baseline to endpoint in all treatment groups. Improvement in disability measured as difference in LS mean change was statistically significantly different in agomelatine 25 mg/d (baseline = 22.7, LS mean change = 7.9) compared to placebo (baseline = 22.3, LS mean change = 6.2), with a mean difference of 1.7 (P = .049). There was no difference in LS mean change between the agomelatine 50 mg/d group and the placebo group (P = .970).

QoL in Depression Scale. Mean change from baseline to week 8 (LOCF) in the QLDS total score was 9.7 in the agomelatine 25 mg/d group (mean baseline = 25.4), 8.4 in the agomelatine 50 mg/d group (baseline = 24.9), and 7.7 in the placebo group (baseline = 24.0). The treatment differences for agomelatine 25 mg/d and agomelatine 50 mg/d when compared to placebo did not achieve statistical significance (P = .082 and .508, respectively).

$HDRS_{17}$ item 1 (depressed mood) analysis. Post hoc analysis showed that the difference in LS mean change from baseline to week 8 (LOCF) in the $HDRS_{17}$ item 1 (ie, depressed mood) score in the ITT population among agomelatine 25 mg/d versus placebo was 0.2 (P = .044), while that of agomelatine 50 mg/d versus placebo was 0.1 (P = .641). The analysis of the LS mean change from baseline in the $HDRS_{17}$ item 1 score by visit showed a statistically significant difference between agomelatine 25 mg/d and placebo from week 1 onward (data not shown).

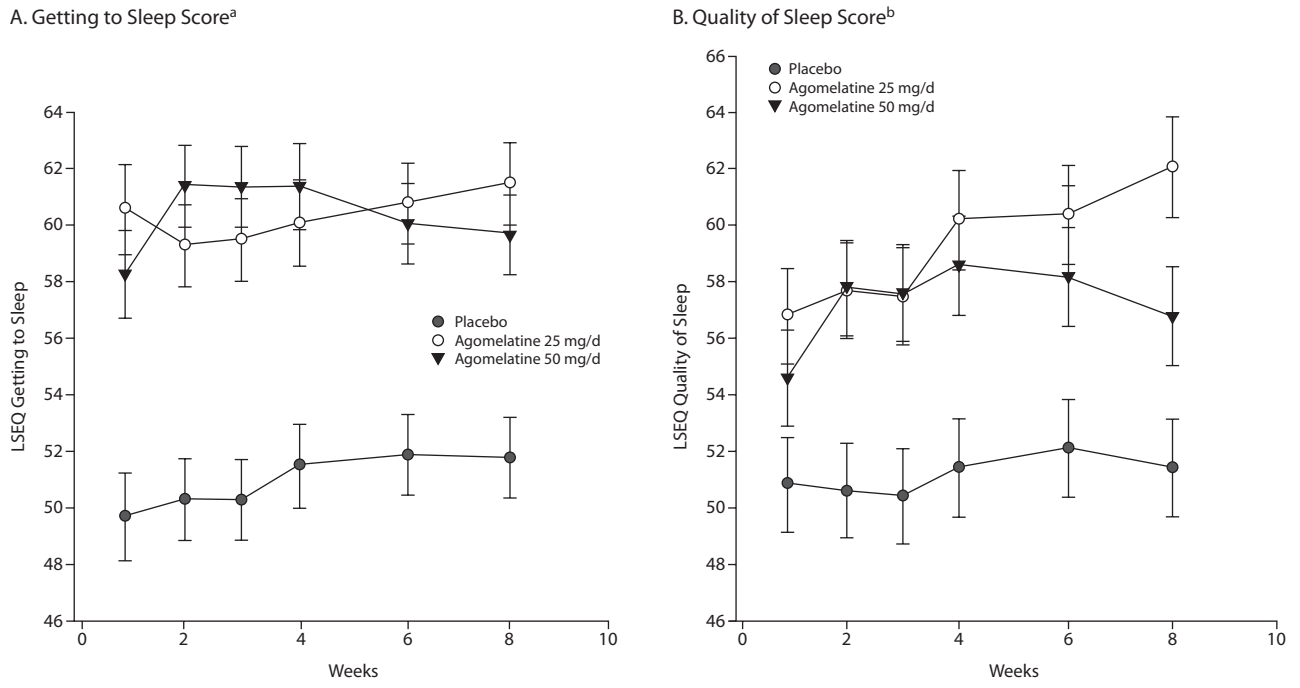
The post hoc analysis of the $HDRS_{17}$ total score excluding the 3 sleep items showed greater LS mean change of 9.2 ± 0.52 for agomelatine 25 mg/d (P = .035) and 8.5 ± 0.51 for agomelatine 50 mg/d (P = .231) compared to placebo (7.7 ± 0.51).

Table 4. Change From Baseline to Week 8 (LOCF) in the Hospital Anxiety and Depression Scale Total Score—ITT Population (n = 482)

Treatment	Baseline Mean (SE)	Endpoint Mean (SE)	LS Mean Change (SE)	Treatment Group vs Placebo Difference in LS Mean Change		
				Mean (SE)	95% CI	*P* Value
Agomelatine 25 mg/d (n = 158)	27.8 (0.49)	18.4 (0.77)	9.5 (0.65)	2.6 (0.90)	0.9 to 4.4	.004
Agomelatine 50 mg/d (n = 161)	27.9 (0.46)	20.2 (0.74)	7.7 (0.64)	0.8 (0.90)	−0.9 to 2.6	.345
Placebo (n = 163)	26.7 (0.47)	20.2 (0.66)	6.9 (0.64)	…	…	…

Abbreviations: ITT = intent-to-treat, LOCF = last observation carried forward, LS = least squares, SE = standard error.

Figure 4. Leeds Sleep Evaluation Questionnaire (LSEQ) Score by Visit (LOCF): ITT Population, Post Hoc Analysis



[a]For "getting to sleep" score, the differences were significantly better for both agomelatine doses at all points of evaluation compared with placebo ($P < .001$).
[b]"Quality of sleep" score was significantly better for agomelatine 25 mg/d at all evaluations and from week 2 to week 8 for agomelatine 50 mg/d compared with placebo.
Abbreviations: ITT = intent-to-treat, LOCF = last observation carried forward.

Safety

In the safety population (n = 495), similar proportions of patients in each of the agomelatine groups and the placebo group experienced AEs. The AEs were mostly mild or moderate in intensity. The most commonly affected system organ classes were nervous system disorders, followed by gastrointestinal disorders.

Adverse events were reported by 69.9%, 70.7%, and 65.5% patients receiving agomelatine 25 mg/d, agomelatine 50 mg/d, and placebo, respectively. In the patients who received agomelatine versus placebo, the most commonly occurring nervous system disorder AEs were headache (13.3% vs 17.0%), somnolence (9.1% vs 4.2%), dizziness (7.3% vs 3.0%), and sedation (5.2% vs 4.2%). Two patients from the agomelatine 25 mg/d group discontinued the study due to dizziness, and none from the placebo group discontinued due to this symptom. Gastrointestinal system disorder–related AEs reported with agomelatine versus placebo were diarrhea (7.3% vs 6.7%), nausea (6.1% vs 4.8%), dry mouth (4.8% vs 8.5%), dyspepsia (2.7% vs 2.4%), and constipation (2.7% vs 1.8%). Other AEs were back pain (3.3% vs 1.2%), fatigue (5.8% vs 2.4%), nasopharyngitis (5.2% vs 4.2%), upper respiratory tract infection (4.2% vs 4.2%), influenza (2.4% vs 1.2%), and pyrexia (2.4% vs 0.6%).

AEs related to psychiatric disorders included insomnia (3.3% vs 6.1%), anxiety (2.4% vs 3.0%), and abnormal dreams (2.1% vs 1.8%). With the exception of the discontinuations due to events revealed by liver function tests (discontinuation of 2 patients in the agomelatine 50 mg/d group), there was no apparent dose-related pattern of AEs.

Table 5. Deaths, Other Serious or Clinically Significant Adverse Events, and Discontinuation Due to Adverse Events, by Treatment (safety population; n = 495)[a]

Event	Agomelatine 25 mg/d (n = 163)	Agomelatine 50 mg/d (n = 167)	All Agomelatine (n = 330)	Placebo (n = 165)
Death	0	0	0	0
Serious adverse events	1 (0.6)	1 (0.6)	2 (0.6)	2 (1.2)
Discontinuation due to adverse events	7 (4.3)	10 (6.0)	17 (5.2)	8 (4.8)
Psychiatric adverse events	32 (19.6)	21 (12.6)	53 (16.1)	23 (13.9)

[a]Values shown as n (%).

One patient in each agomelatine group and 2 patients in the placebo group experienced SAEs (Table 5). No deaths occurred during the study.

Aminotransferase (ALT/AST) elevations occurred more often in the agomelatine 50 mg/d group. Overall, 7 patients experienced clinically notable elevations in ALT/AST values: 1 patient (0.6%) in the agomelatine 25 mg/d group, 5 patients (3.0%) in the agomelatine 50 mg/d group, and 1 patient (1.3%) in the placebo group (the criterion for clinically notable values for AST, ALT, GGT, and alkaline phosphatase was > 3 × upper limit of normal [ULN] and for total bilirubin was > 1.5 × ULN, ie, > 26 μmol/L). ALT elevations occurred in only 2 cases in the agomelatine 50 mg/d group (n = 2; 1.2%) as compared to the agomelatine 25 mg/d group (n = 1; 0.6%) and the placebo group (n = 1; 0.6%). None of the clinically notable liver enzyme elevations were reported as SAEs. In general, the aminotransferase elevations occurred mainly between weeks 6 and 8 of treatment and were transient. Two of the 7 cases of aminotransferase elevations (both in the agomelatine 50 mg/d group) discontinued the study treatment, and the enzyme levels decreased to within normal levels after treatment with the drug was stopped. Among the remaining 5 patients, the aminotransferase levels returned to normal values with continuing agomelatine treatment in 4 patients, while 1 patient (agomelatine 25 mg/d) was lost to follow-up; the 4 patients (50 mg/d group) entered the 1-year open-label phase of the study.

There was no significant effect of agomelatine on the weight of the patients at the end of the 8-week treatment period. Clinically notable changes in weight (increase/decrease in kg ≥ 7%) were observed in 1.9% and 1.3% of patients treated with agomelatine and placebo, respectively, who showed an increase in weight and 2.6%, 1.9%, and 2.0% of patients treated with agomelatine 25 mg/d, agomelatine 50 mg/d, and placebo, respectively, who reported a decrease in weight. The proportions of patients with treatment-emergent electrocardiogram findings were 6.1%, 7.3%, and 9.3% in the agomelatine 25 mg/d, agomelatine 50 mg/d, and placebo groups, respectively. Most of the findings were conduction abnormalities (primarily first-degree atrioventricular block and left anterior hemiblock) and T-wave abnormalities (primarily flat T-waves). The pattern of events was similar in both agomelatine groups and the placebo group.

Discontinuation due to AEs was reported in 4.3% of patients in the agomelatine 25 mg/d group, 6.0% in the agomelatine 50 mg/d group, and 4.8% in the placebo group. The major reasons for discontinuation due to AE were psychiatric disorders (1.8% in each agomelatine group and 2.4% in the placebo group) and nervous system disorders (1.8% in the agomelatine 25 mg group and 1.2% each in the agomelatine 50 mg/d and placebo groups). None of the psychiatric and nervous system disorder AEs leading to discontinuation were reported as SAEs.

DISCUSSION

In the present study, the primary efficacy analysis showed that agomelatine 25 mg/d was associated with statistically significant improvement of MDD symptoms as assessed by the change from baseline to week 8 (ITT-LOCF) in the total score of the clinician-rated $HDRS_{17}$. Agomelatine 50 mg/d did not achieve statistical significance for the primary endpoint at week 8 but showed statistically significant effects on the HDRS total score at weeks 2, 3, and 6.

The MMRM is a reliable tool commonly used for handling missing data in clinical trials.[42] The efficacy of agomelatine 25 mg/d in relation to the primary efficacy endpoint in the primary analysis was supported by an MMRM (ITT-observed cases) analysis at week 8, which showed a statistically significant treatment difference in the change from baseline in $HDRS_{17}$ total score between agomelatine 25 mg/d and placebo. In addition, statistically significant differences in change in $HDRS_{17}$ score (MMRM) between the agomelatine 25 mg/d and placebo groups were observed as early as week 1 and at each time point up to week 8. The treatment difference between agomelatine 50 mg/d group and placebo achieved statistical significance at weeks 2, 3, and 6. These findings support the antidepressant efficacy of agomelatine for both doses.[43,44]

The proportion of patients showing clinical response, remission, or improvement at week 8 was higher in the agomelatine groups compared to the placebo group. These results were similar to previous studies with agomelatine.[30,45,46] A statistically significant difference in comparison to placebo was achieved for clinical response in the agomelatine 25 mg/d group, but not for the agomelatine 50 mg/d group. Although the measures of remission (based on the $HDRS_{17}$ scale) and improvement (based on the CGI-I scale) were greater for the agomelatine 25 mg/d dose, no statistically significant difference was found. Tedlow et al[47] have earlier observed that it is very difficult

to achieve remission in the short-term treatment studies in patients with a relatively high HDRS score. Thus, a longer duration of treatment may be required for many of the patients to achieve remission in antidepressant studies.

On the basis of the CGI-S ratings, patients treated with both doses of agomelatine were less severely ill at week 8 compared with those treated with placebo. A statistically significant difference was achieved for the agomelatine 25 mg/d but not for the agomelatine 50 mg/d dose, compared to placebo. Evaluation of $HDRS_{17}$ subscale scores at week 8 showed statistically significant improvement for agomelatine 25 mg/d compared to placebo in core emotional depressive symptoms (Maier subscale), retardation, and sleep. The analysis of the patient self-rated HADS indicated a statistically significant improvement for agomelatine 25 mg/d in total score as well as depression and anxiety subscale scores. For agomelatine 50 mg/d, none of the $HDRS_{17}$ subscale scores or observed HADS-based improvements reached statistical significance.

Previous studies have shown improvement in the sleep symptoms in the patients receiving agomelatine.[22,23,48] In the present study, agomelatine 25 mg/d resulted in consistent improvement in sleep symptoms when compared to placebo. This conclusion is based on scores from the HDRS sleep subscale, all LSEQ domains of subjective sleep and a lower incidence of insomnia as an AE in the patients receiving agomelatine. However, the statistically significant effects on the HDRS Maier and retardation subscales and HADS total and depression subscale indicate that agomelatine efficacy is also driven by effects on other core symptoms of depression and not only sleep. Therefore, it can be concluded that the short-term antidepressant efficacy of agomelatine 25 mg/d was driven by other effects beyond the beneficial effects on sleep-related symptoms. This is further supported by the statistically significant reduction of the HDRS item 1 (depressed mood) in the agomelatine 25 mg/d group as well as the significant effect of agomelatine 25 mg/d on the $HDRS_{17}$ total score without sleep items.

Depression has a negative impact on QoL,[49] often with a negative impact on social functioning.[50] Despite the short-term treatment period of this study, agomelatine 25 mg/d achieved numerically greater scores on QoL (not statistically significant) and improvements in SDS functional disability scores and statistically significant work subscale scores. These results, based on broad measures of patient well-being, are indicative of the clinical meaningfulness of the antidepressant efficacy of agomelatine treatment in this short-term treatment of major depression.

The study showed antidepressant efficacy of agomelatine 25 mg/d in the short-term treatment of patients with MDD. Agomelatine 50 mg/d showed numerical, but not statistically significant, superiority to placebo at study endpoint. Therefore, there was no evidence of a dose–efficacy response relationship in this study. However, we observed that the efficacy based on the $HDRS_{17}$ total score was statistically significant for agomelatine 50 mg group until week 6, which is consistent with the observation of the efficacy of agomelatine 50 mg/d in another study (unpublished results by authors). At the last visit (week 8), the effect on the $HDRS_{17}$ total score of the agomelatine 50 mg/d dose no longer showed significance at endpoint. The placebo response observed in this study was comparable to that seen in other antidepressant clinical trials and was attributed to the impact of the frequent visit schedule, patients' positive expectations of the drug's efficacy and tolerability, and encouragement by personnel at the study sites, which may have also had an impact on the outcome of the antidepressant efficacy for the 50 mg/d group. Overall, the current results cannot clearly judge the antidepressant efficacy of the 50 mg/d dose over time.

The antidepressant efficacy of agomelatine shown in this study is in agreement with the data from previous studies of agomelatine that also showed improvement in $HDRS_{17}$ with 25–50 mg doses.[51,52]

The overall tolerability and discontinuation rates for AEs were similar between agomelatine and placebo. There was no dose-response relationship in the agomelatine groups with regard to SAEs, AEs, or discontinuations due to AEs. Although the present study was too short to examine the impact of agomelatine on weight, during the 8-week study, agomelatine was found to be weight neutral. Agomelatine was associated with a transient dose-dependent effect on hepatic aminotransferase elevation. Clinically notable aminotransferase elevations occurred more frequently in the agomelatine 50 mg/d group (2.4%), whereas clinically notable aminotransferase elevations were similar in the agomelatine 25 mg/d (0.6%) and placebo groups (0.6%). None of the observed elevations were associated with any sign of liver toxicity (ie, neither clinical symptomatology nor other laboratory findings).

In general, the proportion of patients discontinuing the study drug due to AEs was similar between the agomelatine groups and the placebo group.

The current study, due to its short duration of 8 weeks, limits the implication of these outcomes in longer-term treatments. The generalizability of the results is also limited due to the relatively high baseline $HDRS_{17}$ required for enrollment, and exclusion of patients with any comorbid Axis I disorder. Additional data from the ongoing longer-term trials are required to further support the efficacy and safety of agomelatine in the treatment of MDD.

CONCLUSIONS

The present study confirms that agomelatine is effective in the short-term treatment of moderate to severely depressed patients. Agomelatine 25 mg/d showed a greater and rapid reduction in all core symptoms of depression compared to placebo over the course of the study, whereas

agomelatine 50 mg/d provided evidence for its antidepressant efficacy until week 6 but not at study end. Agomelatine showed significant effects on subjective sleep symptoms, but efficacy was also driven by effects on other core symptoms of depression.

Agomelatine was generally well tolerated, with most AEs being mild to moderate in severity. Clinically notable, transient elevation of aminotransferases was noted in 2.4% of patients of the agomelatine 50 mg/d group. Treatment discontinuations were similar between the agomelatine and placebo groups.

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Potential conflicts of interest: **Dr Stahl**, over the past 12 months (April 2008–May 2009), has served as a consultant to Arena, Azur, Bionevia, Boehringer Ingelheim, Bristol-Myers Squibb, CeNeRx, Dainippon Sumitomo, Eli Lilly, Endo, Forest, Janssen, Jazz, Johnson & Johnson, Labopharm, Lundbeck, Marinus, Neuronetics, Novartis, Noven, Pamlab, Pfizer, Pierre Fabre, Sanofi, Sepracor, Servier, Shire, SK Corporation, Solvay, Somaxon, Tetragenex, and Vanda; has served on speakers bureaus for Wyeth, Pfizer, and Eli Lilly; and has received grant support from Forest, Johnson & Johnson, Novartis, Organon, Pamlab, Pfizer, Sepracor, Shire, Takeda, Vanda, and Wyeth. **Dr Fava** has received research grants from Abbott, Alkermes, Aspect Medical Systems, AstraZeneca, Bio Research, BrainCells, Bristol-Myers Squibb, Cephalon, Clinical Trial Solutions, Eli Lilly, Forest, Ganeden, GlaxoSmithKline, Johnson & Johnson, Lichtwer Pharma, Lorex, NARSAD, NCCAM, NIDA, NIMH, Novartis, Organon, Pamlab, Pfizer, Pharmavite, Roche, Sanofi-Aventis, Shire, Solvay, Synthelabo, and Wyeth-Ayerst; has served as a consultant or advisor for Abbott, Amarin, Aspect Medical Systems, AstraZeneca, Auspex, Bayer, Best Practice Project Management, Biovail, BrainCells, Bristol-Myers Squibb, Cephalon, Clinical Trials Solutions, CNS Response, Compellis, Cypress, Dov, Eli Lilly, EPIX, Fabre-Kramer, Forest, GlaxoSmithKline, Grunenthal GmBH, Janssen, Jazz, Johnson & Johnson, Knoll, Labopharm, Lorex, Lundbeck, MedAvante, Merck, Methylation Sciences, Neuronetics, Novartis, Nutrition 21, Organon, Pamlab, Pfizer, PharmaStar, Pharmavite, Precision Human Biolaboratory, Roche, Sanofi-Aventis, Sepracor, Schering-Plough, Solvay, Somaxon, Somerset, Synthelabo, Takeda, Tetragenex, Transcept, Vanda, and Wyeth-Ayerst; and has had speaking/publishing-related affiliations with Advanced Meeting Partners, American Psychiatric Association, AstraZeneca, Belvoir, Boehringer lngelheim, Bristol-Myers Squibb, Cephalon, Eli Lilly, Forest, GlaxoSmithKline, Imedex, Novartis, Organon, Pfizer, Pharmastar, MGH Psychiatry Academy/Primedia, MGH Psychiatry Academy/Reed-Elsevier, and UBC, and Wyeth-Ayerst; has equity holdings in Compellis; has patent applications for SPCD and for a combination of azapirones and bupropion in MDD; and has received copyright royalties for the MGH CPFQ, SFI, ATRQ, DESS, and SAFER. In the last 12 months, **Dr Trivedi** has received research support from Agency for Healthcare Research and Quality, National Institute of Mental Health, National Institute on Drug Abuse, and Targacept; consulting fees from AstraZeneca, Cephalon, Fabre-Kramer, GlaxoSmithKline, Janssen, Johnson & Johnson, Eli Lilly, Neuronetics, Otsuka, and Pfizer; and consulting fees/honoraria from Bristol-Myers Squibb, Forest, and Wyeth-Ayerst. **Drs Shah, Caputo,** and **Post** are full-time employees of Novartis.

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