Efficacy and Safety of Vilazodone in Patients With Generalized Anxiety Disorder:
A Randomized, Double-Blind, Placebo-Controlled, Flexible-Dose Trial

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ABSTRACT

Objective: To evaluate the efficacy, safety, and tolerability of vilazodone as an acute treatment for generalized anxiety disorder (GAD). Vilazodone is a selective serotonin reuptake inhibitor and 5-HT$_{1A}$ receptor partial agonist approved for the treatment of major depressive disorder in adults.

Methods: This was a randomized, placebo-controlled, parallel-group, multicenter, flexible-dose study conducted from May 2013–March 2014. Adult patients (18–70 years, inclusive) who met *DSM-IV-TR* criteria for GAD were randomized (1:1) to placebo or vilazodone 20–40 mg/d for 8 weeks of double-blind treatment. Primary and secondary efficacy parameters were change from baseline to week 8 in the Hamilton Anxiety Rating Scale (HARS) total score and in the Sheehan Disability Scale (SDS) total score, respectively, analyzed using a mixed-effects model for repeated measures approach on a modified intent-to-treat population. Safety outcomes were summarized descriptively.

Results: Efficacy analyses were based on 400 patients (placebo = 200, vilazodone = 200); 76% completed the study (placebo = 81%, vilazodone = 71%). The least squares mean difference (95% CI) in total score change from baseline to week 8 was statistically significant for vilazodone versus placebo on the HARS (−2.20 [−3.72 to −0.68]; *P* = .0048) and on the SDS (−1.89 [−3.52 to −0.26]; *P* = .0236). Treatment-emergent adverse events reported in ≥ 5% of vilazodone patients and at least twice the rate of placebo were nausea, diarrhea, dizziness, fatigue, delayed ejaculation, and erectile dysfunction.

Conclusion: Statistically significant differences in favor of vilazodone 20–40 mg/d versus placebo were seen on all measures of anxiety and functional impairment in patients with GAD. Vilazodone was generally well tolerated, and no new safety concerns were noted.

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Although worrying is a ubiquitous human experience, the worries that characterize generalized anxiety disorder (GAD) are so pervasive and excessive that they distort cognition and create a considerable burden of illness. The physical symptoms, psychiatric symptoms, and functional impairment associated with GAD collectively generate significant individual, societal, and economic costs.[1] As such, GAD is an important mental health issue that affects patients, families, health care providers, payers, employers, and society at large.[1,2]

Vilazodone is a selective serotonin reuptake inhibitor (SSRI) and 5-HT$_{1A}$ receptor partial agonist that is approved by the US Food and Drug Administration (FDA) for treating major depressive disorder (MDD) in adults. SSRIs are first-line agents approved for treating GAD[3]; unlike other SSRIs, vilazodone also is a 5-HT$_{1A}$ receptor partial agonist. Based on clinical-trial evidence in MDD,[4–7] the recommended daily dose of vilazodone is 20–40 mg.[8] Since SSRI antidepressants used for the treatment of GAD have efficacy at the same dose levels that are effective in treating MDD,[9] vilazodone 20–40 mg/d is being evaluated for GAD treatment.

A potential anxiolytic effect for vilazodone was supported by post hoc analysis of pooled data[10] from patients with anxious depression in 2 MDD studies. In this analysis, a statistically significant difference in Hamilton Anxiety Rating Scale (HARS)[11] total score change from baseline to week 8 was seen in favor of vilazodone 40 mg/d versus placebo (*P* < .001). Preliminary investigations into the effects of vilazodone in GAD have yielded positive results in a fixed-dose study of vilazodone 40 mg/d (20 mg/d did not separate from placebo)[12] and a flexible-dose study of 20–40 mg/d.[13] The present study (ClinicalTrials.gov NCT01844115) was designed to further evaluate the efficacy, safety, and tolerability of flexibly dosed vilazodone as an acute treatment for GAD in adult patients.

METHODS

The study was conducted at 36 US study centers between May 2013 and March 2014 in full compliance with FDA regulations relating to good clinical practices and the ethical principles of the Declaration of Helsinki. The protocol was approved by each site's institutional review board, and all patients provided written informed consent before any study procedures were initiated.

Study Design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose study of vilazodone 20–40 mg/d in adult patients with GAD. The overall study was 10 weeks and comprised a 1-week screening period, 8week double-blind treatment,

and a 1-week double-blind down-taper; all randomized patients were eligible to enter the down-taper period if the investigator considered it medically appropriate. Eligible patients (N = 400) were randomly assigned (1:1) to identically appearing placebo or vilazodone to be taken once daily with food.

Patients randomized to vilazodone received 10 mg/d for week 1 and 20 mg/d for week 2. At the end of week 2 or week 4, patients with inadequate response and no clinically significant tolerability issues could receive a dose increase to 40 mg/d; patients with adequate response continued taking 20 mg/d. No dose increases were allowed after the end of week 4.

Patients were randomized by computer-generated numbers and assigned to identically appearing treatment. Investigators and patients were blinded to the allocation of study drug throughout treatment and down-taper; patients were also blinded to dose increase. The blind was maintained via a secured randomization code list and was broken only in case of emergency; removing the blind for any reason disqualified a patient from further participation.

Patients

Male or female outpatients (18–70 years of age, inclusive) met *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*) criteria[14] for GAD and had the following: HARS total score ≥ 20, HARS items 1 (Anxious Mood) and 2 (Tension) scores ≥ 2, Clinical Global Impressions-Severity (CGI-S)[15] score ≥ 4, and 17-item Hamilton Depression Rating Scale (HDRS$_{17}$)[16] total score ≤ 17. Patients had normal physical examination, clinical laboratory, and electrocardiogram (ECG) findings or abnormal results that were judged to be not clinically significant. Women of childbearing potential had a negative serum β-human chorionic gonadotropin pregnancy test.

Patients were excluded if they had a *DSM-IV-TR*–based Axis I diagnosis other than GAD within 6 months; secondary diagnoses of comorbid social anxiety disorder or specific phobias were allowed. Additional reasons for exclusion included a lifetime diagnostic history of various psychiatric disorders (eg, bipolar disorder, psychotic disorder, depressive episode with psychotic or catatonic features), suicide risk, substance abuse (within 6 months), nonresponse to adequate treatment with ≥ 2 SSRIs or serotonin-norepinephrine reuptake inhibitors (SNRIs) (≥ 8 weeks at the approved dose) for GAD treatment, and intolerance/hypersensitivity to vilazodone, SNRIs, or SSRIs. Medical conditions that could interfere with study conduct, confound the interpretation of results, or endanger patient well-being were exclusionary. Psychoactive drugs were prohibited. Patients requiring concomitant treatment with prohibited medications were excluded; eszopiclone, zopiclone, zaleplon, or zolpidem could be continued for insomnia.

Efficacy and Safety Assessments

Efficacy was assessed at various weeks by the HARS[11] (week −1 [screening]; week 0 [baseline]; weeks 1, 2, 4, 6, 8),

Clinical Points

- Generalized anxiety disorder is characterized by pervasive worries, physical symptoms, psychiatric symptoms, and functional impairment that collectively generate significant individual, societal, and economic costs.
- At week 8, a statistically significant difference in mean change from baseline in Hamilton Anxiety Rating Scale total score was seen in favor of vilazodone 20–40 mg/d compared with placebo, suggesting a reduction in anxiety symptoms for vilazodone-treated patients.
- Statistically significant differences in change from baseline to week 8 on the Sheehan Disability Scale total score and its Work/School, Social Life, and Family Life individual items suggested that all domains of functional impairment decreased at the end of treatment.

Sheehan Disability Scale (SDS)[17] (weeks 0, 2, 4, 6, 8), HDRS$_{17}$ (weeks −1, 0, 8), CGI-S[15] (all weeks), and CGI-Improvement (CGI-I)[15] (weeks 1, 2, 4, 6, 8). Safety was assessed by adverse event (AE) reports, physical examination, clinical laboratory and vital sign measures, ECGs, the Columbia-Suicide Severity Rating Scale (C-SSRS)[18] (all weeks and down-taper), and the Changes in Sexual Functioning Questionnaire (CSFQ)[19] (weeks 0, 4, 8). Metabolic changes were assessed in post hoc analyses that evaluated the percentage of patients that made clinically relevant shifts from normal values at baseline to high values at any visit during double-blind treatment. Normal and high values were respectively defined as total cholesterol < 200 mg/dL and ≥ 240 mg/dL, low-density lipoprotein (LDL) cholesterol < 100 mg/dL and ≥ 160 mg/dL, and glucose < 100 mg/dL and ≥ 126 mg/dL.

Statistical Analyses

Safety analyses were based on the safety population (randomized patients who received ≥ 1 dose of double-blind study drug). Efficacy analyses were based on the modified intent-to-treat (m-ITT) population (patients in the safety population with a baseline and ≥ 1 postbaseline HARS assessment). All statistical tests were 2-sided hypothesis tests performed at the 5% significance level; all confidence intervals (CIs) were 2-sided 95% CIs.

The primary efficacy parameter was change in HARS total score from baseline to week 8. The primary analysis used a mixed-effects model for repeated measures (MMRM) with treatment group, pooled study center, visit, and treatment group–by-visit interaction as fixed effects, and the baseline value and baseline value–by-visit interaction as covariates. This analysis was based on observed cases without imputation of missing values. An unstructured covariance matrix was used to model the covariance of within-patient scores, and the Kenward-Roger approximation[20] was used to estimate the denominator degrees of freedom. Two pre-specified sensitivity analyses were conducted on the primary parameter: a pattern-mixture model approach based on nonfuture dependent missing value restrictions,[21] which tested for violations of the missing at random–missingness assumption, and a last observation carried forward (LOCF)

Figure 1. Patient Disposition
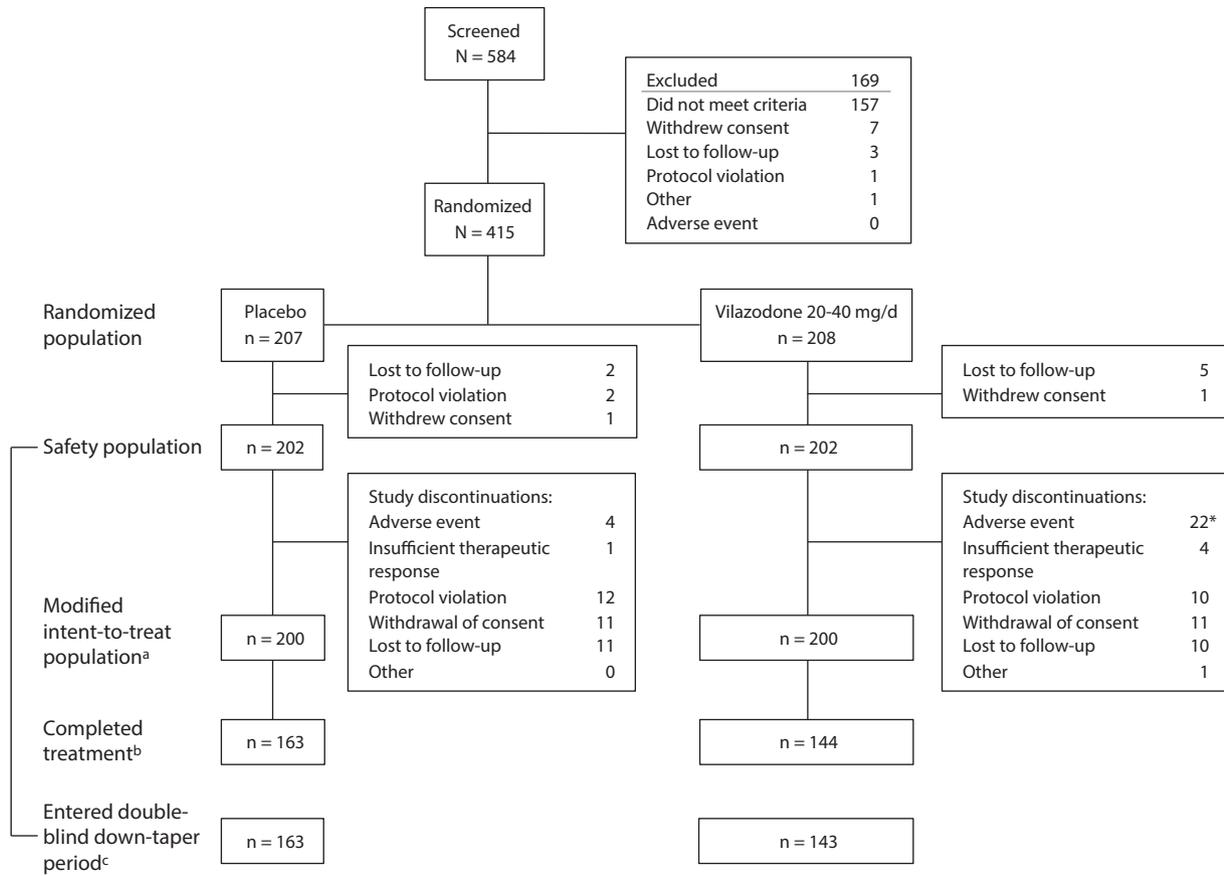
[a]Excludes patients in the safety population who did not have at least 1 postbaseline Hamilton Anxiety Rating Scale assessment.
[b]Based on the number of patients in the safety population.
[c]Based on the number of patients in the safety population. Patients entered the double-blind down-taper period if deemed medically appropriate by the Investigator. A patient did not need to complete the double-blind treatment period in order to enter the down-taper period.
*P < .001 versus placebo (Fisher exact text).

approach, which is a more conservative imputation method than MMRM. Both approaches used an analysis of covariance model with treatment group and pooled study center as factors and baseline HARS total score as a covariate.

The secondary efficacy parameter was change from baseline to week 8 in SDS total score. Analysis was conducted using the MMRM approach on an m-ITT population consisting of patients with evaluable assessments on the 3 SDS domain items (Work/School, Social Life, Family Life); SDS total score was calculated as the sum of the domain items. A pre-specified LOCF sensitivity analysis was also performed. The fixed sequence testing procedure was applied to control the overall family-wise type I error rate for testing the primary and secondary efficacy parameters; analyses of the secondary efficacy parameter were carried out inferentially only if the null hypothesis for the primary efficacy parameter was rejected. Effect sizes were calculated for the primary and secondary efficacy outcomes using Cohen d.

Additional efficacy parameters included change from baseline to week 8 on the HARS Psychic Anxiety and Somatic Anxiety subscales,[11] HARS items 1 and 2, SDS items (Work/School, Social Life, Family Life), HDRS$_{17}$, and

CGI-S; the CGI-I score at week 8; and the rates of response on the HARS (≥ 50% improvement from baseline) and CGI-I (score ≤ 2). Response rates were analyzed using a generalized linear mixed model with random intercept and fixed terms of treatment group, visit, treatment-by-visit interaction, and baseline score. Other additional efficacy parameters were analyzed using an MMRM approach; baseline CGI-S score was an explanatory variable for CGI-I analysis. Post hoc analyses estimated the rate of SDS remission (total score ≤ 6 with item scores ≤ 2)[22] and the number needed to treat for HARS response, CGI-I response, and SDS remission. Safety analyses presented the number and percentage of patients with AEs, and descriptive statistics were used to evaluate change from baseline in laboratory values and vital signs.

RESULTS

Patient Disposition and Demographic Characteristics

Of the patients randomized to double-blind treatment, 11 did not receive study drug and were not included in the safety population (Figure 1). Double-blind treatment was completed by 76% of patients in the safety population; significantly more vilazodone- (29%) than placebo-treated

Table 1. Demographic Characteristics and Anxiety Disorder History (safety population)

Demographic Characteristics	Placebo (n = 202)	Vilazodone 20–40 mg/d (n = 202)
Age, mean (SD), y	40.7 (13.4)	39.2 (12.8)
Women, n (%)	137 (67.8)	127 (62.9)
Race, n (%)		
White	153 (75.7)	158 (78.2)
Black	38 (18.8)	33 (16.3)
Other	11 (5.4)	11 (5.4)
Not Hispanic or Latino	177 (87.6)	180 (89.1)
Weight, kg[a]		
Mean (SD)[b]	75.8 (15.2)	80.7 (18.8)
Median (min, max)	75.2 (49, 118)	80.1 (42, 143)
BMI, kg/m²		
Mean (SD)[b]	27.0 (5.0)	28.1 (5.6)
Median (min, max)	26.1 (18, 40)	27.6 (18, 40)
Anxiety Disorder History		
Duration of GAD, median (min, max), y	9.98 (0.0, 45.3)	9.69 (0.6, 51.3)
Age at GAD onset, mean (SD), y	27.5 (14.3)	25.5 (13.0)
Previous treatment for GAD, n (%)		
Yes	26 (12.9)	31 (15.3)
No	176 (87.1)	171 (84.7)
Nonresponders to previous GAD treatment, n (%)[c]	13 (50.0)	14 (45.2)
Previous or current anxiety disorder other than GAD, n (%)	9 (4.5)	12 (5.9)
Social phobia (social anxiety disorder)	7 (3.5)	9 (4.5)
Agoraphobia (no panic disorder history)	2 (1.0)	3 (1.5)
Posttraumatic stress disorder	0	1 (0.5)

[a]To convert from kilograms (kg) to pounds (lb), multiply kilograms by 2.2.
[b]$P < .05$ (vilazodone vs placebo; Fisher exact test).
[c]Percentage based on number of patients with previous treatment.
Abbreviations: BMI = body mass index; GAD = generalized anxiety disorder.

Figure 2. HARS Least Squares Mean Change by Week (modified ITT population, MMRM)[a]
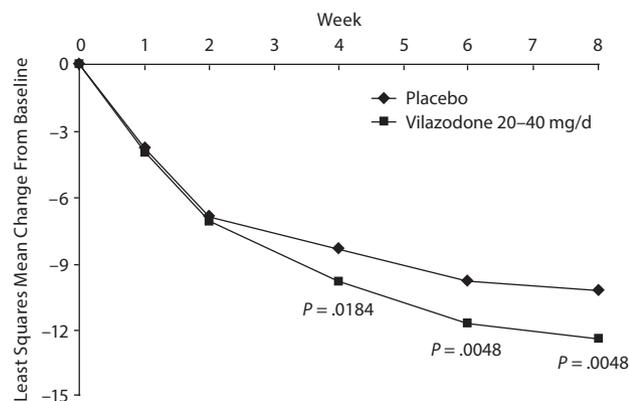
[a]P values are for vilazodone 20–40 mg/d versus placebo.
Abbreviations: HARS = Hamilton Anxiety Rating Scale, ITT = intent to treat, MMRM = mixed-effects model for repeated measures.

(19%) patients prematurely discontinued the study ($P < .05$ [Fisher exact test]). AEs were the most common reason for discontinuation in the vilazodone group ($P = .0004$ vs placebo).

Demographics and baseline physical characteristics were similar between groups except for weight and body mass index (Table 1). Overall, mean age was 39.9 years, 65% of patients were women, and 77% were white. Baseline efficacy scores were generally similar between treatment groups. The mean baseline score was higher on the HARS Psychic Anxiety subscale (approximately 14) than on the Somatic Anxiety subscale (approximately 10). Mean HDRS$_{17}$ baseline scores were 13 in both groups, suggesting a nondepressed/mildly depressed patient population.[23]

Analysis of Efficacy

The least squares mean difference in change from baseline to week 8 in HARS total score was statistically significant in favor of vilazodone 20–40 mg/d versus placebo using the primary MMRM approach (Table 2), with an estimated effect size of 0.31. The difference between vilazodone and placebo was statistically significant beginning at week 4, and it remained so through week 8 (Figure 2). In pre-specified sensitivity analyses (data not shown), pattern-mixture model analysis supported the primary results, and the between-group difference using the LOCF approach was not statistically significant.

The difference in mean change from baseline to week 8 in SDS total score was statistically significant for vilazodone versus placebo using the MMRM approach (Table 2), with an estimated effect size of 0.29. The between-group difference on the pre-specified LOCF analysis was not statistically significant (data not shown).

Statistically significant differences in score change from baseline to week 8 were noted on all additional efficacy parameters in favor of vilazodone versus placebo (MMRM); the difference in CGI-I score at week 8 was also statistically significant (Table 2). Differences in the rate of HARS and CGI-I response and SDS remission were statistically significant for vilazodone versus placebo; the number needed to treat for HARS and CGI-I response was 6, and for SDS remission it was 7.

Safety and Tolerability

Extent of exposure. The mean duration of treatment was 46.7 days in the vilazodone group and 50.1 days in the placebo group. Patient-years of exposure ([total treatment duration in days]/365.25) were 27.7 and 25.8 for placebo and vilazodone, respectively. The majority of vilazodone patients (63.9%) were titrated to 40 mg/d, and the mean (SD) daily dose was 26.2 (8.1) mg/d.

Adverse events. An overall summary of AEs is presented in Table 3. Treatment-emergent AEs (TEAEs) were reported for 64% of placebo- and 79% of vilazodone-treated patients. AEs leading to study discontinuation were more frequent in the vilazodone-treatment group than in the placebo-treatment group ($P < .001$); the only AEs that resulted in discontinuation of ≥ 2 vilazodone patients were nausea (n = 6), dizziness (n = 5), diarrhea (n = 4), and headache (n = 2).

TEAEs reported in at least 5% of vilazodone patients and at least twice the rate of placebo were nausea, diarrhea, dizziness, fatigue, delayed ejaculation, and erectile

Table 2. Efficacy Outcomes (modified ITT population)

Efficacy Measure	Placebo		Vilazodone 20–40 mg/d	
	n	Outcome	n	Outcome
Primary and secondary efficacy parameters (MMRM)				
HARS total score				
Baseline, mean (SD)	200	25.0 (3.69)	200	24.5 (3.64)
Change from baseline to week 8, LS mean (SE)		−10.19 (0.543)		−12.39 (0.564)
LSMD (95% CI)		…		−2.20 (−3.72 to −0.68)
P Value		…		.0048
SDS total score				
Baseline, mean (SD)	154	15.9 (5.57)	150	15.7 (6.02)
Change from baseline to week 8, LS mean (SE)		−6.13 (0.602)		−8.02 (0.630)
LSMD (95% CI)		…		−1.89 (−3.52 to −0.26)
P Value		…		.0236
Additional efficacy parameters (MMRM)				
HARS Psychic Anxiety subscale[a]				
Baseline, mean (SD)	200	14.5 (2.25)	200	14.3 (2.33)
Change from baseline to week 8, LS mean (SE)		−5.66 (0.338)		−7.12 (0.352)
LSMD (95% CI)		…		−1.47 (−2.41 to −0.52)
P Value		…		.0024
HARS Somatic Anxiety subscale[b]				
Baseline, mean (SD)	200	10.6 (2.80)	200	10.2 (2.95)
Change from baseline to week 8, LS mean (SE)		−4.55 (0.254)		−5.36 (0.265)
LSMD (95% CI)		…		−0.81 (−1.52 to −0.10)
P Value		…		.0250
HARS item 1 (Anxious Mood)				
Baseline, mean (SD)	200	2.9 (0.49)	200	2.8 (0.50)
Change from baseline to week 8, LS mean (SE)		−1.13 (0.075)		−1.44 (0.078)
LSMD (95% CI)		…		−0.31 (−0.52 to −0.10)
P Value		…		.0038
HARS item 2 (Tension)				
Baseline, mean (SD)	200	2.8 (0.54)	200	2.8 (0.51)
Change from baseline to week 8, LS mean (SE)		−1.08 (0.076)		−1.39 (0.080)
LSMD (95% CI)		…		−0.31 (−0.53 to −0.10)
P Value		…		.0042
SDS Work/School item				
Baseline, mean (SD)	154	5.1 (2.37)	150	5.1 (2.53)
Change from baseline to week 8, LS mean (SE)		−2.11 (0.218)		−2.73 (0.229)
LSMD (95% CI)		…		−0.62 (−1.21 to −0.02)
P Value		…		.0423

(continued next column)

Efficacy Measure	Placebo		Vilazodone 20–40 mg/d	
	n	Outcome	n	Outcome
Additional efficacy parameters (MMRM) (continued)				
SDS Social Life item				
Baseline, mean (SD)	198	5.7 (2.30)	196	5.6 (2.36)
Change from baseline to week 8, LS mean (SE)		−2.20 (0.190)		−3.06 (0.198)
LSMD (95% CI)		…		−0.87 (−1.39 to −0.34)
P Value		…		.0012
SDS Family Life item				
Baseline, mean (SD)	198	5.2 (2.14)	196	5.1 (2.42)
Change from baseline to week 8, LS mean (SE)		−1.99 (0.184)		−2.74 (0.192)
LSMD (95% CI)		…		−0.75 (−1.26 to −0.25)
P Value		…		.0036
CGI-S				
Baseline, mean (SD)	200	4.3 (0.50)	200	4.3 (0.49)
Change from baseline to week 8, LS mean (SE)		−1.15 (0.087)		−1.61 (0.090)
LSMD (95% CI)		…		−0.45 (−0.70 to −0.21)
P Value		…		.0003
CGI-I				
Score at week 8	166	2.5 (1.07)	146	2.1 (1.06)
LSMD (95% CI)		…		−0.35 (−0.58 to −0.12)
P Value		…		.0032
$HDRS_{17}$ total score				
Baseline, mean (SD)	183	13.0 (2.30)	181	12.7 (2.50)
Change from baseline to week 8, LS mean (SE)		−3.92 (0.368)		−5.51 (0.389)
LSMD (95% CI)		…		−1.59 (−2.58 to −0.60)
P Value		…		.0018
Rates of response and remission at week 8, n (%) (GLMM)				
HARS response (≥50% improvement from baseline)	65/166	(39.2)	83/147	(56.5)
OR (95% CI)		…		2.719 (1.394 to 5.304)
P Value		…		.0034
CGI-I response (CGI-I ≤2)	82/166	(49.4)	96/146	(65.8)
OR (95% CI)		…		2.631 (1.306 to 5.297)
P Value		…		.0068
SDS remission (total score ≤6 with item scores ≤2)	46/137	(33.6)	61/125	(48.8)
OR (95% CI)		…		2.302 (1.081 to 4.906)
P Value		…		.0307

[a]HARS Psychic Anxiety subscale: items 1 (Anxious Mood), 2 (Tension), 3 (Fears),4 (Insomnia), 5 (Intellectual), 6 (Depressed Mood), and 14 (Anxious Behavior at Interview).
[b]HARS Somatic Anxiety subscale: items 7 (Somatic [muscular]), 8 (Somatic [sensory]), 9 (Cardiovascular Symptoms), 10 (Respiratory Symptoms), 11 (Gastrointestinal Symptoms), 12 (Genitourinary Symptoms), and 13 (Autonomic Symptoms).
Abbreviations: CGI-I = Clinical Global Impressions-Improvement; CGI-S = CGI-Severity; GLMM = generalized linear mixed model; HARS = Hamilton Anxiety Rating Scale; $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale; LS = least squares; LSMD = least squares mean difference; MMRM = mixed-effects model for repeated measures; OR = odds ratio, SDS = Sheehan Disability Scale.
Symbol: … = not applicable.

Table 3. Summary of Adverse Events (safety population)[a]

Adverse Event Summary	Placebo (n = 202)	Vilazodone 20–40 mg/d (n = 202)
Deaths	0	0
Patients with ≥ 1 TEAE	130 (64.4)	159 (78.7)
Patients with SAE	0	3 (1.5)
Patients with newly emergent AE[b]	10 (5.0)	5 (2.5)
Common double-blind, treatment-emergent adverse events (≥ 5% in either treatment group)		
Nausea	26 (12.9)	60 (29.7)
Diarrhea	12 (5.9)	56 (27.7)
Dizziness	8 (4.0)	22 (10.9)
Headache	36 (17.8)	22 (10.9)
Insomnia	8 (4.0)	15 (7.4)
Dry mouth	12 (5.9)	12 (5.9)
Somnolence	6 (3.0)	12 (5.9)
Ejaculation delayed[c]	1 (1.5)	4 (5.3)
Erectile dysfunction[c]	1 (1.5)	4 (5.3)
Fatigue	4 (2.0)	10 (5.0)

[a]All values are n (%). Adverse events coded using MedDRA version 16.1 (http://www.meddra.org/).
[b]TEAE that occurred during the double-blind down-taper period that not present before or was present before or increased in severity.
[c]Percentage relative to the number of male patients: placebo, n = 65; vilazodone, n = 75.
Abbreviations: AE = adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

dysfunction. The majority of TEAEs in both groups were considered mild (about 60%) or moderate (about 36%) in severity and related to the double-blind treatment (placebo = 63%, vilazodone = 77%). Only 3 serious AEs were reported (laceration/stab wound, urinary tract infection, and impaired gastric emptying [1 vilazodone patient each]); none were considered related to study drug or resulted in study discontinuation.

Clinical laboratory, vital sign, electrocardiogram evaluation. Mean changes from baseline to end of double-blind treatment in most laboratory parameters, vital signs, and liver enzyme parameters were small and similar between groups. No patient met Hy's law criteria (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] elevation ≥ 3 × upper limit of normal [ULN], total bilirubin elevation > 2 × ULN, and alkaline phosphatase < 2 × ULN). Clinically relevant shifts (normal to high) were similar for vilazodone- versus placebo-treated patients, respectively, for total cholesterol (1.0% vs 2.0%), LDL cholesterol (0% vs 1.3%), and glucose (2.6% vs 1.3%) levels. The most frequently reported potentially clinically significant postbaseline values in metabolic parameters (> 1.1 × ULN) for vilazodone and placebo, respectively, were for total cholesterol (16% and 12%) and triglycerides (11% and 10%).

The incidence of orthostatic hypotension (≥ 20 mm Hg systolic blood pressure reduction or ≥ 10 mm Hg diastolic blood pressure reduction while changing position from supine to standing) was similar for vilazodone and placebo (7%). Increases in mean body weight were small in the vilazodone (0.39 kg [0.86 lb]) and placebo (0.30 kg [0.66 lb]) groups. No patients had an ECG finding that was considered clinically significant, and no patient had a QTc Bazett (QTcB) or QTc Fridericia (QTcF) interval increase to > 500 ms.

Suicidality and suicide-related adverse events. CSSRS–rated suicidal ideation was reported in 16 (8%) vilazodone- and 11 (5%) placebo-treated patients; no suicidal behavior was reported in either group. TEAEs of suicidal ideation were reported in 1 patient in each treatment group; both TEAEs resolved the same day they were reported, were not considered related to study drug, and did not result in discontinuation.

Sexual functioning. At the end of double-blind treatment, mean CSFQ total score changes from baseline were +0.9 and +0.5 in the placebo- and vilazodone-treatment groups, respectively (increase indicates improvement on this scale). Vilazodone-treated men had a small mean decrease (−0.3) in score, while placebo-treated men (+0.5) and women in both the vilazodone (+1.0) and placebo (+1.1) groups had small mean increases. Sexual function TEAEs occurred in 17 patients (8%) in the vilazodone group and in 4 (2%) patients in the placebo group; 1 vilazodone patient discontinued due to sexual function TEAEs. The only sexual function TEAEs that occurred in more than 2 vilazodone patients were delayed ejaculation, erectile dysfunction (4 [5% male only] patients each), and decreased libido (5 [2%] patients).

DISCUSSION

In this positive clinical study of patients with GAD, the difference in mean change from baseline to week 8 in HARS total score was statistically significant for vilazodone 20–40 mg/d compared with placebo using the primary MMRM approach. The effect size for vilazodone was 0.31, which is comparable to what has been observed for second-generation antidepressants in the treatment of GAD (0.32; 95% CI, 0.25–0.39).[24]

Broad anxiolytic efficacy was suggested by significant differences in favor of vilazodone on all other anxiety measures. Improvement in functional impairment was demonstrated by statistically significant differences for vilazodone versus placebo in mean change from baseline in SDS total score and each item score (MMRM). Further indications of symptomatic and overall improvement for patients treated with vilazodone were suggested by statistically significant differences versus placebo in rates of HARS and CGI-I response, CGI-I score at week 8, and mean change from baseline on the CGI-S. The difference in mean change on the HDRS$_{17}$ was also statistically significant, but this result may not be clinically meaningful given the low level of depressive symptoms in this patient population.

Although numerous pharmaceutical agents are approved for the treatment of GAD, as many as 50% of patients have inadequate response,[25] and considerable unmet medical and social needs persist. GAD and MDD frequently present as comorbid conditions[26] and are associated with comparable degrees of impairment.[27,28] Similar to MDD, GAD more likely generates considerable public health and economic ramifications.[1] For example, patients with anxiety disorders overutilize medical resources, which accounts for substantial direct and indirect health care costs.[29–32] Despite high medical

resource use, however, GAD is frequently unrecognized or untreated in primary care,[33,34] suggesting that inadequate or inappropriate medical intervention contributes to overall costs. Anxiety disorders are also associated with excess workplace costs due to lost productivity and absenteeism,[32] which adds to the economic and social burdens of GAD.

Evidence suggests that recovery from psychiatric disorders is associated with improved functional impairment.[35–37] In studies that use mean change from baseline as an outcome, minimal clinically important differences are used as benchmarks to suggest the point at which patients are likely to recognize the benefits of treatment. On the SDS, the suggested minimal clinically important differences are approximately 4 for total score and 1–2 on each item.[22] These thresholds suggest that the magnitude of SDS mean change in the vilazodone group in our study (total score: −8.02 Work: −2.73, Social Life: −3.06, Family Life: −2.74) may have been sufficient for patients to perceive improvement in functional impairment. Additionally, the difference in the rate of SDS remission was statistically significant in favor of vilazodone- versus placebo-treated patients. This remission result is relevant to recovery as shown by a prior GAD investigation[38] in which significantly more patients who returned to normative levels on functional assessments achieved symptomatic remission compared with patients who did not return to normative values.

Safety findings in this population of patients with GAD were similar to what has been observed in vilazodone studies in patients with MDD. Gastrointestinal effects, especially nausea and diarrhea, occurred more frequently in vilazodone-treated patients than placebo patients but resulted in few study discontinuations for vilazodone patients (nausea = 6; diarrhea = 4). Overall, mean changes in clinical laboratory values, metabolic parameters, vital signs, and ECG findings were low and similar between treatment groups. Although epidemiologic data suggest that GAD may be associated with suicidality,[1,39] no suicidal behavior was reported during the study; only 2 suicidal ideation TEAEs (1 patient each group), which resolved the same day, were reported.

Sexual dysfunction, a known effect of SSRI treatment, is considered by patients to be one of the most unacceptable side effects.[40] Mean increases in CSFQ scores were seen in the placebo (+0.9) and vilazodone-treatment groups (+0.5). The incidence of sexual function TEAEs was higher in vilazodone- than placebo-treated patients, but only 1 patient discontinued as a result.

Limitations of the study include its short duration and lack of an active comparator. Since GAD typically presents with comorbid anxiety and mood disorders, exclusion of patients with significant depressive symptoms and most anxiety comorbidities limits the ability to generalize these results to patients with a broader symptom profile or comorbid MDD. Additionally, some analyses were performed post hoc and should be interpreted accordingly.

In this positive study, mean differences in change from baseline to week 8 on HARS total score, SDS total score, and SDS individual items were statistically significant in favor of vilazodone versus placebo, suggesting a reduction in anxiety symptoms and a decrease in functional impairment for vilazodone-treated patients. These results indicate that vilazodone may be a treatment option for GAD, a disorder that is associated with considerable psychiatric and functional impairment, as well as pronounced individual, economic, and societal burdens.

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