A Randomized, Double-Blind, Placebo-Controlled, 8-Week Study of Vilazodone, a Serotonergic Agent for the Treatment of Major Depressive Disorder

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Objective: To evaluate the efficacy, and further establish the safety profile, of oral once-daily vilazodone, a potent and selective serotonin 1A receptor partial agonist and reuptake inhibitor, in the treatment of major depressive disorder (MDD).

Method: This phase 3, randomized, double-blind, placebo-controlled, 8-week study (conducted March 2008–February 2009) enrolled 481 adults with *DSM-IV-TR*–defined MDD. Patients received vilazodone (titrated to 40 mg/d) or placebo. The primary efficacy endpoint was change in Montgomery-Asberg Depression Rating Scale (MADRS) total score from baseline to end of treatment. Secondary efficacy measures included MADRS and 17-item Hamilton Depression Rating Scale (HDRS-17) response and change in HDRS-17, HDRS-21, Hamilton Anxiety Rating Scale (HARS), Clinical Global Impressions-Severity of Illness (CGI-S), and Clinical Global Impressions-Improvement (CGI-I) scores. The Changes in Sexual Functioning Questionnaire (CSFQ) was administered at baseline and week 8.

Results: Vilazodone-treated patients had significantly greater improvement ($P = .009$) according to the MADRS than placebo patients (intent-to-treat; least-squares mean changes: –13.3, –10.8). MADRS response rates were significantly higher with vilazodone than placebo (44% vs 30%, $P = .002$). Remission rates for vilazodone were not significantly different based on the MADRS (vilazodone, 27.3% vs placebo, 20.3%; $P = .066$) or HDRS-17 (vilazodone, 24.2% vs placebo, 17.7%; $P = .088$). Vilazodone-treated patients had significantly greater improvements from baseline in HDRS-17 ($P = .026$), HDRS-21 ($P = .029$), HARS ($P = .037$), CGI-S ($P = .004$), and CGI-I ($P = .004$) scores than placebo patients. Rates of discontinuation due to adverse events were 5.1% (vilazodone) and 1.7% (placebo). The most common adverse events (vilazodone vs placebo) were diarrhea (31% vs 11%), nausea (26% vs 6%), and headache (13% vs 10%). Treatment-related effects on sexual function as measured by the CSFQ were small and similar to placebo. Effects on weight were no different from placebo.

Conclusions: Vilazodone 40 mg/d was well tolerated and effective in adult patients with MDD.

Trial Registration: clinicaltrials.gov Identifier: NCT00683592

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Major depressive disorder (MDD), a prevalent and often recurrent disorder, is associated with significant medical and psychiatric morbidity, functional disability, and health care costs.[1–5] Although the treating clinician can choose from a variety of treatments, many patients do not achieve an adequate response even after multiple treatment regimens. For example, after up to 14 weeks of treatment with the selective serotonin reuptake inhibitor (SSRI) citalopram in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, the response rate was 47%, with incremental gains of about 25% with augmentation of citalopram (with bupropion sustained release) or with switching to another SSRI (sertraline) or to a serotonin-norepinephrine reuptake inhibitor (venlafaxine extended release).[6] Thus, while treatment effects are generally modest overall regardless of initial therapy, some patients who do not respond to one regimen may still respond to an alternative. Also confounding success is poor compliance; while long-term treatment decreases the odds of relapse by as much as 70%,[7] only 25%–50% of patients adhere to a prescribed maintenance regimen.[8] Premature discontinuation may stem from a variety of underlying factors, including lack of efficacy and tolerability issues, especially weight gain and sexual dysfunction.[9]

Therefore, there is a need for new antidepressants with novel mechanisms of action that can offer patients other treatment options. Vilazodone is a new molecule that is a selective and potent serotonin 1A receptor partial agonist and reuptake inhibitor and is approved by the US Food and Drug Administration for the treatment of MDD in adults.[10–12] Although vilazodone's selectivity for serotonin reuptake inhibition relative to norepinephrine or dopamine reuptake inhibition is comparable to that of the SSRI fluoxetine, its potency for serotonin reuptake inhibition is 30-fold greater.[13] However, in contrast to SSRIs, vilazodone is also a selective 5-HT_{1A} partial agonist.[14] This dual modulation of serotonin neurotransmission by vilazodone has been shown to enhance serotonin levels compared with SSRIs in nonclinical studies.[10] It has been suggested, on the basis of animal studies, that the high selectivity of vilazodone for the 5-HT_{1A} receptor, compared with other neuronal receptors, may lead to antidepressant activity with improved tolerability.[15]

Vilazodone was evaluated in five 8-week phase 2 placebo-controlled studies in patients with MDD, exploring doses ranging from 5 to 100 mg/d, with most patients dosed at ≤ 20 mg/d. In these studies, no statistically significant differences were observed between vilazodone and placebo or

between the active comparator (included in 3 of the 5 studies) and placebo on the primary endpoint of change from baseline on the 17-item Hamilton Depression Rating Scale (HDRS-17).[16]

A previous 8-week phase 3, double-blind, placebo-controlled efficacy trial demonstrated the efficacy (compared to placebo) and tolerability of vilazodone in the treatment of patients with MDD.[17] This second 8-week, phase 3, placebo-controlled efficacy study confirms the findings of the previous study.

Clinical Points

- Patients may prematurely discontinue antidepressant therapy for several different reasons including lack of efficacy and tolerability issues.
- Some patients who do not respond to one treatment regimen for major depressive disorder respond to an alternative treatment option.
- Vilazodone, a new molecule that is a selective and potent serotonin 1A receptor partial agonist and reuptake inhibitor, is a new treatment option in the management of depression.

METHOD

Study Objectives

The primary objective of the study was to compare the efficacy of vilazodone with placebo, using change from baseline to end of treatment in the Montgomery-Asberg Depression Rating Scale (MADRS)[18] total score. Secondary objectives included comparison of the efficacy of vilazodone with that of placebo on supplementary depression and depression-related measures, evaluations of overall disease severity and improvement, and further evaluation of the drug's safety profile.

Study Design

This randomized, double-blind, placebo-controlled clinical trial (clinicaltrials.gov identifier: NCT00683592) was conducted at 15 centers in the United States between March 2008 and February 2009. The study included both washout and screening periods followed by an 8-week, double-blind treatment period. During washout, patients were required to discontinue any antidepressant or psychotropic medication (4 weeks for monoamine oxidase inhibitors or fluoxetine, 12 weeks for depot neuroleptics, 2 weeks for all others).

After the washout and screening periods, eligible patients underwent baseline assessments and were randomly assigned (1:1) to receive vilazodone or placebo orally once daily in the morning with food. Visits were scheduled 1, 2, 4, 6, and 8 weeks after the initiation of treatment. Patients were titrated to the target dose of 40 mg/d according to a fixed-titration schedule of 10 mg/d for 7 days, followed by 20 mg/d for the next 7 days. Compliance was assessed by tablet counts, and noncompliance was defined as < 80% or > 120% of prescribed study drug taken during any evaluation period (visit to visit).

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was approved by the institutional review board for each center in accordance with US Code of Federal Regulations, and all patients gave written informed consent.

Subjects

The study enrolled adult patients (18–70 years of age) with a diagnosis of MDD (single episode or recurrent) as defined by the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Text Revision (*DSM-IV-TR*)[19] and a current major depressive episode with a duration of ≥ 4 weeks and < 2 years. Patients were required to have an HDRS-17[20] score ≥ 22 and an HDRS item 1 (depressed mood) score ≥ 2 at screening and baseline visits. Patient incentives included psychiatric and medical assessments, treatment during the trial, and a modest stipend to compensate for travel and time.

Patients were excluded if they had an Axis I disorder other than MDD within 6 months of screening (exceptions: generalized anxiety disorder, social phobia, simple phobia); schizophrenia, schizoaffective disorder, or bipolar disorder; or MDD with postpartum onset, psychotic features, or seasonal pattern or if they met *DSM-IV-TR* substance abuse (alcohol or drugs) criteria within 3 months or substance dependence within 6 months of the screening visit. Other exclusionary conditions were psychotherapy within the preceding 12 weeks, failure to respond to an adequate trial of 2 antidepressants of different drug classes, or concurrent use of psychotropic drugs, including migraine medications, with a serotonergic mechanism of action. Patients with significant comorbid conditions that might interfere with trial participation were excluded at the investigator's discretion.

Assessments

The primary efficacy endpoint was mean change in MADRS total score from baseline to end of treatment. Secondary efficacy endpoints included mean change from baseline to end of treatment in the HDRS-17 and 21-item Hamilton Depression Rating Scale (HDRS-21),[20] Hamilton Anxiety Rating Scale (HARS),[21] and Clinical Global Impressions-Severity of Illness (CGI-S) and -Improvement (CGI-I) scales[22] scores; MADRS response (defined as ≥ 50% decrease from baseline)[23]; MADRS remission (defined as MADRS score < 10)[24]; HDRS-17 response (defined as ≥ 50% decrease from baseline); and HDRS-17 remission (defined as HDRS-17 score < 7). Treatment response was assessed at weeks 1, 2, 4, 6, and 8 (or end of treatment) by experienced raters blinded to treatment assignment.

Safety measures included adverse events, clinical laboratory tests, electrocardiograms, physical examinations, and vital signs. Patients were monitored for the emergence of suicidality at each study visit using the Columbia-Suicide Severity Rating Scale (C-SSRS).[25] To evaluate changes in sexual function, the Changes in Sexual Functioning Questionnaire (CSFQ)[26,27] was completed by patients at baseline and week 8 (or upon discontinuation).

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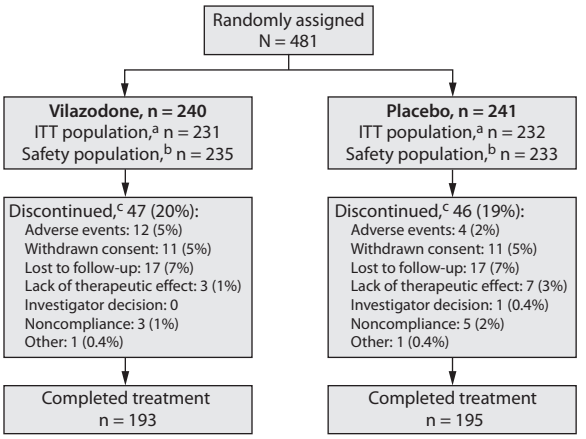
Figure 1. Patient Disposition



[a]Randomly assigned patients who received at least 1 dose of study medication and who had at least 1 postbaseline efficacy assessment.
[b]All randomly assigned patients who received at least 1 dose of study drug.
[c]N (%) of randomly assigned patients in each group.
Abbreviation: ITT = intent to treat.

Table 1. Baseline Demographics and Disease Characteristics of MDD Patients Receiving Vilazodone or Placebo (safety population)

Characteristic	Vilazodone (n = 235)	Placebo (n = 233)
Sex, n (%)		
Men	96 (40.9)	109 (46.8)
Women	139 (59.1)	124 (53.2)
Race, n (%)		
White	182 (77.4)	191 (82.0)
Black/African American	35 (14.9)	31 (13.3)
Other	18 (7.7)	11 (4.7)
Age, y		
Mean (SD)	41.1 (12.2)	42.4 (12.5)
Range	18–69	19–70
Weight, mean (SD), kg	86.4 (24.8)	88.9 (21.2)
Age at onset of depression, mean (SD), y	32.0 (13.4)	33.2 (14.1)
First lifetime episode of depression, n (%)	66 (28.1)	67 (28.8)
Duration of current MDD episode, n (%)		
1–6 mo	110 (46.8)	120 (51.5)
> 6–12 mo	61 (26.0)	59 (25.3)
> 12 mo	63 (26.8)	54 (23.2)
Severity of current episode, n (%)		
Moderate	175 (74.5)	165 (70.8)
Severe	60 (25.5)	68 (29.2)
Patients taking any previous or concomitant psychiatric medication, n (%)	48 (20.4)	47 (20.2)

Abbreviations: MDD = major depressive disorder, SD = standard deviation.

Statistical Analysis

A sample size of 470 patients randomly assigned 1:1 to vilazodone or placebo was planned so as to provide 90% power at $\alpha = .05$ to detect a difference of at least 3.0 points (SD ± 10.0; effect size = 0.30) between the vilazodone and placebo groups in mean change from baseline to week 8 in MADRS total score.

The intent-to-treat (ITT) group included randomly assigned patients receiving study drug with a postbaseline efficacy assessment. The safety population comprised all patients receiving study drug with a postbaseline safety assessment.

Primary efficacy analysis was conducted in the ITT population using the last-observation-carried-forward (LOCF) method. Treatment group comparisons were based on differences in least-squares mean (LSM) changes from baseline to week 8/end of treatment from an analysis-of-covariance (ANCOVA) model containing terms for treatment and center, with baseline MADRS score included as a covariate. Two centers with fewer than 8 patients were pooled. To confirm the robustness of the primary efficacy analysis, mixed-effects model repeated-measures (MMRM) analysis was performed on mean changes from baseline in the MADRS total score. This model included fixed categorical terms for treatment, center, visit, and treatment-by-visit interaction and continuous fixed covariates for baseline MADRS score and baseline-by-visit interaction. Similar ANCOVA models were used to analyze change from baseline in HDRS-17, HDRS-21, HARS, and CGI-S scores. CGI-I scores at endpoint were assessed with analysis of variance, including treatment group and center in the model. Response and remission rates at end of treatment were compared using the Cochran-Mantel-Haenszel test for general association, stratified by center.

No formal hypothesis testing was performed on safety data. Safety outcomes were summarized by treatment group and study visit (observed cases) using descriptive statistics. Except where indicated, safety results are presented for week 8 findings and, therefore, represent patients who completed the study. Any clinically significant findings among patients who terminated early are discussed separately. All analyses were conducted using SAS Version 9.1.3 (SAS Institute, Inc; Cary, North Carolina). Statistical comparisons of efficacy outcomes were 2-sided and considered significant at $P < .05$. Comparisons for secondary endpoints were not adjusted for multiplicity.

RESULTS

Patient Disposition

Six hundred fifty-nine patients were screened, and 481 were randomly assigned to vilazodone (n = 240) or placebo (n = 241) treatment (Figure 1). The ITT population comprised 231 vilazodone-treated patients and 232 placebo patients; 388 subjects (80.7%) completed study treatment. The safety population comprised 235 patients receiving vilazodone and 233 receiving placebo.

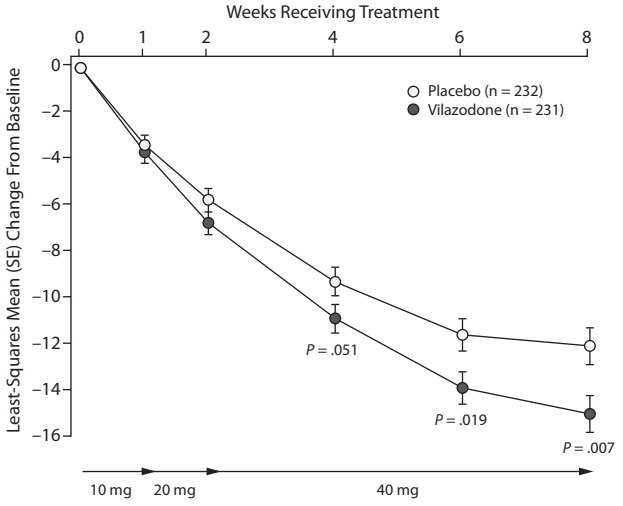
Both treatment groups were similar with respect to demographic and clinical characteristics at baseline (Table 1). The mean age was 41.7 years, and the mean age at first occurrence of MDD was 32.6 years. The current episode of MDD was predominantly of moderate severity and represented the first lifetime episode for 28.4% of patients. The duration of the current episode of depression was > 6 months for ~50% of patients in both groups, and ~ 20% of patients in each group previously used or were concurrently using psychiatric medication. At each visit, treatment compliance exceeded 90% for both groups.

Table 2. Efficacy Analyses (ITT population, LOCF analysis)

Least-Squares Mean (SE) Change From Baseline to End of Treatment						
	Baseline		LSM Change at Week 8		LSM Treatment Difference	
	Vilazodone (n = 231)	Placebo (n = 232)	Vilazodone (n = 231)	Placebo (n = 232)	(95% CI)	*P*
MADRS	31.9 (3.5)	32.0 (3.6)	−13.3 (0.9)	−10.8 (0.9)	−2.5 (−4.4 to −0.6)	.009
HDRS-17	25.0 (2.4)	25.3 (2.6)	−10.7 (0.7)	−9.1 (0.7)	−1.6 (−3.1 to −0.2)	.026
HDRS-21	26.8 (3.0)	27.2 (3.0)	−11.6 (0.7)	−9.9 (0.7)	−1.7 (−3.3 to −0.2)	.029
HARS	18.0 (5.3)	18.1 (5.8)	−7.0 (0.6)	−5.7 (0.6)	−1.2 (−2.4 to −0.1)	.037
CGI-S	4.5 (0.5)	4.5 (0.5)	−1.4 (0.1)	−1.1 (0.1)	−0.4 (−0.6 to −0.1)	.004
CGI-I	…	…	2.5 (0.1)	2.8 (0.1)	−0.3 (−0.5 to −0.1)	.004
Response and Remission Rates at End of Treatment, n (%)						
	Vilazodone (n = 231)		Placebo (n = 232)		Risk Difference (95% CI)	*P*
MADRS response	101 (43.7)		70 (30.3)		13.4 (4.7 to 22.1)	.002
MADRS remission	63 (27.3)		47 (20.3)		6.9 (−0.8 to 14.7)	.066
HDRS-17 response	102 (44.2)		76 (32.9)		11.3 (2.4 to 20.1)	.013
HDRS-17 remission	56 (24.2)		41 (17.7)		6.5 (−0.9 to 13.9)	.088

Symbol: … = not applicable.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, CI = confidence interval, HARS = Hamilton Anxiety Rating Scale, HDRS = Hamilton Depression Rating Scale, ITT = intent to treat, LOCF = last-observation-carried-forward, LSM = least-squares mean, MADRS = Montgomery-Asberg Depression Rating Scale, SE = standard error.

Figure 2. Mean Change From Baseline in MADRS Total Score by Week (ITT population, MMRM analysis)



Abbreviations: ITT = intent to treat, MADRS = Montgomery-Asberg Depression Rating Scale, MMRM = mixed-effects model repeated-measures, SE = standard error.

Similar numbers of patients in each group discontinued treatment prematurely (vilazodone, 19.6%; placebo, 19.1%; Figure 1). The most frequent reasons for discontinuation were loss to follow-up and withdrawal of consent (7.1% and 4.6%, respectively, overall). Adverse events led to discontinuation of more patients in the vilazodone group (5.1% vs 1.7% with placebo); lack of efficacy resulted in more discontinuations in the placebo group (1.3% with vilazodone vs 3.0% with placebo).

Efficacy

Compared with placebo patients, vilazodone-treated patients showed significantly greater improvement from baseline to end of treatment in mean MADRS scores, with a statistically significant LSM treatment difference of −2.5 between both groups (ITT population, LOCF analysis, $P = .009$) (Table 2) and an effect size of 0.23 (95% confidence interval, 0.05–0.41). MMRM analysis of MADRS change scores revealed numerically greater improvement in the vilazodone group than the placebo group at each time point; the difference showed a trend favoring vilazodone that approached statistical significance at week 4 (LSM difference between vilazodone and placebo: −1.6 [$P = .0513$]) and that was statistically significant at weeks 6 ($P = .019$) and 8 ($P = .007$) (Figure 2).

Statistically significant improvements from baseline to end of treatment with vilazodone were also observed for the HDRS-17 ($P = .026$), HDRS-21 ($P = .029$), HARS ($P = .037$), and CGI-S ($P = .004$) scores (Table 2). CGI-I scores at week 8 showed significantly greater global improvement with vilazodone ($P = .004$).

MADRS and HDRS response and remission rates at endpoint, as defined in the protocol, were higher in the vilazodone group than in the placebo group (Table 2). The MADRS response rate was significantly greater among patients treated with vilazodone (43.7%) compared with placebo (30.3%; $P = .002$), as was the HDRS-17 response rate (vilazodone, 44.2% vs placebo, 32.9%; $P = .013$). Remission rates for vilazodone were not significantly different based on the MADRS (vilazodone, 27.3% vs placebo, 20.3%; $P = .066$) or HDRS-17 (vilazodone, 24.2% vs placebo, 17.7%; $P = .088$).

Safety

Overall exposure to study drug and placebo was similar. More patients in the vilazodone group (193, 82.1%) than in the placebo group (150, 64.4%) experienced a treatment-emergent adverse event (Table 3). The most frequent adverse events in the vilazodone group were diarrhea (30.6% vs 10.7% with placebo), nausea (26.0% vs 5.6%), and headache (12.8% vs 10.3%). Median time to initial onset of diarrhea was shorter for vilazodone patients than placebo patients (2 days vs 8 days), while median time to initial onset of nausea was greater (4 days vs 2 days). Median duration of the

Table 3. Treatment-Emergent Adverse Events in ≥5% of Patients in Either Treatment Group (safety population)[a]

Preferred Term[b]	Vilazodone (n = 235)	Placebo (n = 233)
Diarrhea	72 (30.6)	25 (10.7)
Nausea	61 (26.0)	13 (5.6)
Headache	30 (12.8)	24 (10.3)
Dry mouth	21 (8.9)	9 (3.9)
Dizziness	21 (8.9)	9 (3.9)
Insomnia	17 (7.2)	7 (3.0)
Abnormal dreams	14 (6.0)	4 (1.7)
Vomiting	12 (5.1)	1 (0.4)
Upper respiratory infection	8 (3.4)	21 (9.0)

[a]Values shown as number (%) of patients.
[b]Medical Dictionary for Regulatory Activities (MedDRA), Version 11.1.

initial occurrence of diarrhea was 8 days in the vilazodone group versus 5 days in the placebo group and was, for nausea, 5 days for both treatment groups.

Most adverse events were considered mild to moderate. Fifteen patients (6.4%) in the vilazodone group and 13 (5.6%) in the placebo group had a severe adverse event; severe adverse events involving more than a single vilazodone patient were insomnia (3 vs 1), nausea (2 vs 0), vomiting (2 vs 0), headache (2 vs 0), and decreased libido (2 vs 0). The incidences of treatment-emergent suicidal ideation and/or behavior were small, as detected by the C-SSRS; in addition, there were no incidences of suicidal ideation or behavior that were reported as treatment-emergent adverse events during the study in either the vilazodone group or the placebo group.

Twelve vilazodone patients (5.1%) discontinued treatment due to adverse events compared with 4 placebo patients (1.7%). Gastrointestinal events resulted in treatment discontinuation for 4 patients in the vilazodone group (2 nausea, 1 vomiting, 1 dyspepsia) and none in the placebo group. Four patients in the vilazodone group had a total of 5 serious adverse events (angina pectoris, carotid arteriosclerosis, chest pain, cholecystitis, and pneumonia), and 2 patients in the placebo group had a total of 3 serious adverse events (ankle fracture, 1; asthma, 2). None of these was considered by the investigator to be related to vilazodone, and no deaths occurred.

The incidence of abnormal laboratory values was low and similar in the 2 treatment groups, and no patterns of changes were associated with vilazodone treatment. Three patients (vilazodone, 2; placebo, 1) had isolated elevation (3 × the upper limit of normal) of γ-glutamyl transferase levels while on treatment. Mean systolic blood pressure change from baseline to week 8 was –1.3 mm Hg in the vilazodone group and –0.1 mm Hg in the placebo group, and mean diastolic blood pressure changes were minimal (≤ 1 mm Hg) in both groups during treatment. Similarly, mean change in heart rate did not differ between the 2 groups, and there were no treatment-related electrocardiogram (ECG) abnormalities. Overall mean change in weight at week 8 was 0.2 kg for vilazodone and 0.4 kg for placebo.

Mean CSFQ scores at baseline in the vilazodone and placebo groups were 46.5 and 46.6 for men and 39.4 and 40.2 for women. At week 8, mean (SD) change from baseline in CSFQ total score for vilazodone versus placebo, respectively, showed improvement of 0.6 (7.5) and 1.8 (6.4) points for men and 1.9 (7.9) and 2.3 (6.2) points for women. Similar trends were observed for patients terminating early. Subscale results for the CSFQ at week 8 were consistent with those for the total score in that neither treatment group demonstrated a mean change less than 0 on any of the subscale scores. Sexual dysfunction adverse events were more frequent with vilazodone (n = 21) than placebo (n = 1); the most common was libido decreased, which was reported by 4.7% of vilazodone patients (6 men, 5 women) and no placebo patients.

DISCUSSION

This placebo-controlled, double-blind trial corroborates the findings of a previous phase 3 study and confirms the antidepressant efficacy and safety of oral vilazodone in adults with MDD at a once-daily dose of 40 mg.[17] During 8 weeks of treatment with vilazodone, improvement in symptoms of depression, while of modest clinical effect, were statistically significant and observed on multiple measures, including MADRS, HDRS-21, HDRS-17, and HARS. Similarly, vilazodone was associated with improvements in measures of overall illness severity (CGI-S and CGI-I). Treatment effect as measured by the MADRS was consistent with previous findings with the 40-mg dose of vilazodone[17] (and comparable to effect sizes previously reported in the literature[28]). Improvements on the other depression scales were consistent with the MADRS results.[17] Response rates at endpoint, as measured by ≥ 50% reduction in MADRS and HDRS-17 scores, were significantly higher with vilazodone than placebo, a finding also consistent with the previous trial.[17] Remission rates at endpoint were not statistically different for vilazodone compared to placebo.

This study is the second positive phase 3 study of vilazodone 40 mg/d in adults with MDD. Vilazodone was evaluated in five 8-week phase 2 placebo-controlled studies in patients with MDD, exploring doses ranging from 5 to 100 mg/d, with most patients dosed at ≤ 20 mg/d. In these studies, no statistically significant differences were observed between vilazodone and placebo or between the active comparator (included in 3 of the 5 studies) and placebo on the primary endpoint of change from baseline on the HDRS-17.[16]

Side effects are a common reason for premature discontinuation, especially early in treatment.[29] Overall, vilazodone was well tolerated in this study, and the discontinuation rate was relatively low. The most frequent adverse events with vilazodone were diarrhea and nausea, which were predominantly of mild or moderate intensity and, while they tended to occur early in treatment during the titration period, only infrequently resulted in treatment discontinuation.

Although impaired sexual functioning is a common feature of depression, treatment-induced sexual dysfunction due to antidepressants (particularly serotonergic agents) is both common, occurring in at least 30%–40% of patients,[30,31] and a frequent cause of treatment noncompliance.[9] In this

study, sexual dysfunction adverse events were more frequent with vilazodone treatment than with placebo. The most commonly occurring sexual dysfunction adverse event was libido decreased, which was reported by 4.7% of patients receiving vilazodone. However, the effect of vilazodone on overall sexual function as measured by the CSFQ was similar to that of placebo for both men and women.

Weight gain is also recognized as a leading cause of antidepressant noncompliance.[9] In this 8-week study, patients experienced minimal and similar weight changes during treatment with either vilazodone or placebo. Additionally, there were no clinically significant treatment-related effects on ECGs, laboratory tests (including liver function tests), or vital signs.

This study had several limitations. Remission rates for vilazodone were not significantly different from placebo based on MADRS or HDRS-17 assessments. An 8-week trial has limited ability to assess remission rates, and, because of titration, patients received the minimally effective dose of vilazodone for only 6 weeks. Evaluations of changes in weight are also limited due to duration of the study. No measures of quality of life were included beyond assessments of overall global measures of illness.

There were differences between qualitative (adverse events) and quantitative (CSFQ) measures of the effect of vilazodone on sexual function. This inconsistency may reflect the difficulty in distinguishing sexual dysfunction related to antidepressants from sexual dysfunction related to depression itself. Further exploration of the subscales of the CSFQ and the reported adverse events might help to clarify these differences.

In summary, this study demonstrated the efficacy of vilazodone compared to placebo, showing statistically significant improvement of depressive symptoms associated with vilazodone in the acute treatment of MDD. Additionally, vilazodone was generally well tolerated, and no new concerns regarding its safety profile over 8 weeks of treatment were noted from the findings of this study. Thus, vilazodone, a new molecule that is a selective and potent serotonin 1A receptor partial agonist and reuptake inhibitor, may prove to be a new treatment option in the management of depression.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), citalopram (Celexa and others), fluoxetine (Prozac and others), sertraline (Zoloft and others), venlafaxine (Effexor and others), vilazodone (Viibryd).

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Potential conflicts of interest: **Dr Khan** has been a principal investigator of more than 330 clinical trials sponsored by more than 55 pharmaceutical companies and 30 clinical research organizations (CROs). He was a principal investigator for both vilazodone phase 3 studies enrolling 242 patients. He has not received compensation for speaking or consulting on their behalf, nor does he own stock in any of these companies. **Dr Cutler** has received research grants from Alkermes, AstraZeneca, Bristol-Myers Squibb, Cephalon, Forest, GlaxoSmithKline, Janssen, Johnson & Johnson PRD, Lilly, Merck, Novartis, Ortho-McNeil Janssen, Otsuka, Pfizer, PGxHealth (now Trovis Pharmaceuticals, LLC), a division of Clinical Data, Inc, Sanofi (including Sanofi-Synthelabo, Sanofi-Aventis), Shire, Solvay, Sunovion, Supernus, and Takeda; has been a consultant for Arbor Scientia, AstraZeneca, Bristol-Myers Squibb, Forest, GlaxoSmithKline, Janssen, Lilly, Merck, Neuronex, Neuroscience Education Institute, Novartis, Ortho-McNeil Janssen, Otsuka, Pamlab, Pfizer, PGxHealth (now Trovis Pharmaceuticals, LLC), Shire, Sunovion, Supernus, and Takeda; has been a speaker for Arbor Scientia, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Lilly, Merck, Neuroscience Education Institute, Novartis, Ortho-McNeil Janssen, Otsuka, Pamlab, Pfizer, Shire, Sunovion, and Takeda; and has been a participant in a CME advisory board for Neuroscience Education Institute. **Drs Kajdasz** and **Reed** and **Mss Gallipoli** and **Whalen** are full-time employees and stockholders of Trovis Pharmaceuticals, LLC, a division of Clinical Data, Inc. **Dr Athanasiou** is a consultant to and a stockholder of Trovis Pharmaceuticals, LLC, a division of Clinical Data, Inc, and has been an employee of PGxHealth. **Dr Robinson** is a consultant to Trovis Pharmaceuticals, LLC, a division of Clinical Data, Inc, Takeda, Bristol-Myers Squibb, and Dey Pharma, L.P.

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