

Gepirone Extended-Release in the Treatment of Adult Outpatients With Major Depressive Disorder: A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study

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Objective: To evaluate the efficacy and tolerability of extended-release gepirone (gepirone-ER), a 5-HT_{1A} agonist, versus placebo in the treatment of adult outpatients with major depressive disorder (MDD).

Method: A double-blind, randomized, placebo-controlled, parallel-group, 8-week study was conducted from October 2003 to August 2004 in outpatients 18 to 64 years old with moderate-to-severe MDD, as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR), and a baseline Hamilton Rating Scale for Depression (HAM-D₁₇) total score ≥ 20 . Patients were titrated from 20 to 80 mg/day of gepirone-ER or placebo (most patients received gepirone-ER 60 or 80 mg/day by week 3). The primary outcome measure was baseline-to-endpoint mean change in HAM-D₁₇ total score. Secondary outcome measures included the 28-item version of the HAM-D, HAM-D depressed mood (item 1), Bech Six-Item Scale, Montgomery-Asberg Depression Rating Scale, and Clinical Global Impressions scale.

Results: Significantly greater reductions in HAM-D₁₇ total scores occurred in gepirone-ER-treated patients compared with placebo-treated patients by week 4 ($p = .004$) and continued through weeks 6 ($p = .006$) and 8 ($p = .032$). Secondary outcomes also improved significantly at multiple timepoints, including at endpoint. The most frequently reported adverse events in the gepirone-ER versus placebo groups were dizziness (45% vs. 10%), nausea (36% vs. 13%), and headache (24% vs. 16%). Dizziness occurred most frequently during initial dosing and up-titration.

Conclusions: Gepirone-ER significantly reduced depression symptoms and illness severity in MDD outpatients through the end of the study and was generally well tolerated, confirming previous findings.

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Major depressive disorder (MDD) affects approximately 14 million people in the United States and 340 million people worldwide, making it one of the leading causes of disability.^{1,2} Despite the availability of a variety of antidepressants, many patients do not respond adequately to current medications for MDD or lapse from therapy owing to adverse events (AEs). The recent Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial assessed the effectiveness of a wide variety of currently available treatment options under “real-world” conditions.^{3,4} In the first phase of that study, during a maximum of 14 weeks of first-level treatment with citalopram, 53% of patients failed to respond adequately, and 72.5% failed to achieve remission (Hamilton Rating Scale for Depression [HAM-D₁₇]⁵ score ≤ 7), the primary outcome measure. Even after receiving a sequence of as many as 4 medication alternatives, an estimated 33% of patients remained refractory to treatment, suggesting the need for additional pharmacologic alternatives for patients with MDD.

A direct link between serotonin (5-HT) and depression was first hypothesized 40 years ago⁶ and has since become well established based on evidence from a variety of preclinical, clinical, and postmortem studies.⁷ At the same time, drugs that block the neuronal reuptake of 5-HT (especially selective serotonin reuptake inhibitors [SSRIs]) have emerged as standard treatment for depression. Although SSRIs may be selective for the 5-HT transporter, they can affect neurotransmitter levels at any of the 14 5-HT receptor subtypes identified to date, although not all are thought to be involved in the pathophysiology of depression. This lack of selectivity may be responsible for some of the AEs commonly observed with SSRIs, such as nausea and sexual dysfunction.⁸ Therefore, targeting of specific 5-HT receptor subtypes could represent a more focused approach to the treatment of MDD.

Gepirone, a member of the azapirone class, a group of compounds that has shown promise in the treatment of anxiety and depression,^{9–13} has a mechanism of action different from those of SSRIs and other agents currently used in the treatment of depression.^{9–13} Evidence suggests that gepirone and its 3-hydroxy metabolite are highly selective agonists at 5-HT_{1A} presynaptic and postsynaptic receptors.^{14–16} Although several 5-HT_{1A} receptor agonists have been investigated clinically, their short half-lives have necessitated frequent administration, and the resulting high peak plasma drug concentrations have often led to dose-limiting AEs. An extended-release (ER) form of gepirone was developed to allow once-daily dosing and administration of a larger single dose, with the intent of maintaining relatively low peak concentrations, thereby improving tolerability relative to earlier immediate-release formulations.¹⁷

The antidepressant activity of gepirone has been suggested in animal models and confirmed in clinical trials.^{7,13} A previous large-scale, multicenter, randomized, double-blind, placebo-controlled trial of gepirone-ER demonstrated antidepressant efficacy and favorable tolerability in adult outpatients with MDD, including a low risk of sexual dysfunction and weight gain.¹⁸ The present study sought to confirm the efficacy and tolerability of gepirone-ER in the treatment of depression.

METHOD

Patient Selection

Male and female outpatients, 18 to 64 years of age, with moderate-to-severe MDD, as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR)¹⁹ criteria; an investigator-rated HAM-D₁₇ score ≥ 20 at screening and baseline (confirmed by Interactive Voice Response System [IVRS] at baseline); and significant dysphoria for ≥ 4 weeks prior to screening were eligible for study participation. The IVRS system was used to confirm eligibility

only; total HAM-D₁₇ scores obtained during the IVRS session were not provided to investigators.

Patients were excluded if they had a $\geq 20\%$ decrease in HAM-D₁₇ total scores between screening and baseline; a primary DSM-IV Axis I diagnosis other than MDD (e.g., bipolar disorder); a history or presence of any DSM-IV Axis II disorder; a seizure disorder; treatment-refractory depression (defined as incomplete or no response to 2 prior courses of antidepressants at adequate dosage and duration); any clinically meaningful, nonstable renal, hepatic, cardiovascular, respiratory, or cerebrovascular disease, or other serious progressive physical disease; or any clinically abnormal finding on screening physical examination or laboratory assessments or if they were currently undergoing psychotherapy or at significant risk for suicide according to the clinical judgment of the investigator. In addition, patients were excluded if they had received electroconvulsive shock therapy within the previous year, monoamine oxidase inhibitor therapy within 3 weeks, fluoxetine or other SSRIs within 4 weeks, or other psychotropic drugs within 2 weeks or were pregnant or lactating.

Study Treatments

This double-blind, randomized, placebo-controlled, parallel-group, multicenter, 8-week treatment study (Protocol No. FKGBE007), evaluating the safety and efficacy of gepirone-ER versus placebo in outpatients with MDD, was conducted from October 2003 to August 2004 at 9 U.S. study sites. Each study site obtained institutional review board approval prior to study commencement, and patients were required to provide written consent prior to study participation, in accordance with the Declaration of Helsinki.

All patients participated in a placebo washout period (1 placebo tablet/day administered for 4–7 days) before the active treatment period and a 1-week follow-up period after the active treatment period. Patients were randomly assigned to receive gepirone-ER or placebo and were titrated according to therapeutic response and tolerability as follows: days 1 to 3, 20 mg (1 gepirone-ER 20-mg tablet or placebo tablet); days 4 to 7, 40 mg (2 gepirone-ER 20-mg tablets or placebo tablets), titration to 40 mg/day could be delayed to day 8 if patients experienced significant tolerability issues; days 8 to 14, 40 to 60 mg (2 or 3 gepirone-ER 20-mg tablets or placebo tablets); days 15 to 56, 40 to 80 mg (2–4 gepirone-ER 20-mg tablets or placebo tablets). A minimum dose of 40 mg/day was required to continue in the study. Patients were instructed to take the prescribed dose of study medication in the morning, after breakfast. After 1 week, patients were permitted to switch to evening dosing.

Study Assessments

The HAM-D was administered at screening and, along with the Montgomery-Asberg Depression Rating Scale

(MADRS)²⁰ and the Clinical Global Impressions scale (CGI)²¹ (which includes severity and improvement ratings), at baseline and at weeks 2, 3, 4, 6, and 8. The HAM-D was administered according to the structured interview guide for the HAM-D₂₁.²² The change in HAM-D₁₇ (first 17 of 31 administered items) total score was the primary efficacy outcome measure. Change in HAM-D₂₈ total score was a secondary outcome. This measure contains the same items as the HAM-D₁₇, with additional items measuring depersonalization/derealization, paranoia, obsessive/compulsive symptoms, hyperphagia, hypersomnia, retardation, helplessness, hopelessness, and worthlessness. The additional items of the HAM-D₂₈ were administered as part of an unstructured interview. The Bech Six-Item Scale (Bech-6)²³ consisting of HAM-D items 1, 2, 9, 10, 12, and 16, which measure the core depression symptoms of depressed mood, work and activities, somatic symptoms-general, feelings of guilt, anxiety-psychic, and retardation, respectively, was also administered at baseline and at weeks 2, 3, 4, 6 and 8.

For the HAM-D₁₇ and MADRS, responders at each postbaseline assessment were prospectively defined as patients who experienced at least a 50% reduction from their baseline score. Similarly, for the CGI-Improvement scale (CGI-I), responders at each postbaseline assessment were prospectively defined as patients with a score of 1 ("very much improved") or 2 ("much improved"). Remitters at each postbaseline assessment were prospectively defined as patients with a HAM-D₁₇ total score ≤ 7 .

Data Analysis

Efficacy analyses were performed on the intent-to-treat (ITT) population, defined as all randomized patients who had a baseline assessment, at least 1 dose of study medication, and at least 1 postbaseline HAM-D₁₇ assessment score within 3 days of receiving study medication. The primary statistical analyses were performed using the last-observation-carried-forward (LOCF) method for imputing missing values. An analysis for each measure was also performed using observed cases.

Assuming a common standard deviation of 7.75, a sample size of 120 subjects per treatment group was intended to provide a type I error rate of 5%, with 85% power to detect a 3.0-point difference between placebo and active treatment.

As specified in the statistical analysis plan, the primary efficacy parameter was analyzed by means of an analysis of variance (ANOVA) model. The estimates of treatment effects and corresponding 95% confidence intervals were based on the additive 2-way ANOVA (including both treatment groups) with factors for treatment and center. A test for interaction between treatment and center was performed by extending the additive model with the interaction term. In case of a significant interaction ($p < .10$), the kind of interaction (i.e., the differences between the cen-

ters with respect to the treatment effects) was to be further explored to evaluate whether the presentation of an overall estimate of treatment effects was justified. Categorical outcome measures (i.e., proportions of responders and remitters) were analyzed using the Cochran-Mantel-Haenszel test, adjusted by center.

Tolerability

Vital signs and AEs were monitored at all study visits, and clinical laboratory tests and physical examinations were performed at screening and at the end of treatment period. Adverse events were also assessed at a follow-up visit, 1 week after the last dose of study medication, and by phone, 30 days after the last dose of study medication was taken.

RESULTS

Patient Characteristics

In total, 248 patients (gepirone-ER, $N = 124$; placebo, $N = 124$) were enrolled at 9 U.S. centers. A total of 238 patients (gepirone-ER, $N = 116$; placebo, $N = 122$) with a mean age (\pm SD) of 38.0 (\pm 11.2) years, 68% of whom were female and 65% of whom were white, were included in the ITT population on which efficacy analyses were performed (Table 1). Patient demographic and clinical characteristics were similar between the 2 treatment groups, with most patients (57.3% of the gepirone-ER group and 60.5% of the placebo group) at the time of study entry suffering from recurrent MDD with full recovery between episodes and a current episode that had lasted longer than 12 months. The mean age (\pm SD) at first episode of depression was 27.8 (\pm 11.9) years, indicating that the average patient had been experiencing depression intermittently for approximately 10 years. The final prescribed dose was ≥ 60 mg for 88% of ITT patients receiving gepirone-ER.

Efficacy

Continuous measures. HAM-D₁₇ mean total scores at baseline were comparable between the gepirone-ER and placebo groups; by week 4, the mean change from baseline was significantly greater in the gepirone-ER group compared with placebo ($p = .004$), a difference that remained significant (Figure 1A) at week 6 ($p = .006$) and week 8 ($p = .032$). MADRS mean total scores (Figure 1B) also showed significantly greater reductions from baseline in the gepirone-ER group compared with placebo at weeks 4, 6, and 8 ($p < .001$, $p = .003$, and $p = .008$, respectively). CGI-Severity of Illness (CGI-S) mean scores showed greater improvement for the gepirone-ER group compared with placebo at weeks 4, 6, and 8 ($p = .002$, $p = .001$, and $p = .015$, respectively). Analyses of observed cases produced the same pattern of statistical significance as the LOCF analyses of the HAM-D₁₇, MADRS, and CGI-S.

Table 1. Patient Disposition, Baseline Demographics, and Clinical Characteristics

Variable	Gepirone-ER (N = 124)	Placebo (N = 124)	Overall (N = 248)
Patients included in efficacy analysis, N ^a	116	122	238
Patients discontinued, N (%)	27 (21.8)	22 (17.7)	49 (19.8)
Reason for discontinuing, N (%)			
Lack of efficacy	4 (3.2)	3 (2.4)	7 (2.8)
Adverse event(s)	5 (4.0)	3 (2.4)	8 (3.2)
Noncompliance	1 (0.8)	NA	1 (0.4)
Withdrew consent	5 (4.0)	2 (1.6)	7 (2.8)
Lost to follow-up	11 (8.9)	12 (9.7)	23 (9.3)
Other	1 (0.8)	2 (1.6)	3 (1.2)
Patients completed treatment, N (%)	97 (78.2)	102 (82.2)	199 (80.2)
Age, mean ± SD, y	38.2 ± 11.4	37.9 ± 11.1	38.0 ± 11.2
Gender, female, N (%)	82 (66.1)	87 (70.2)	169 (68.1)
Race, N (%)			
White	78 (62.9)	83 (66.9)	161 (64.9)
Black	31 (25.0)	27 (21.8)	58 (23.4)
Other	15 (12.1)	14 (11.3)	29 (11.7)
Duration of present episode, N (%)			
1 to 6 mo	48 (38.7)	44 (35.5)	92 (37.1)
7 to 12 mo	29 (23.4)	31 (25.0)	60 (24.2)
> 12 mo	47 (37.9)	49 (39.5)	96 (38.7)
Age at first episode of depression, y			
Mean (SD)	28.2 (12.2)	27.5 (11.6)	27.8 (11.9)
Median	25	25	25
Course of illness, N (%)			
First episode	31 (25.0)	26 (21.0)	57 (23.0)
Chronic (full criteria for MDD met)	12 (9.7)	8 (6.5)	20 (8.1)
Recurrent with partial recovery	10 (8.1)	15 (12.1)	25 (10.1)
Recurrent with full recovery	71 (57.3)	75 (60.5)	146 (58.9)
No comorbid anxiety disorder, N (%)	116 (93.5)	121 (97.6)	237 (95.6)

^aExcludes patients who received at least 1 dose of study drug but did not have a postbaseline assessment within 3 days of study drug administration.
Abbreviations: ER = extended-release, MDD = major depressive disorder, NA = not applicable.

HAM-D₂₈ total mean scores also showed significantly greater improvement in the gepirone-ER group compared with the placebo group at weeks 4, 6, and 8 ($p < .05$ for all), as did the mean HAM-D depressed mood (item 1) score at weeks 4 and 6 ($p = .004$ and $p = .009$, respectively). Gepirone-ER also significantly improved core symptoms of depression (Bech-6) compared with placebo at weeks 4, 6, and 8 ($p = .007$, $p = .006$, and $p = .016$, respectively). Analyses of observed cases produced the same pattern of statistical significance as the LOCF analyses. Table 2 summarizes baseline and mean change scores for HAM-D₁₇, MADRS, and HAM-D₂₈ total scores, and for HAM-D depressed mood (item 1), Bech-6, and CGI-S.

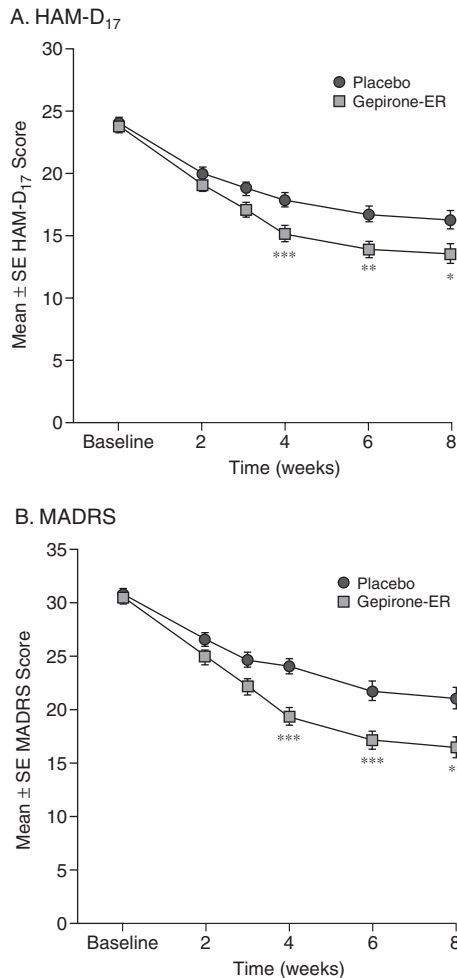
The primary efficacy analysis indicated that a significant ($p = .070$) treatment-by-center interaction was present. This was further explored via several methods: (1) visual inspection of each center's mean scores over time for patterns that diverged from the aggregated outcome; (2) alternative analyses of the HAM-D₁₇ total scores using type II (weighted) and type III (unweighted) analyses, and using baseline score as a covariate; and (3) alternative analyses dropping the 2 centers with the greatest and least drug-placebo difference. The results of these analyses were consistent: a significant drug versus placebo effect remained, including in the type III analysis at

weeks 6 and 8 when there was no significant center effect, and in the analysis trimming the 2 most extreme centers, which eliminated the significance of the interaction at all visits. Moreover, none of the additional analyses suggested any nonrandom variation in treatment effects between centers.

Responders and remitters. Response and remission rates measured by the HAM-D₁₇ (Figures 2A and 2B) and secondary outcome measures were consistent with mean score changes in demonstrating greater efficacy for gepirone-ER than for placebo. By week 4, the proportion of HAM-D₁₇ responders in the gepirone-ER group was significantly higher than in the placebo group (34% vs. 18%, $p = .008$), and this difference was sustained at weeks 6 and 8 (43% vs. 25%, $p = .007$ and 46% vs. 30%, $p = .014$, respectively). The proportion of HAM-D₂₈ responders in the gepirone-ER group was also significantly higher than in the placebo group at weeks 3, 4, 6, and 8 ($p < .05$ for all).

The proportion of MADRS responders was significantly higher in the gepirone-ER group versus the placebo group at weeks 3 (24% vs. 11%, $p = .011$), 4 (35% vs. 15%, $p < .001$), 6 (47% vs. 27%, $p = .003$), and 8 (51% vs. 32%, $p = .005$), as was the proportion of CGI-I responders at weeks 6 and 8 (50% vs. 34%, $p = .018$ and 48% vs. 35%, $p = .045$, respectively).

Figure 1. Scores on the (A) HAM-D₁₇ and (B) MADRS in MDD Patients Treated With Gepirone-ER (N = 116) or Placebo (N = 122) (LOCF)



*p < .05.

**p < .01.

***p < .005.

Abbreviations: ER = extended release, HAM-D₁₇ = Hamilton Rating Scale for Depression, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder.

The proportion of HAM-D₁₇ remitters (Figure 2B) was significantly greater for the gepirone-ER group compared with placebo at weeks 3, 4, 6, and 8 (p = .026, p = .036, p = .023, and p = .019, respectively), with 34.5% of patients receiving gepirone-ER versus 20.5% of patients receiving placebo classified as remitters (p = .019) at week 8.

Tolerability

Treatment-emergent AEs occurring in ≥ 5% of patients in the gepirone-ER group are shown in Table 3. The most frequent AEs (dizziness, nausea, and headache), all of which had a higher incidence in the gepirone-ER group,

Table 2. Gepirone-ER Efficacy Across Primary and Secondary Measures (LOCF)

Variable	Gepirone-ER (N = 116), Mean ± SE	Placebo (N = 122), Mean ± SE	p Value ^a
HAM-D ₁₇			
Baseline	23.9 ± 0.3	24.2 ± 0.3	
Mean change	-10.2 ± 0.8	-8.0 ± 0.7	.032
MADRS			
Baseline	30.3 ± 0.3	30.8 ± 0.3	
Mean change	-13.7 ± 1.0	-9.9 ± 1.0 ^b	.008
HAM-D ₂₈			
Baseline	33.9 ± 0.5	34.3 ± 0.5	
Mean change	-15.0 ± 1.1	-11.8 ± 1.0	.032
HAM-D depressed mood (item 1)			
Baseline	2.8 ± 0.1	2.9 ± 0.1	
Mean change	-1.2 ± 0.1	-1.0 ± 0.1	.101 ^c
Bech-6			
Baseline	12.6 ± 0.1	13.0 ± 0.1	
Mean change	-5.6 ± 0.4	-4.2 ± 0.4	.016
CGI-S			
Baseline	4.3 ± 0.1	4.3 ± 0.1	
Mean change	-1.3 ± 0.1	-0.9 ± 0.1 ^b	.015

^aChange from baseline to week 8 (reduced model without center interaction) gepirone-ER versus placebo, least squares means approach.

^bN = 121.

^cp < .005, change from baseline to weeks 4 and 6 (reduced model without center interaction) gepirone-ER versus placebo.

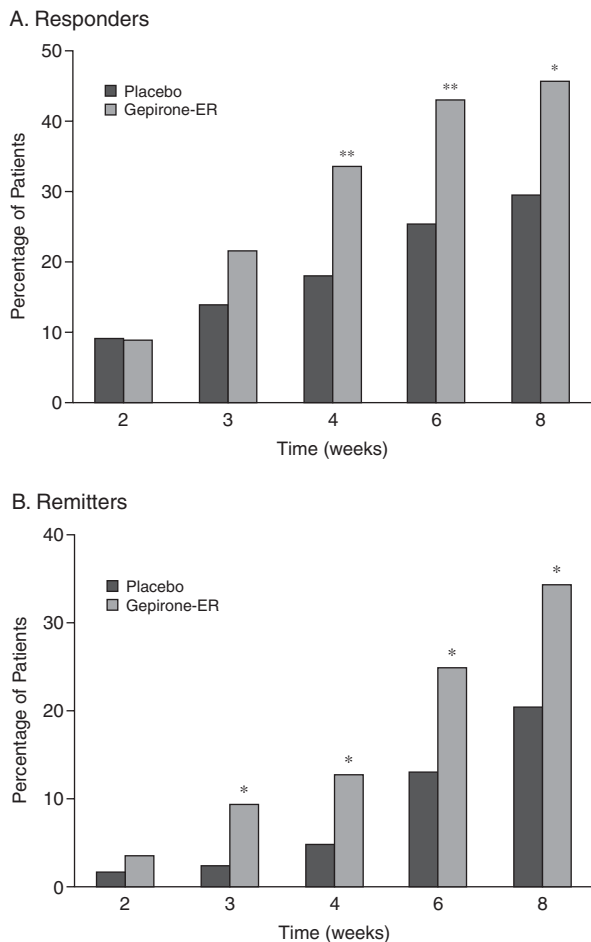
Abbreviations: Bech-6 = Bech Six-Item Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, ER = extended release, HAM-D = Hamilton Rating Scale for Depression, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale.

were rated as mild or moderate in at least 85% of patients in the placebo group and 95% of patients in the gepirone-ER group (Table 3). By week 6, the incidence of these AEs in the gepirone-ER group was comparable to that in the placebo group (gepirone-ER 2.9%, 0%, and 2.9% vs. placebo 3.6%, 4.5%, and 3.6% for dizziness, nausea, and headache, respectively).

Overall, treatment with gepirone-ER was well tolerated by the majority of patients. No deaths occurred during the study, and the incidences of severe AEs and serious AEs were low and comparable in both the gepirone-ER and placebo groups (severe AEs, 8.9% of patients in each group; serious AEs, 3.2% of patients in each group). One serious AE (suicidal ideation in a placebo-treated patient) was considered by the study investigator to be possibly related to study drug. One additional gepirone-ER patient experienced suicidal ideation/dissociative disorder, which was considered by the investigator unlikely to be related to study drug.

The percentages of patients discontinuing due to AEs or in whom the investigator indicated that study medication was stopped for an AE were 6.5% in the gepirone-ER group and 2.4% in the placebo group; all of the AEs resolved without additional treatment. The most common AEs leading to discontinuation were suicidal ideation (N = 3, 2 placebo and 1 gepirone ER), nausea (N = 2,

Figure 2. Proportion of Patients With MDD Treated With Gepirone-ER (N = 116) or Placebo (N = 122) Who (A) Responded to Therapy and (B) Remitted, as Assessed by the HAM-D₁₇ (LOCF)



*p < .05.

**p < .01.

Abbreviations: ER = extended release, HAM-D₁₇ = Hamilton Rating Scale for Depression, LOCF = last observation carried forward, MDD = major depressive disorder.

both in the gepirone-ER group), and dizziness (N = 2, both in the gepirone-ER group). All events resolved without sequelae.

At week 8, there was a small increase from baseline in mean (± SE) weight of 0.2 (± 1.9) kg and 0.3 (± 2.0) kg for the placebo and gepirone-ER groups, respectively. No clinically significant trends were observed for changes in vital signs, hematology, chemistry, or urinalysis parameters for either treatment group during the study.

DISCUSSION

The results of this study demonstrate the efficacy of gepirone-ER, a novel 5-HT_{1A} agonist, in reducing symp-

Table 3. Incidence of Adverse Events Occurring in at Least 5% of Patients in the Gepirone-ER Group, N (%)

Adverse Event	Gepirone-ER (N = 124)	Placebo (N = 124)
Dizziness	56 (45.2)	12 (9.7)
Nausea	45 (36.3)	16 (12.9)
Headache	30 (24.2)	20 (16.1)
Somnolence	13 (10.5)	6 (4.8)
Upper respiratory tract infection	12 (9.7)	11 (8.9)
Dry mouth	9 (7.3)	7 (5.6)
Increased appetite	9 (7.3)	6 (4.8)
Diarrhea	8 (6.5)	6 (4.8)
Fatigue	8 (6.5)	9 (7.3)
Dyspepsia	7 (5.6)	2 (1.6)
Insomnia	7 (5.6)	3 (2.4)
Palpitations	7 (5.6)	1 (0.8)

Abbreviation: ER = extended-release.

toms of depression and global illness severity in patients with moderate-to-severe MDD, relative to placebo. Depressed patients treated with gepirone-ER showed a significantly greater baseline-to-endpoint reduction in mean HAM-D₁₇ total score, the primary outcome measure, versus patients treated with placebo. Significant improvements in depressive symptoms were observable after 2 weeks of patients having received the minimum recommended dose of 60 mg/day, and improvements persisted to the week 8 study endpoint. It is possible that a more rapid dose escalation could have resulted in earlier improvement, but at the potential expense of increased side effects. Differences between the gepirone-ER and placebo groups on secondary efficacy assessments, which included mean baseline-to-endpoint changes on the HAM-D₂₈, HAM-D depressed mood (item 1), Bech-6, MADRS, and CGI-S, were all consistent with results seen with the primary endpoint, as was the observed cases analysis. The Bech-6 results indicate that gepirone was effective against core symptoms of MDD, whereas the HAM-D₂₈ results suggest efficacy against additional dimensions of the disorder. Response (at least a 50% reduction from baseline score on any postbaseline assessment on continuous measures, and/or a rating of 1 or 2 on the CGI-I) and HAM-D₁₇ remission rates were also significantly higher in patients in the active treatment group than in the group treated with placebo, providing evidence for a clinically meaningful antidepressant effect following treatment with gepirone-ER.

Overall, treatment with gepirone-ER was well tolerated. The most commonly reported treatment-emergent AEs were dizziness, nausea, and headache, which were predominantly mild or moderate in severity. There were 2 discontinuations attributed to nausea and 2 discontinuations attributed to dizziness. Dizziness refers to a collection of MedDRA coding terms describing mild, transitory, and vague sensations, including vertigo and light-headedness, that may be postural, positional, or exertional. In this study, dizziness tended to occur most frequently during initial dosing and up-titration.

The main limitation of this study was the lack of an active comparator, although the symptom reduction observed in this study was comparable in magnitude to that found in pivotal clinical trials of SSRIs and non-SSRI antidepressants.²⁴ Another limitation was that only patients 18 to 64 years of age were studied, limiting the ability to generalize the findings to younger and older patients. Patients with DSM-IV comorbid diagnoses (e.g., generalized anxiety disorder) were excluded, limiting the ability to generalize the findings to this population as well. A further limitation is that the 8-week duration of this acute study did not allow for the assessment of long-term efficacy or tolerability.

The results of this study confirm the findings of a previous, similarly designed, short-term, multicenter, double-blind, placebo-controlled trial¹⁸ and earlier studies with the immediate-release formulation¹³ that demonstrated the efficacy and favorable tolerability of gepirone-ER in the treatment of patients with MDD. These results, along with its novel mechanism of action, suggest that gepirone-ER should be a useful addition to the armamentarium of pharmacologic treatments for depression.

Drug names: citalopram (Celexa and others), fluoxetine (Prozac and others).

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