Gepirone Extended-Release: New Evidence for Efficacy in the Treatment of Major Depressive Disorder

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Objective: To assess the efficacy and tolerability of the 5-HT_{1A} agonist gepirone in extended-release formulation (gepirone-ER) versus placebo in patients with major depressive disorder.

Method: Patients aged 18 to 70 years were eligible if they satisfied DSM-IV criteria for moderate-to-severe major depressive disorder and had a baseline 17-item Hamilton Rating Scale for Depression (HAM-D-17) score ≥ 20. After a 4- to 7-day placebo washout period, patients were randomly assigned to receive either placebo (N = 106) or gepirone-ER (20–80 mg/day) (N = 103) for 56 days. Assessments were done at weeks 1–4, 6, and 8.

Results: Mean change from baseline in HAM-D-17 score within the intent-to-treat group (gepirone, N = 101; placebo, N = 103) was significantly greater with gepirone-ER than placebo at weeks 3 ($p = .013$) and 8 ($p = .018$). Significantly ($p < .05$) more patients receiving gepirone-ER than placebo were HAM-D-17 responders at weeks 3 (33.7% vs. 18.8%, respectively) and 4 (38.6% vs. 24.8%, respectively) and HAM-D-17 remitters at weeks 6 (24.8% vs. 13.9%, respectively) and 8 (28.7% vs. 14.9%, respectively). Mean change from baseline for HAM-D-25 total score was significantly ($p \leq .05$) greater with gepirone-ER at all assessments except week 6. The proportion of HAM-D-25 responders was significantly greater ($p \leq .05$) with gepirone-ER at weeks 3 and 8. Gepirone-ER was well tolerated: 9.8% of the gepirone-ER group and 2.8% of the placebo group discontinued due to adverse events. Common adverse events were considered mild and included dizziness, nausea, and insomnia. Gepirone-ER did not differ statistically compared with placebo in weight gain or sedation. Furthermore, preliminary evidence suggested that gepirone-ER may not be associated with sexual dysfunction. No serious adverse events occurred in gepirone-treated patients.

Conclusion: Gepirone-ER is effective for the short-term treatment of major depressive disorder and is well tolerated.

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Gepirone is a 5-HT_{1A} agonist in the azapirone class of compounds. It is one of several 5-HT_{1A} agonists brought to development in the mid-1980s and through the 1990s. The promise of the selective 5-HT_{1A} agonists stems from their interaction with the regulatory autoreceptors on the serotonin (5-HT) neuron. Through this interaction, these agents may help correct the dysregulation in serotonergic neurotransmission that may underlie anxiety and depression. In addition, they may spare other 5-HT receptor subtypes the overstimulation responsible for side effects common to other serotonergic agents. Despite the interest generated by this 5-HT_{1A} hypothesis over the years,[1–3] the 5-HT_{1A} agonists have only been approved by the U.S. Food and Drug Administration (FDA) as monotherapy for the treatment of anxiety. There are currently no FDA-approved 5-HT_{1A} compounds available for the treatment of depression.

5-HT is recognized as a major neurotransmitter involved in the regulation of mood, among many other functions. The 5-HT_{1A} receptor has been implicated in brain mechanisms related to anxiety and depression.[4–7] Recently, Stockmeier and colleagues[8] reported an increase in the number of 5-HT_{1A} receptors in the dorsal raphe nucleus in suicide victims but not in control patients. Positron emission tomography studies have reported that major depressive disorder (MDD) is associated with a reduction in 5-HT_{1A} receptor binding potential in the raphe nucleus and several cortical regions.[9–11]

Many drugs that demonstrate affinity for the 5-HT_{1A} receptor have been shown to exhibit antidepressant-like characteristics in preclinical tests.[12–15] Early clinical studies with both partial and full 5-HT_{1A} receptor agonists

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suggested that they were also effective in psychiatric patients with anxiety disorders and MDD.[3,16,17]

Gepirone exhibits significant affinity for the 5-HT_{1A} receptor,[18,19] at which it behaves as a partial agonist in vitro. However, the intrinsic activity of gepirone does vary in vivo according to the brain region studied.[20,21] Preclinical experiments have demonstrated that presynaptic 5-HT_{1A} autoreceptors in the raphe nuclei regulate the activity of serotonergic neurons.[5] Consequently, acute treatment with gepirone decreases the firing rate of serotonergic neurons and diminishes their release of 5-HT.[20,22] However, following prolonged treatment with gepirone, the 5-HT_{1A} autoreceptors become desensitized and the firing rate of serotonergic neurons recovers.[20] The recovery in 5-HT neuronal activity in combination with the postsynaptic agonist action of gepirone achieves a net increase in postsynaptic 5-HT neurotransmission.[6,23] Since gepirone stimulates 5-HT_{1A} specifically, the net result is a preferential activation of 5-HT_{1A} receptors.

The antidepressant effect of gepirone in immediate-release (IR) formulation has been evaluated in several phase 2 clinical trials in which evidence of efficacy was observed.[24–26] This formulation was found effective in a trial of atypical depression[27] and in a relapse prevention trial in patients with MDD.[28] Subsequently, a controlled study with an extended-release (ER) formulation of gepirone found evidence of efficacy[29] and, importantly, improved tolerability at higher doses.

The ER formulation of gepirone was developed to allow once-daily dosing and to reduce high peak plasma concentrations that may be associated with the intensity of common adverse events, such as light-headedness and nausea. The ER formulation eliminates the peak/trough fluctuations associated with the IR formulation and appears to lessen the severity of adverse events. As such, gepirone-ER can be administered at higher doses than the IR formulation, providing enhanced efficacy for more patients. The present study demonstrates the efficacy and tolerability of gepirone-ER at doses of 40 to 80 mg/day. In doing so, it provides important support for the 5-HT_{1A} hypothesis and the clinical utility of the 5-HT_{1A} agonists.

METHOD

This study was a 56-day, randomized, double-blind, placebo-controlled investigation of gepirone-ER in outpatients with moderate-to-severe MDD. The study was conducted at 5 U.S. sites in the period 1999–2000. This 8-week double-blind study was followed by a 44-week open-label extension phase available to all completers regardless of clinical response. The data presented in this article will focus on the acute-phase results only. The study protocol was approved by appropriate institutional review boards at each study site and was conducted according to Good Clinical Practice guidelines. All patients provided written informed consent prior to enrollment in the study.

Patient Selection

Patients at least 18 but not more than 70 years of age were eligible if they satisfied DSM-IV criteria for MDD and had a total score of at least 20 (at screening and baseline) on the 17-item Hamilton Rating Scale for Depression (HAM-D-17).[30] Clinically significant daily dysphoria as determined by the investigator was required to be present for the past 4 weeks.

Patients were excluded from the study if they had ≥ 20% decrease in the HAM-D-17 total score between baseline and screening. In addition, patients with a primary DSM-IV Axis I disorder other than depression or with an Axis II disorder were excluded, as were those with a history of seizure disorder, bipolar disorder, refractory depression, psychoactive substance disorder, or alcohol dependence. Patients with any clinically meaningful medical disorder or clinical laboratory abnormality and those currently in psychotherapy or at significant suicidal risk were not eligible. Patients who had received electroconvulsive therapy within the past year, monoamine oxidase inhibitors within 3 weeks, fluoxetine within 5 weeks, or other psychotropic drugs within 2 weeks were not eligible. Women who were pregnant or lactating at screening were excluded.

All diagnoses were made by the senior investigator at each study center. HAM-D, Montgomery-Asberg Depression Rating Scale (MADRS),[31] and Clinical Global Impressions-Improvement (CGI-I) and -Severity (CGI-S)[32] were rated by the investigator or by dedicated raters who were certified in advance by the sponsor. By protocol, every study center was to be limited to 2 raters. Raters performed all of the ratings on a particular patient, with only rare substitutions allowed for emergencies or planned absences.

Study Treatments

Eligible patients were randomly assigned to placebo or gepirone-ER treatment groups and entered a 4- to 7-day single-blind placebo washout period in which they were blind to treatment. Study medications were supplied as gepirone-ER 20-mg tablets and matching placebo. Patients who were randomly assigned to gepirone-ER initiated therapy at a dose of 20 mg once daily (1 gepirone-ER tablet and 1 placebo tablet). At day 4, the dose was increased to 2 gepirone-ER 20-mg tablets once daily. Increases to gepirone-ER, 60 mg, once daily (3 tablets) after day 7 and to 80 mg once daily (4 tablets) after day 14 were permitted according to therapeutic response and tolerability. A reduction in dose was permitted if gepirone-ER was poorly tolerated, but the minimum dose allowed was 40 mg/day. No concomitant psychotropic medications, including sleeping medications, were permitted during the

Table 1. Disposition of Patients by Treatment Group

Status	Gepirone-ER	Placebo	p Value[a]
Randomized, N	103	106	
Received treatment, N	102	106	
Intent-to-treat group, N	101	103	
Discontinued, N (%)	28 (27.5)	25 (23.6)	.530
Adverse events	10 (9.8)	3 (2.8)	.046
Lack of efficacy	4 (3.9)	4 (3.8)	1.000
Other reasons	14 (13.7)	18 (17.0)	.568
Completed, N (%)	74 (72.5)	81 (76.4)	

[a]p Values from Fisher exact test.
Abbreviation: ER = extended release.

study. All patients were instructed to take the medication in the morning with breakfast.

Study Assessments

Patients were administered the HAM-D, the MADRS, and the CGI-I and CGI-S at each study assessment. The first 21 items of the HAM-D were administered according to the Structured Interview Guide for the HAM-D.[33] In addition, 7 items measuring atypical symptoms (hyperphagia, hypersomnia, and retardation; HAM-D-25) and 3 items measuring feelings of helplessness, hopelessness, and worthlessness (HAM-D-28) were administered. By protocol, the primary efficacy variable was the HAM-D-17 total score change from baseline to endpoint. Changes from baseline in the MADRS total score, CGI-S, and HAM-D-21, -25, and -28 total scores were analyzed as secondary parameters.

Assessments at the screening visit included complete medical and psychiatric histories, a physical examination, routine laboratory tests, urinalysis, electrocardiogram (ECG), and the HAM-D. A serum pregnancy test was performed for women. At the baseline evaluation, vital signs and a blood sample were obtained from patients, and the HAM-D, MADRS, and CGI were scored. Vital signs were recorded and the HAM-D, MADRS, and CGI were scored at weeks 1, 2, 3, 4, 6, and 8. At the final evaluation, all patients underwent a complete physical examination, including routine laboratory investigations and an ECG. At each visit, patients were questioned about adverse events, and all new complaints and symptoms were recorded. The Derogatis Interview for Sexual Function–Self-Report (DISF-SR)[34] was administered at baseline and endpoint. At the conclusion of the 8-week acute phase of the study, patients who did not enroll in the long-term 44-week extension phase were given a 7-day follow-up evaluation to assess for continuing or new adverse events. At 30 days posttreatment, patients were assessed for new serious adverse events or death.

Data Analysis

Efficacy data were analyzed using the intent-to-treat (ITT) population, which included all randomized patients who received at least 1 dose of trial medication and had at least 1 postbaseline assessment of efficacy. Data were analyzed for the last-observation-carried-forward (LOCF) dataset. Change from baseline to each treatment visit was evaluated by least-squares analysis of variance (ANOVA) using treatment as the only effect, as there was no treatment-by-center interaction at any timepoint for the primary efficacy parameter. The percentage of patients who met response criteria on the HAM-D (≥ 50% decrease from baseline) or CGI-I ("much" or "very much" improved from baseline) or the remission criterion for the HAM-D scale (total score ≤ 7) was assessed with the Cochran-Mantel-Haenszel test, adjusting for center. Changes from baseline for the CGI-S and CGI-I, the HAM-D depressed mood item (item 1), and the Bech 6-item core depression factor[35] (calculated as the sum of HAM-D items 1 [depressed mood], 2 [work and activities], 9 [somatic symptoms, general], 10 [feelings of guilt], 12 [anxiety, psychic], and 16 [retardation]) were tested with ANOVA, with treatment and center as factors. All statistical tests were 2-sided at an alpha level ≤ .05.

Table 2. Baseline Demographics and Clinical Characteristics[a]

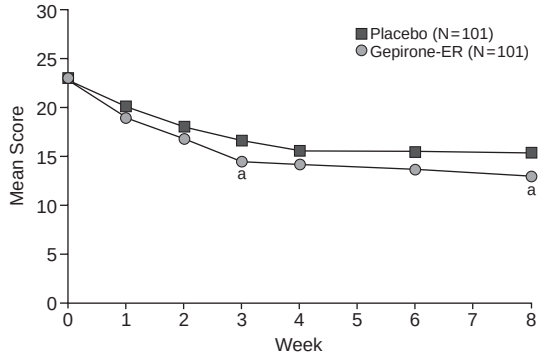
Characteristic	Gepirone-ER (N = 102)	Placebo (N = 106)	p Value[b]
Age, y			
Mean (SD)	39.5 (11.3)	40.6 (11.7)	.486
Range	18–63	19–69	
Female:male ratio	69:33	57:49	.041
Race			.520
Asian	1 (1.0)	3 (2.8)	
Black	8 (7.8)	11 (10.4)	
White	74 (72.5)	78 (73.6)	
Other	19 (18.6)	14 (13.2)	
Duration of present episode			.282
1–6 mo	32 (31.4)	23 (21.7)	
7–12 mo	16 (15.7)	20 (18.9)	
> 12 mo	54 (52.9)	63 (59.4)	
Prior antidepressant treatment	48 (47.1)	35 (33.0)	.226
Course of illness			.131
First episode	29 (28.4)	39 (36.8)	
Chronic	13 (12.7)	19 (17.9)	
Recurrent with partial recovery	25 (24.5)	14 (13.2)	
Recurrent with full recovery	35 (34.3)	34 (32.1)	

[a]Values shown as N (%) unless otherwise noted.
[b]p Values from analysis of variance for continuous variables and from chi-square test for categorical variables.
Abbreviation: ER = extended release.

RESULTS

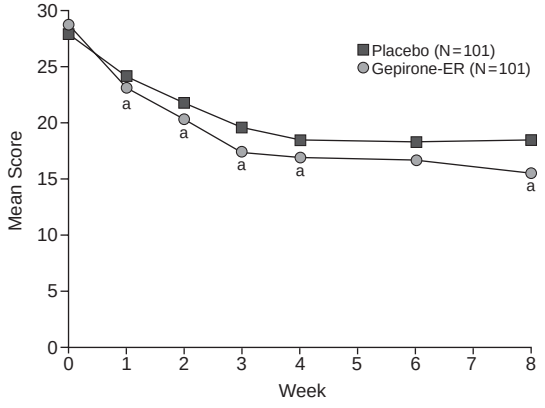
Two hundred nine patients were randomized, 103 to gepirone-ER and 106 to placebo (Table 1). One patient did not receive trial medication and was excluded from the safety analysis. Four patients had no baseline or postbaseline efficacy assessments and were excluded from the ITT group. Thus, the ITT population consisted of 101 patients in the gepirone-ER group and 103 in the placebo group. For the efficacy analysis, 2 placebo-treated patients were excluded from the ITT population because the postbaseline efficacy assessments occurred more than 3

Figure 1. HAM-D-17 Scores From Baseline to Endpoint (LOCF)



[a]Significant at p ≤ .05 by least-squares means analysis of variance.
Abbreviations: ER = extended release, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, LOCF = last observation carried forward.

Figure 2. HAM-D-25 Scores From Baseline to Endpoint (LOCF)



[a]Significant at p ≤ .05 by least-squares means analysis of variance.
Abbreviations: ER = extended release, HAM-D-25 = 25-item Hamilton Rating Scale for Depression, LOCF = last observation carried forward.

days after their last day of medication. No important differences were noted between treatment groups at baseline (Table 2). The mean ± SD dose of gepirone-ER for the ITT group was 70.3 ± 14.9 mg/day.

Efficacy

Continuous measures. A significant effect in favor of gepirone-ER was observed for the mean change from baseline to endpoint in the HAM-D-17 total score at weeks 3 (p = .013) and 8 (p = .018) (Figure 1). The effect size at endpoint was 2.29 HAM-D-17 points (least-squares means ANOVA estimates).

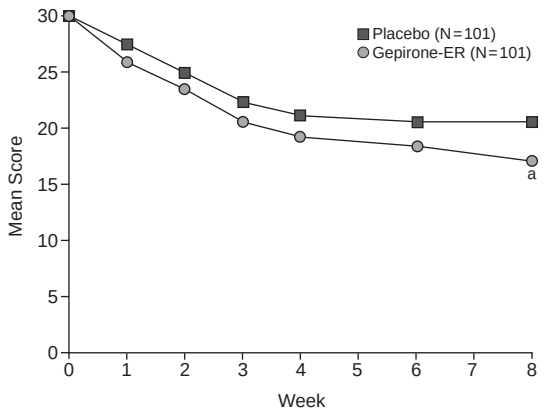
On the HAM-D-25 total score, patients in the gepirone-ER group showed a significantly greater change from baseline than did patients in the placebo group (p ≤ .05;

Table 3. Gepirone-ER Efficacy Across Primary and Secondary Parameters (LOCF)

Efficacy Parameter	Baseline Score Mean ± SD	Change From Baseline to Endpoint Mean ± SD	p Value[a]
HAM-D-17			
Gepirone	22.73 ± 2.45	9.77 ± 7.11	.018
Placebo	22.75 ± 2.51	7.43 ± 6.64	
HAM-D-25			
Gepirone	28.33 ± 3.88	12.49 ± 9.16	.007
Placebo	27.75 ± 3.84	9.07 ± 8.55	
HAM-D depressed mood item			
Gepirone	2.73 ± 0.47	1.24 ± 0.96	.005
Placebo	2.72 ± 0.53	0.84 ± 0.98	
Bech-6			
Gepirone	12.50 ± 1.63	5.51 ± 4.11	.007
Placebo	12.17 ± 1.51	3.97 ± 3.93	
MADRS			
Gepirone	29.50 ± 4.56	12.28 ± 9.38	.024
Placebo	29.89 ± 4.84	9.22 ± 9.68	
CGI-S change			
Gepirone	4.35 ± 0.54	1.28 ± 1.15	.016
Placebo	4.19 ± 0.42	0.88 ± 1.13	

[a]Based on least-squares means analysis of variance, with treatment and center as factors.
Abbreviations: Bech-6 = Bech 6-item core depression factor, CGI-S = Clinical Global Impressions-Severity of Illness, ER = extended release, HAM-D = Hamilton Rating Scale for Depression, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale.

Figure 3. MADRS Scores From Baseline to Endpoint (LOCF)

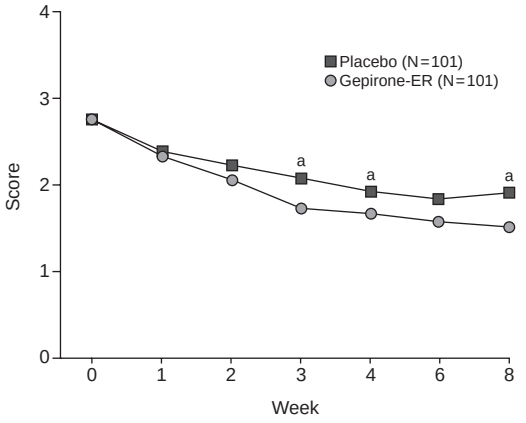


[a]Significant at p ≤ .05 by least-squares means analysis of variance.
Abbreviations: ER = extended release, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale.

Figure 2, Table 3) at all timepoints except week 6. On the MADRS, a significant effect for gepirone-ER was seen at endpoint (p ≤ .05; Figure 3, Table 3). A repeated-measures analysis of change in HAM-D-17, HAM-D-25, and MADRS scores from baseline showed a statistically significant difference in favor of patients receiving gepirone-ER (p < .05).

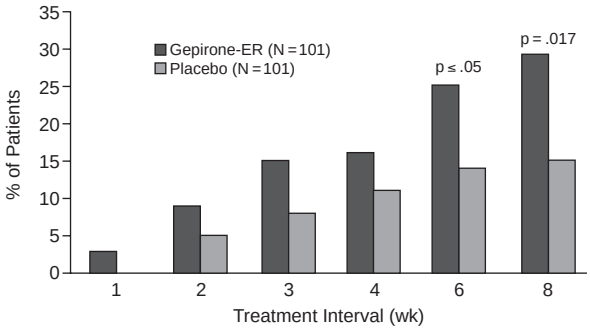
HAM-D item 1 (depressed mood) (Figure 4) demonstrates that gepirone-ER has an early and significant effect

Figure 4. HAM-D Item 1 (depressed mood) Scores From Baseline to Endpoint (LOCF)



[a]Significant at p ≤ .05 by least-squares means analysis of variance.
Abbreviations: ER = extended release, HAM-D = Hamilton Rating Scale for Depression, LOCF = last observation carried forward.

Figure 5. Percentage of Patients Achieving a Remission (HAM-D-17 total score ≤ 7) (LOCF)



Abbreviations: ER = extended release, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, LOCF = last observation carried forward.

Table 4. Potency of Gepirone-ER in Producing Clinical Response and Remission at Endpoint (LOCF; all patients)

Parameter	N	%	p Value
HAM-D-17 responders			
Gepirone	44	43.6	.059
Placebo	31	30.7	
HAM-D-17 remitters			
Gepirone	29	28.7	.017
Placebo	15	14.9	
HAM-D-25 responders			
Gepirone	46	45.5	.014
Placebo	29	28.7	
CGI responders			
Gepirone	44	43.6	.251
Placebo	36	35.6	

Abbreviations: CGI = Clinical Global Impressions scale, ER = extended release, HAM-D = Hamilton Rating Scale for Depression, LOCF = last observation carried forward.

on depressed mood. Item 1 (depressed mood) change from baseline was significantly greater for patients treated with gepirone-ER than for patients receiving placebo at weeks 3 (p = .007), 4 (p = .042), and 8 (p = .005).

Table 3 presents the effect of gepirone-ER on the primary efficacy parameter and several secondary parameters. The Bech 6-item factor, a measure of core depressive symptoms, was positively affected by gepirone-ER from week 2 onward (data not shown), with a moderate effect size at endpoint (p = .007, Table 3). The effect of gepirone-ER in reducing disease severity as measured by the CGI-S showed a significant effect at all timepoints (only the endpoint data [p = .016] are shown in Table 3).

Responders and remitters. Table 4 presents data on categorical measures important in ascertaining the impact that gepirone-ER therapy may have in the clinic. Responders are defined as those achieving at least a 50% reduction from baseline in HAM-D-17 or HAM-D-25 total scores. The percentage of HAM-D-17 responders was significantly (p < .05) higher in the gepirone-ER group than in the placebo group at week 3 (33.7% vs. 18.8%, respectively) and week 4 (38.6% vs. 24.8%, respectively). At week 8, the proportion of HAM-D-17 responders was 43.6% in the gepirone-ER group and 30.7% in the placebo group (p = .059; Table 4). A larger percentage of patients in the gepirone-ER group than in the placebo group responded to therapy at week 3 (36.6% vs. 21.8%, respectively; p ≤ .05) and endpoint (45.5% vs. 28.7%; p = .014) on the HAM-D-25 (Table 4). The percentage of CGI responders (patients achieving a rating of "much improved" or "very much improved") was higher in the gepirone-ER group (43.6%) than in the placebo group (35.6%) at endpoint, though this difference was not statistically significant (Table 4).

The number of patients achieving remission (HAM-D-17 score ≤ 7) was significantly greater (p ≤ .05) in the gepirone-ER group than in the placebo group at week 6 (24.8% vs. 13.9%, respectively) and week 8 (28.7% vs. 14.9%, respectively) (Figure 5). At endpoint (Table 4), the percentage of remitters was nearly twice as great in the gepirone-ER group as in the placebo group (28.7% vs. 14.9%; p = .017).

Tolerability

All adverse events as described by the investigators were coded using a modified version of COSTART-5. Overall, 83 patients (81.4%) receiving gepirone-ER and 59 patients (55.7%) receiving placebo experienced at least 1 drug-related (investigator-attributed) adverse event. The incidence of adverse events occurring in at least 5% of patients and with twice the frequency in the gepirone group as in the placebo group is listed in Table 5. Ten patients (9.8%) on treatment with gepirone-ER and 3 (2.8%) on

Table 5. Incidence of Adverse Events Occurring in at Least 5% of Patients in the Gepirone-ER Group and at Least Twice the Frequency of the Placebo Group (%)

Adverse Event	Gepirone-ER (N = 102)	Placebo (N = 106)	p Value[a]
Dizziness	52.0	11.3	< .001
Nausea	35.3	14.2	< .001
Insomnia	19.6	6.6	.007
Nervousness	10.8	5.7	.211
Vomiting	9.8	4.7	.186
Dry mouth	9.8	3.8	.101
Abdominal pain	9.8	1.9	.017
Dyspepsia	7.8	3.8	.245
Paresthesia	5.9	1.9	.164

[a]p Value from Fisher exact test.
Abbreviation: ER = extended release.

treatment with placebo discontinued therapy because of adverse events. Within the gepirone-ER group, 3 patients (2.9%) discontinued due to dizziness, and 2 patients (2.0%) discontinued due to nausea. Tachycardia, vomiting, stupor, nervousness, and agitation each led to the discontinuation of 1 gepirone-ER subject (1.0%). No deaths or serious adverse events were reported with gepirone-ER. Four patients on treatment with placebo (2 during screening and 2 during the double-blind phase of treatment) had serious adverse events (suicide attempt, myocardial infarct, injuries from a motor-vehicle accident, and torn cartilage of knee).

No clinically meaningful changes in laboratory parameters were observed in either treatment group. No clinically meaningful changes in physical examination, vital signs, or ECG parameters were observed in either treatment group.

Sedation was not prevalent in gepirone-ER–treated patients (8.8% of the gepirone-ER group vs. 13.2% of the placebo group complained of somnolence [NS]). Clinically significant weight gain was not associated with gepirone-ER: the mean ± SD change from baseline to week 8 was 0.6 ± 2.12 kg (1.3 ± 4.71 lb) for the gepirone-ER group, while that for the placebo group was 0.0 ± 1.88 kg (0.0 ± 4.18 lb) (NS). Weight change was not listed as a reason for discontinuation in either group.

Sexual Dysfunction

Among patients providing complete data on the DISF-SR, sexual functioning tended to improve from baseline to endpoint in the gepirone-treated patients. In women, mean ± SD DISF-SR total scores were 39.7 ± 28.8 at baseline (N = 53) and 53.0 ± 37.4 at endpoint (N = 44) for gepirone-ER compared with 38.0 ± 29.2 at baseline (N = 52) and 38.0 ± 27.9 at endpoint (N = 42) for placebo ($p < .05$). In men, mean DISF-SR total scores were 46.8 ± 35.9 at baseline (N = 23) and 59.3 ± 40.2 at endpoint (N = 22) for gepirone-ER compared with 56.1 ± 32.0 at baseline (N = 36) and 58.2 ± 30.9 at endpoint (N = 35) for placebo (NS). There were very few spontaneous reports of sexual problems in patients in both groups: 1 gepirone-ER–treated patient and 5 placebo-treated patients complained of decreased libido/abnormal sexual function.

DISCUSSION

Our study demonstrates that gepirone-ER, a 5-HT_{1A} agonist, is effective and well tolerated in patients with MDD. The relatively large percentage of patients who experienced *remission* of symptoms when treated with gepirone-ER versus placebo suggests that gepirone-ER is tolerated by outpatients long enough to achieve this clinically relevant effect.

In addition, the current results help to further characterize gepirone-ER in depressed outpatients, providing practical guidance for its use in the clinic. Gepirone-ER appears to be an antidepressant that may not be associated with clinically significant sedation, weight gain, or sexual dysfunction.

The study found a relatively high incidence of COSTART-5–coded "dizziness" among gepirone-ER–treated patients. Patients and investigators use several terms to describe a mild, transitory, and vague sensation of light-headedness, all of which code to the COSTART-5 term "dizziness." Among the 52% of gepirone-treated patients who reported some light-headedness or dizziness during the trial, 91% described the effect as mild to moderate, and only 3 gepirone-ER–treated patients discontinued because of light-headedness/dizziness. There were no discontinuations due to orthostatic hypotension (1 gepirone-ER patient discontinued secondary to tachycardia), and vital signs and ECG parameters were not significantly affected by gepirone-ER. It appears likely that the light-headedness/dizziness reported by patients is not of cardiovascular origin but is a mild central nervous system effect expected of this class of drugs. There were no falls among the gepirone-ER–treated patients, and the 2 accidental injuries (as compared with 6 in the placebo group) were due to electrical shock and back strain, with neither patient complaining of light-headedness/dizziness. In conclusion, it is clear that while light-headedness/dizziness is prevalent among patients treated with gepirone-ER, 40 to 80 mg/day, it remains a mild side effect that does not cause significant distress or risk of injury to the typical outpatient. Importantly, dizziness is not a major reason for early discontinuation of therapy, although caution may be needed in patients who are at high risk for falls.

Despite the large number of consistent positive results in this trial, a few caveats must be pointed out. First, the lack of an active comparator in this trial makes it difficult to compare the strength of effect of gepirone-ER with that of marketed compounds. Comparison of effect sizes gives some indication that gepirone-ER can produce an effect similar to that of the selective serotonin reuptake inhibi-

tors (SSRIs). With respect to HAM-D-17 mean change from baseline, gepirone-ER displayed an effect size at endpoint of 2.29 HAM-D-17 points, consistent with that of the SSRIs. The effect sizes for gepirone in Table 3 are of the same magnitude as those found in a recent reanalysis of several clinical trials examining the effects of fluoxetine and tricyclics on several HAM-D components.[36]

Second, it is a shortcoming of this trial that the CGI response results are inconsistent with the HAM-D and the MADRS response results. The CGI response rate for placebo was high (35.6%) at endpoint, possibly explaining the lack of effect seen on this scale.

In summary, the results of this clinical trial provide consistent and positive evidence of an antidepressant effect for the 5-HT_{1A} agonist gepirone-ER. In addition, this study provided evidence of effects on core symptoms of depression, including lethargy and anxiety. The majority of patients were able to tolerate doses of 40 mg to 80 mg daily, and no serious adverse events or clinically relevant safety issues were observed. Gepirone-ER appears safe and effective in the short-term treatment of MDD and appears to be free of common side effects (e.g., weight gain, sexual dysfunction, and sedation) seen with SSRIs.

Drug name: fluoxetine (Prozac and others).

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