Evidence for Efficacy and Tolerability of Vilazodone in the Treatment of Major Depressive Disorder: A Randomized, Double-Blind, Placebo-Controlled Trial

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Objective: The efficacy and tolerability of vilazodone, a combined selective serotonin reuptake inhibitor and partial 5-hydroxytryptamine-1A (5-HT_{1A}) receptor agonist, were evaluated in adult patients with major depressive disorder (MDD).

Method: This was a randomized, double-blind, placebo-controlled trial conducted from February 2006 to May 2007. Patients aged 18 through 65 years with MDD (DSM-IV criteria) and a baseline 17-item Hamilton Rating Scale for Depression (HAM-D-17) score of ≥ 22 were randomly assigned to vilazodone or placebo for 8 weeks. Vilazodone was titrated from 10 mg to 40 mg once a day over 2 weeks. Efficacy was assessed by mean change from baseline to week 8 on the Montgomery-Asberg Depression Rating Scale (MADRS), HAM-D-17, and Hamilton Rating Scale for Anxiety. Response rates were determined at week 8 for the MADRS, HAM-D-17, and Clinical Global Impressions-Severity of Illness (CGI-S) and -Improvement (CGI-I) scales. Data were analyzed using a modified last-observation-carried-forward method in the intention-to-treat (ITT) sample. The Arizona Sexual Experience Scale (ASEX) was also measured at baseline and week 8.

Results: Of 410 randomly assigned patients, 198 receiving vilazodone and 199 receiving placebo were included in the ITT population. The mean changes in MADRS and HAM-D-17 total scores from baseline to week 8 were significantly ($p = .001$ and $p = .022$, respectively) greater with vilazodone than with placebo. Significant ($p < .05$) improvements in MADRS and HAM-D-17 scores were noted at week 1, the earliest time point measured. Response rates were significantly higher with vilazodone than with placebo on the MADRS ($p = .007$), HAM-D-17 ($p = .011$), and CGI-I ($p = .001$). Treatment-emergent adverse events with vilazodone included diarrhea, nausea, and somnolence; most adverse events were of mild or moderate intensity. There were no clinically significant differences for either gender in ASEX scores at end of treatment.

Conclusions: Vilazodone is effective for the treatment of MDD in adults, with symptom relief starting at 1 week, and is well tolerated at a dose of 40 mg/day.

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Major depressive disorder (MDD) is a chronic, often debilitating illness that contributes to functional impairment and increases morbidity and mortality.[1,2] The National Comorbidity Survey Replication reported that the 12-month prevalence of MDD in the United States was 6.7% in 2003, and 80% of respondents were categorized as having moderate or severe depression.[1] Despite the burden of MDD, many patients remain untreated or are inadequately treated after diagnosis.[1,3–6] In fact, little evidence is available to guide the initial choice of therapy, and discontinuations and switching prescriptions are common.[7]

Limitations of current antidepressant treatments include wide interindividual variability in response, difficulty in maintaining remission, delayed onset of effect, safety concerns, and intolerable side effects.[6,8] Adverse events are the primary reason for premature discontinuation of antidepressant medication in one third of patients, especially early in treatment.[7,9] Patients who prematurely discontinue treatment appear to be at greater risk for relapse and recurrence, as well as for poor long-term outcomes.[10] The results from the Sequenced Treatment

Alternatives to Relieve Depression (STAR*D) study indicated that antidepressants exhibit similar efficacy in treating the overall population of depressed patients, although there are differences in tolerability.[11] This study also revealed that augmentation with a second drug is a useful adjunct to treatment.[12,13] Thus, there is need for alternative antidepressants or treatment regimens that offer improved predictability of response and better tolerability, including less sexual dysfunction, than existing agents. Novel treatments are needed, offering more rapid onset of action than currently available antidepressants, which often require weeks to achieve a response and remission.[14]

Vilazodone, the first of a new class of antidepressants, the indolalkylamines, is in development for the treatment of MDD and combines properties of a selective serotonin reuptake inhibitor (SSRI) with 5-hydroxytryptamine-1A (5-HT_{1A}) partial agonist activity.[15] Drugs active at the 5-HT_{1A} receptor are approved for the treatment of anxiety, have been shown to have antidepressant activity, and may be useful for augmenting the response to other antidepressants.[16–18] On the basis of its mechanism of action, vilazodone offers potential utility for a more rapid antidepressant effect and an adverse event profile characterized by good tolerability and a lower risk of sexual dysfunction than current therapies. The primary objective of this phase 3 study was to evaluate the efficacy and tolerability of vilazodone for the treatment of adult patients with MDD.

METHOD

The study involved 10 investigative sites comprising 18 main and satellite sites in the United States and was conducted from February 2006 to May 2007 in accordance with Good Clinical Practices and the International Conference on Harmonisation guidelines. The study protocol received prior approval by appropriate institutional review boards, and all patients provided written informed consent prior to participation in the study.

Study Design

This was a randomized, double-blind, placebo-controlled, multicenter, 8-week trial designed with 3 study periods: washout, screening, and an 8-week, double-blind, treatment period. The washout period allowed patients to discontinue their current antidepressant medications and other medications prohibited by the protocol. During the screening period, patients were evaluated to determine if they satisfied inclusion and exclusion criteria. Following the washout and screening periods, eligible patients were randomly assigned to receive either vilazodone or placebo in a 1:1 ratio. Patients randomly assigned to vilazodone received 10 mg once daily (q.d.) for 7 days, 20 mg q.d. for the next 7 days, and 40 mg q.d. for the duration of the study. Patients who experienced side effects at 20 mg q.d. could remain at that dose. A decrease to 20 mg q.d. was allowed for patients who experienced intolerable side effects at 40 mg q.d., and these patients remained at the 20 mg q.d. dose for the remainder of the study. During the dose-titration phase, patients were provided with tablets containing 10 mg of vilazodone or matching placebo. During the first week they took 1 tablet of vilazodone or 1 of placebo, and, during the second week, they took 2 vilazodone tablets or 2 of placebo. Thereafter, patients were given tablets containing vilazodone 20 mg or matching placebo and took 2 tablets of one or the other.

Patient Selection

Adult patients, 18 through 65 years of age, were eligible if they had a *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR)[19] diagnosis of MDD, single or recurrent episode, and the duration of their current major depressive episode was at least 4 weeks and no more than 2 years. Patients were required to have a 17-item Hamilton Rating Scale for Depression (HAM-D-17) score ≥ 22 and a HAM-D-17 item 1 (depressed mood) score ≥ 2.[20]

Patients were excluded if they had a current Axis I disorder other than MDD or had one within 6 months of the screening visit (with the exception of generalized anxiety disorder and social phobia or simple phobia, which were allowed); a history of schizophrenia, schizoaffective disorder, or bipolar I or II disorder; substance abuse within 3 months of or substance dependence within 6 months of the screening visit; MDD with psychotic features, postpartum onset, or seasonal pattern; or current psychotherapy or had received psychotherapy within 12 weeks of the screening visit. Also excluded were patients who posed a serious suicidal or homicidal risk or who had made a suicide attempt; those who had an inadequate response to at least 2 consecutive antidepressants from different classes given at adequate doses for an adequate duration for the current episode; patients who received electroconvulsive therapy; patients who were taking psychotropic drugs and/or migraine medications with a serotonergic mechanism of action; patients with known hypersensitivity to SSRIs or 5-HT_{1A} agonists; patients with a history of clinically significant cardiac, renal, neurologic, cerebrovascular, hepatic, hematologic, metabolic, or pulmonary disease; patients with Sicca syndrome; or patients who had taken an investigational drug or participated in an investigational drug trial within the past 30 days.

Efficacy Measures

Treatment response was assessed at weeks 1, 2, 4, 6, and 8. All efficacy assessments were made by trained, qualified raters. The primary efficacy endpoint was mean change from baseline to week 8 (end of treatment) on the Montgomery-Asberg Depression Rating Scale (MADRS)

total score.[21] Mean change from baseline to week 8 was also assessed for the HAM-D-17 total score, Hamilton Rating Scale for Anxiety (HAM-A) total score,[22] Clinical Global Impressions-Severity of Illness (CGI-S) and -Improvement (CGI-I) scores.[23] Secondary efficacy endpoints were response, defined as ≥ 50% decrease in total score from baseline to week 8 on the MADRS and HAM-D-17 total scores, or a score of 1 or 2 on the CGI-I at week 8.

Safety and Tolerability

Safety assessments included routine clinical laboratory tests, physical examination, vital signs, body weight, 12-lead electrocardiogram (ECG), and adverse events, including premature discontinuation due to adverse events. Adverse events were obtained from patient reports, investigator questioning and observations, and clinical laboratory testing and were rated by type, severity, and relationship to treatment. Adverse events were recorded as serious adverse events, if applicable. The Medical Dictionary for Regulatory Activities (MedDRA)[24] was utilized to standardize adverse event terms. The Arizona Sexual Experience Scale (ASEX), a 5-item scale used to assess sexual dysfunction, was administered at each visit.[25] The ASEX total score ranges from 5 to 30, with higher scores indicating more severe sexual dysfunction.

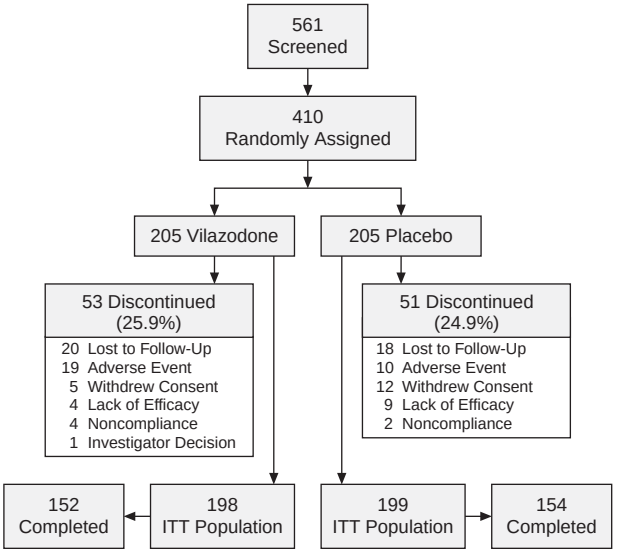
Statistical Analysis

The intention-to-treat (ITT) population included all randomly assigned patients who took study medication and had a postbaseline efficacy measurement within 7 days of the last dose of study medication. The modified ITT population (completer analysis) included all patients in the ITT population who completed the MADRS at week 8. The safety population included all randomly assigned patients who took a dose of study medication.

Sample size was calculated to be 408 patients randomly assigned 1:1 to vilazodone or placebo, which provided greater than 90% power at $\alpha = .05$, assuming a difference of at least 4 points (standard deviation ± 10) between vilazodone and placebo treatment groups for the mean change from baseline to week 8 in the MADRS total score.

For efficacy comparisons, the ITT population with last-observation-carried-forward (LOCF) method was used. For the primary efficacy analysis, an analysis-of-covariance (ANCOVA) model was applied, with terms for treatment and center, and adjusted for baseline MADRS score. Similar models were used for comparing response on secondary efficacy endpoints on the HAM-D, HAM-A, CGI-I, and CGI-S. Response and remission rates were compared with the Cochran-Mantel-Haenszel (CMH) test, stratified by study center. For safety analyses, descriptive statistics and categorical methods were used to summarize safety variables by treatment group. All statistical comparisons were 2-sided and considered significant at $p < .05$.

Figure 1. Disposition of Adult Patients With Major Depressive Disorder Who Were Randomly Assigned To Either Vilazodone or Placebo



Abbreviation: ITT = intention to treat.

RESULTS

Patient Disposition

Five hundred sixty-one patients were screened and 410 were randomly assigned to double-blind treatment with vilazodone (N = 205) or placebo (N = 205). The safety population comprised 409 patients; 205 received vilazodone and 204 received placebo. The ITT population included 198 vilazodone-treated patients and 199 placebo-treated patients. Five patients in each group did not receive study drug, and 2 patients in the vilazodone group and 1 in the placebo group did not have a postbaseline efficacy assessment within 7 days of last dose of study medication. Patient disposition is shown in Figure 1. At baseline, the 2 treatment groups were similar with respect to demographic and clinical characteristics, although more patients in the vilazodone group had a current episode of depression > 12 months duration (Table 1). Similar numbers of patients in the vilazodone group (25.9%) and in the placebo group (24.9%) discontinued the study prematurely.

Of 152 patients in the vilazodone group who completed the 8-week study, 139 (91.4%) completed the dosage titration at 2 weeks and were maintained on vilazodone 40 mg/day. Five study completers (3.3%) continued with the 20 mg/day dose of vilazodone after the second week, 3 study completers (2.0%) continued at 20 mg/day of vilazodone through week 4 and then

Table 1. Baseline Demographic and Clinical Characteristics of Adult Patients With Major Depressive Disorder in the Safety Population Who Were Randomly Assigned to Either Vilazodone or Placebo

Characteristic	Vilazodone, N = 205	Placebo, N = 204
Female gender, n (%)	127 (62.0)	130 63.7)
Race, n (%)		
White[a]	181 (88.3)	157 (77.0)
Black/African American[a]	20 (9.7)	36 (17.6)
Other	4 (2.0)	11 (5.4)
Age, mean (SD), y	40.0 (12.1)	39.8 (12.7)
Range, y	18–63	18–65
Age at onset of depression, mean (SD), y	33.4 (13.4)	31.9 (13.8)
First episode of depression, n (%)	72 (35.1)	76 (37.3)
Duration of current episode, n (%)		
1–6 mo	107 (52.2)	110 (53.9)
> 6–12 mo	68 (33.2)	78 (38.2)
> 12 mo[a]	30 (14.6)	16 (7.9)
Severity of current episode, n (%)		
Moderate	147 (71.7)	147 (72.1)
Severe	58 (28.3)	57 (27.9)
Melancholia, n (%)	99 (48.3)	89 (43.6)
Recurrent depression, n (%)	133 (64.9)	128 (62.7)
GAD or SAD within past 6 mo, n (%)	13 (6.3)	15 (7.4)

[a]$p < .05$, Fisher exact test.
Abbreviations: GAD = generalized anxiety disorder, SAD = social anxiety disorder.

received 40 mg/day for the remainder of the study, and 4 completers (2.6%) in the vilazodone group had a decrease in dose from 40 mg/day to 20 mg/day sometime during the study.

Efficacy

Mean change from baseline to week 8 (LOCF) on the MADRS total score was significantly ($p = .001$) greater with vilazodone (–12.9) compared with placebo (–9.6) (Table 2). The mean change from baseline on the MADRS total score was significantly greater for vilazodone compared with placebo beginning at week 1 ($p < .001$) and at each subsequent visit ($p < .05$) (Figure 2A).

Mean change from baseline to week 8 (LOCF) on the HAM-D-17 total score was significantly ($p = .022$) greater in the vilazodone group (–10.4) than in the placebo group (–8.6). Mean change from baseline on HAM-D-17 total score also was significantly ($p < .05$) greater in the vilazodone group than in the placebo group beginning at week 1 and continuing at each postbaseline visit (Figure 2B). The mean score change from baseline to week 8 on the CGI-S showed greater improvement in the vilazodone group (–1.4) than in the placebo group (–1.0), and the difference between treatment groups was significant ($p = .001$) (Table 2). At endpoint, the mean CGI-I score was significantly ($p = .001$) improved (lower score) in the vilazodone group (2.6) compared with the placebo group (3.0). The mean change from baseline to week 8 on the HAM-A total score was greater with vilazodone (–6.6) than with placebo (–5.1), and the difference between groups was –1.5 ($p = .045$). Response rates on the MADRS, HAM-D-17, and CGI-I were significantly better with vilazodone than with placebo (Table 3).

In the completer analysis of patients who completed the MADRS at week 8, significant ($p < .05$) differences were observed between vilazodone and placebo in mean change from baseline (data not shown).

Tolerability

Discontinuation for reason of adverse event(s) occurred in 19 patients (9.3%) in the vilazodone group and 10 (4.9%) in the placebo group. Adverse events were recorded in 164 patients (80.0%) in the vilazodone group and 130 (63.7%) in the placebo group. The most frequently reported adverse events among patients in the vilazodone group were diarrhea (23.9%), nausea (18.5%), and headache (13.2%). In the placebo group, the incidence of diarrhea (7.3%) and nausea (4.4%) was lower than with vilazodone, but the incidence of headache (14.2%) was similar to that seen in the vilazodone group (Table 4). The median duration of nausea and diarrhea in the vilazodone group was 4 and 5 days, respectively, and, in the placebo group, 4.5 and 4 days, respectively. Most of these adverse events occurred in the vilazodone group during the first week of treatment. The majority of adverse events were of mild or moderate intensity; only 18 patients (8.8%) in the vilazodone group and 11 patients (5.4%) in the placebo group had an adverse event rated as severe. In the vilazodone group, these included diarrhea, fatigue, flatulence, gastroenteritis, palpitations, and paresthesias. In the placebo group, these included headache and somnolence.

The ASEX scores were not indicative of treatment-associated effects. At baseline, mean ASEX scores among men were 15.8 and 16.5 in the placebo and vilazodone groups, respectively, and, among women, the mean ASEX score was 21.2 in both the placebo and vilazodone groups. Differences of the observed ASEX mean scores between baseline and week 8 ranged from –0.4 to –1.3 in men or women in vilazodone and placebo groups, suggesting overall slight improvement in sexual function.

Five patients in each treatment group experienced a serious adverse event. Five psychiatric serious adverse events (2 depression and 3 suicidal ideation) were reported in 5 patients (2.5%) in the placebo group, and 3 psychiatric serious adverse events (2 depression and 1 suicide attempt) were reported in 2 patients (1.0%) in the vilazodone group. Lymphadenopathy, concussion, and prostate cancer each occurred as a serious adverse event once in the vilazodone group. No deaths occurred, and no clinically relevant effects on laboratory parameters, vital signs, physical examination, or ECG were observed.

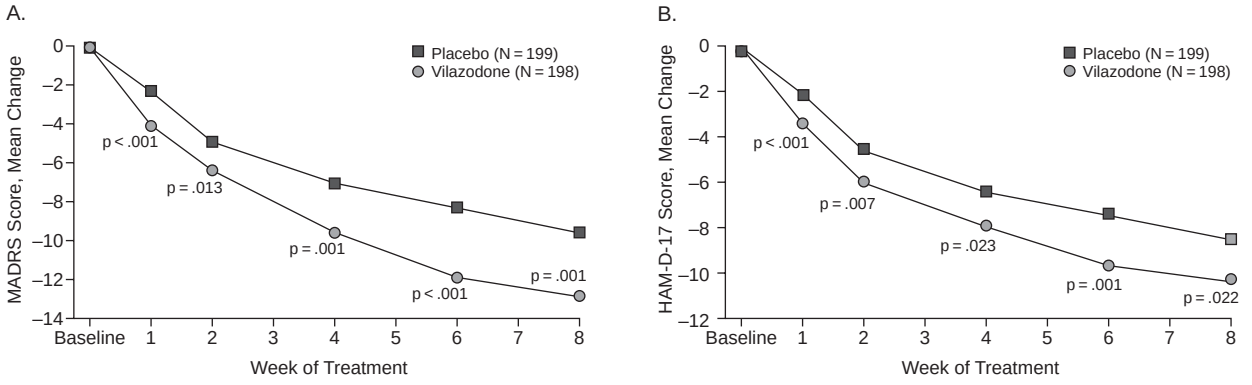
Treatment-emergent worsening of suicidal ideation was examined among patients who had a baseline score

Table 2. Mean Change From Baseline at Week 8 (end of treatment) in Intention-to-Treat (ITT) Population, Last-Observation-Carried-Forward (LOCF) Analysis

	Baseline[a]		Least-Squares Mean Change at Week 8[b]		
Scale	Vilazodone, N = 198	Placebo, N = 199	Vilazodone, N = 198	Placebo, N = 199	p Value[c]
MADRS	30.8 ± 3.9	30.7 ± 3.9	–12.9 ± 0.8	–9.6 ± 0.8	.001
HAM-D-17	24.8 ± 2.4	24.9 ± 2.4	–10.4 ± 0.6	–8.6 ± 0.6	.022
CGI-I	…	…	2.6 ± 0.1	3.0 ± 0.1	.001
CGI-S	4.5 ± 0.5	4.4 ± 0.5	–1.4 ± 0.1	–1.0 ± 0.1	.001
HAM-A	18.3 ± 5.1	18.5 ± 5.3	–6.6 ± 0.6	–5.1 ± 0.5	.045

[a]Values are mean ± SD.
[b]Values are mean ± SE.
[c]Least-squares mean comparison with analysis of covariance, ITT LOCF sample.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale.

Figure 2. Least-Squares Mean Change From Baseline for the MADRS (A) and HAM-D-17 (B) Total Scores by Visit (ITT population and LOCF analysis)[a]



[a]p Values are for comparisons of vilazodone and placebo by analysis of covariance.
Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, ITT = intention to treat, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale.

of 0 on the MADRS item 10 and HAM-D-17 item 3. On MADRS item ten, 15 patients receiving vilazodone and 25 receiving placebo had a baseline score of 0, which increased during the study. On HAM-D-17 item three, 17 patients receiving vilazodone and 22 receiving placebo had a baseline score of 0, which increased at least 1 point during the study.

DISCUSSION

In this study, vilazodone was found to produce a statistically and clinically significant reduction in depressive symptoms during short-term (8-week) treatment of MDD in adults. Statistically significant reductions in MADRS, HAM-D-17, CGI-I, and CGI-S scores were observed with vilazodone versus placebo, including significant differences on the MADRS and HAM-D-17 at week 1, the earliest time point. The consistency of response across multiple depression rating scales strongly supports the efficacy of vilazodone. The 40% or greater response rate observed with vilazodone is comparable to response rates reported with SSRIs and tricyclic antidepressants (TCAs).[6,8]

Limited information is available defining a clinically meaningful change in the MADRS score. In a meta-analysis of clinical trials of escitalopram for MDD, the mean difference between active drug and placebo was 3.0 on the MADRS.[26] The authors concluded that a 2-point difference in the MADRS score was clinically meaningful.[26] Analyses of the U.S. Food and Drug Administration (FDA) database of antidepressant drugs have determined that a difference of 1.7 to 1.9 points in the HAM-D-17 score between active drug and placebo is clinically meaningful,[27] which is consistent with the mean difference of 3.3 on the MADRS scale in our study.

The MADRS response rate in this trial was 40% with vilazodone versus 28% with placebo, a 12% difference. A meta-analysis of 5 placebo-controlled trials of

Table 3. Response at Week 8 for Intention-to-Treat Population, Last-Observation-Carried-Forward Analysis

	Vilazodone, N = 198		Placebo, N = 199		
Parameter	n (%)	95% CI, %	n (%)	95% CI, %	p Value[a]
MADRS response[b]	80 (40.4)	33.6 to 47.2	56 (28.1)	21.9 to 34.4	.007
HAM-D-17 response[b]	88 (44.4)	37.5 to 51.4	65 (32.7)	26.1 to 39.2	.011
CGI-I response[c]	95 (48.0)	41.0 to 54.9	65 (32.7)	26.1 to 39.2	.001

[a]Cochran-Mantel-Haenszel test.
[b]Score decrease ≥ 50%.
[c]Score of 1 or 2.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale.

Table 4. Treatment-Emergent Adverse Events Experienced by ≥ 5% of Patients in Any Group of the Safety Population, by Intensity of Event, n (%)

	Vilazodone, N = 205			Placebo, N = 204		
Adverse Event	Mild	Moderate	Severe	Mild	Moderate	Severe
Diarrhea[a]	32 (15.6)	14 (6.8)	3 (1.5)	6 (2.9)	9 (4.4)	0
Dizziness	9 (4.4)	7 (3.4)	0	5 (2.5)	5 (2.5)	0
Dry mouth	9 (4.4)	5 (2.4)	0	9 (4.4)	4 (2.0)	0
Fatigue	3 (1.5)	6 (2.9)	1 (0.5)	2 (1.0)	5 (2.5)	0
Headache	9 (4.4)	18 (8.8)	0	9 (4.4)	18 (8.8)	2 (1.0)
Nasopharyngitis	5 (2.4)	8 (3.9)	0	3 (1.5)	6 (2.9)	0
Nausea[a]	24 (11.7)	14 (6.8)	0	2 (1.0)	7 (3.4)	0
Somnolence	6 (2.9)	4 (2.0)	0	1 (0.5)	2 (1.0)	1 (0.5)
Upper respiratory infection	9 (4.4)	2 (1.0)	0	8 (3.9)	4 (2.0)	0

[a]$p < .05$, Fisher exact test.

escitalopram reported a response rate on the MADRS scale of 52% versus 37% with placebo, a 15% difference.[26] A meta-analysis of placebo-controlled trials with TCAs found response rates of 39% with active drug versus 28% with placebo.[28] An analysis of antidepressant studies submitted to the FDA found similar differences in response rates of approximately 15% between active and placebo groups.[27] In that analysis, response rates were lower in trials that used fixed doses of active drug and in placebo-controlled trials versus flexible dose and active-controlled trials.

The placebo response rate in this study was 28%. Walsh and colleagues[29] evaluated the placebo response rate in antidepressant trials and found highly variable rates ranging from 12.5% to 51.8%. Others have reported placebo response rates of 27% in ITT analyses of antidepressant trials.[30] Both reports identified an increase in placebo response rates over time.

Preclinical and clinical evidence support a role for 5-HT_{1A} receptor stimulation as an important antidepressant mechanism.[16] 5-HT_{1A} receptors are located on serotonergic neurons and on postsynaptic neurons in the brain and spinal cord. Neuropharmacology studies show that 5-HT_{1A} receptors exert a negative feedback on firing rate of 5-HT neurons and initially decrease synaptic release of 5-HT into the synaptic cleft. The adaptive effects of 5-HT_{1A} receptor changes in depressed patients were evaluated before and after 8-week treatment with citalopram in 30 consecutive outpatients with MDDs.[31] Other clinical studies assessing 5-HT_{1A} receptor function concluded that 5-HT_{1A} receptor function is impaired in depressives and is involved in the pathogenesis of depression and anxiety.[16] Recent results of a large clinical trial with a 5-HT_{1A} agonist demonstrate significant antidepressant efficacy.[32]

Previous studies have shown that patients with anxious depression were less responsive to antidepressant therapy than those with nonanxious depression[33] and that 5-HT_{1A} agonists have significant effects in patients with symptoms of anxiety and depression.[17,34] In this study, vilazodone resulted in a statistically significant improvement on the HAM-A compared with placebo, indicating possible utility in the management of patients with anxiety and depression.

In this study, vilazodone was safe and generally well tolerated. The most frequently reported adverse events in the vilazodone group (> 10%) were diarrhea, nausea, and headache, and the majority of these adverse events were of mild or moderate intensity. Nausea and diarrhea generally occurred during the first week of treatment in the vilazodone group and tended to diminish with ongoing treatment. The adverse events observed in this study were similar to those in previous phase 2 trials (data on file, Carol R. Reed, M.D., Clinical Data, Inc., 2003). Less than 10% of patients in the vilazodone group discontinued treatment due to adverse events, which is comparable to the 8% to 10% rate with other serotonergic

antidepressants and less than the 20% discontinuation rate reported with TCAs.[35]

Adverse events are the most frequent reason for premature discontinuation of antidepressant medication, particularly in the first month of treatment.[7,9] As many as 70% of patients taking antidepressants are noncompliant, and the majority attribute adverse events as the principal reason for treatment discontinuation.[36,37] The tolerability of SSRIs can vary considerably,[38,39] which is an important consideration for physicians when selecting initial therapy.[40,41] The widespread use of SSRIs in recent years has increased awareness of their potential adverse effects on sexual function. These unwanted side effects are largely attributable to serotonergic properties, although most antidepressant drugs can induce sexual dysfunction.[42–44] Antidepressant-associated sexual dysfunction occurs in 30% to 40% of patients taking SSRIs,[42,45] and a majority of these prematurely discontinue use, resulting in treatment failure. In this trial, ASEX mean scores (20 for women and 15 for men) were indicative of moderate pretreatment levels of sexual dysfunction. The level of sexual function at baseline was not changed with vilazodone and was comparable to placebo treatment on the basis of ASEX scores.

Pharmacotherapy represents standard treatment for MDD, with response rates of approximately 40% customary with short-term treatment.[8] Selective serotonin reuptake inhibitors became the mainstay of depression therapy in the late 1980s, and few differences in efficacy are noted among these agents or different pharmacologic classes of antidepressants.[8,39] These observations were confirmed by the STAR*D results, which found few differences in response between antidepressants[46]; any changes were largely governed by other concerns, such as pharmacokinetic factors, comorbid medical conditions, and previous response to treatment. Hence, an unmet therapeutic need exists, warranting development of novel antidepressant agents.

Vilazodone has a novel dual mechanism of action, acting as both a potent SSRI and as a 5-HT_{1A} partial agonist,[15] combining the pharmacologic mechanisms of action of current first-line and second-line agents as well as that of augmentation therapy. Evidence exists for the efficacy of 5-HT_{1A} partial agonists for the treatment of both MDD and anxiety.[16–18,32] Results from clinical trials, including STAR*D, have demonstrated therapeutic benefit of the 5-HT_{1A} agonist buspirone for augmenting response to SSRIs in the management of depression.[13,47,48] In fact, results from STAR*D suggest that a combination of antidepressants or treatment augmentation may be more effective than monotherapy in achieving higher rates of remission.[46] Use of combination or augmentation therapy earlier in the course of treatment for MDD might improve remission rates by offering broader and more potent pharmacologic activity to increase antidepressant efficacy.[46]

This was a short-term, fixed-dose study of vilazodone versus placebo. As such, the study was too short to adequately assess remission rates. In addition, due to its short duration, the impact of vilazodone on certain adverse events such as weight gain and sexual dysfunction cannot be adequately determined. A long-term study is currently underway that will provide information on these and other adverse events.

In summary, this trial demonstrates antidepressant efficacy in adults with MDD who take vilazodone, an antidepressant with a novel mechanism of action that may offer an effective treatment option in depressive disorders.

Drug names: buspirone (BuSpar and others), citalopram (Celexa and others), escitalopram (Lexapro and others).

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