Research Article

A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, FIXED-DOSE PHASE III STUDY OF VILAZODONE IN PATIENTS WITH GENERALIZED ANXIETY DISORDER

Carl Gommoll, M.S.,1* Suresh Durgam, M.D.,1 Maju Mathews, M.D.,2 Giovanna Forero, M.A.,2 Rene Nunez, M.D.,2 Xiongwen Tang, Ph.D.,1 and Michael E. Thase, M.D.3

Background: Vilazodone, a selective serotonin reuptake inhibitor and 5-HT1A receptor partial agonist, is approved for treating major depressive disorder in adults. This study (NCT01629966 ClinicalTrials.gov) evaluated the efficacy and safety of vilazodone in adults with generalized anxiety disorder (GAD).

Methods: A multicenter, double-blind, parallel-group, placebo-controlled, fixed-dose study in patients with GAD randomized (1:1:1) to placebo (n = 223), or vilazodone 20 mg/day (n = 230) or 40 mg/day (n = 227). Primary and secondary efficacy parameters were total score change from baseline to week 8 on the Hamilton Rating Scale for Anxiety (HAMA) and Sheehan Disability Scale (SDS), respectively, analyzed using a predefined mixed-effect model for repeated measures (MMRM). Safety outcomes were presented by descriptive statistics.

Results: The least squares mean difference (95% confidence interval) in HAMA total score change from baseline (MMRM) was statistically significant for vilazodone 40 mg/day versus placebo (–1.80 [–3.26, –0.34]; P = .0312 [adjusted for multiple comparisons]), but not for vilazodone 20 mg/day versus placebo. Mean change from baseline in SDS total score was not significantly different for either dose of vilazodone versus placebo when adjusted for multiplicity; significant improvement versus placebo was noted for vilazodone 40 mg/day without adjustment for multiplicity (P = .0349). The incidence of adverse events was similar for vilazodone 20 and 40 mg/day (~71%) and slightly lower for placebo (62%). Nausea, diarrhea, dizziness, vomiting, and fatigue were reported in ≥5% of patients in either vilazodone group and at least twice the rate of placebo.

Conclusions: Vilazodone was effective in treating anxiety symptoms of GAD. No new safety concerns were identified.

Key words: generalized anxiety disorder; antidepressant; anxiety/anxiety disorders; pharmacotherapy; clinical trials

© 2015 The Authors. Depression and Anxiety published by Wiley Periodicals, Inc.

DOI 10.1002/da.22365
Published online 17 April 2015 in Wiley Online Library (wileyonlinelibrary.com).
INTRODUCTION

Generalized anxiety disorder (GAD), a disorder characterized by pervasive and highly distressing worries, is associated with impairment that is comparable to major depressive disorder (MDD). Although numerous agents from various drug classes are available to treat GAD, as many as 50% of patients have inadequate response, constituting a considerable unmet medical need.

Vilazodone is a selective serotonin reuptake inhibitor (SSRI) and 5-HT1A receptor partial agonist approved by the U.S. Food and Drug Administration (FDA) for the treatment of MDD in adults. The efficacy of vilazodone 40 mg in MDD was established in two short-term, double-blind, placebo-controlled Phase III trials (NCT00285376 and NCT00683592). Two recent positive Phase IV randomized, placebo-controlled clinical trials (NCT01473394 and NCT01473381) confirmed and supported the evidence base for vilazodone 40 mg; in one of the trials, evidence for efficacy of a 20-mg dose in MDD was also supported. Safety and tolerability findings were supported in a 1-year, open-label trial of vilazodone 40 mg/day (NCT00644358). Vilazodone was generally well tolerated in all trials; common adverse events (AEs), including diarrhea, nausea, and insomnia, were generally transient in nature and considered mild in severity.

The potential for vilazodone to have efficacy in treating GAD is suggested by its pharmacodynamic profile. Agents approved for treating anxiety disorders support the hypothesis that SSRI and 5-HT1A receptor partial agonist activities may produce positive outcomes in GAD. SSRIs and serotonin norepinephrine reuptake inhibitors (SNRIs) are considered first-line GAD treatments, and buspirone, a 5-HT1A receptor partial agonist, has demonstrated clinical trial efficacy in conditions that roughly correspond to GAD and is approved for the treatment of anxiety disorders. In addition, a pooled post hoc analysis of patients with anxious depression from two vilazodone MDD studies demonstrated statistically significant improvements in favor of vilazodone versus placebo on most anxiety measures, suggesting efficacy potential in treating anxiety symptoms associated with MDD. The objective of the current study (NCT01629966) was to characterize the efficacy, safety, and tolerability of vilazodone for the treatment of anxiety in patients with GAD.

METHODS

The study was conducted at 37 study centers in the United States between June 2012 and March 2014 in full compliance with FDA guidelines for Good Clinical Practice 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.

STUDY DESIGN

This was a multicenter, randomized, double-blind, parallel-group, placebo-controlled, fixed-dose study of vilazodone in adult patients with GAD. The 10-week study duration consisted of a 1-week screening period, 8-week double-blind treatment, and 1-week double-blind down-taper if it was considered medically appropriate by the investigator. Following screening, eligible patients were randomized (1:1:1) to placebo, vilazodone 20 mg/day, or vilazodone 40 mg/day, to be taken once daily with food. Vilazodone was initiated at 10 mg/day for week 1; dosage was increased to 20 mg/day at week 2 and maintained for the remainder of double-blind treatment for patients in the 20-mg/day group, patients in the 40-mg/day group received 20 mg/day at week 2 for 7 days and then increased to 40 mg/day for the remainder of treatment.

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. 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) who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria for GAD were included. Participants were required to have a Hamilton Rating Scale for Anxiety (HAMA) total score ≥20, HAMA items 1 (Anxious Mood) and 2 (Tension) scores ≥2, Clinical Global Impressions–Severity (CGI-S) score ≥4, and 17-item Hamilton Depression Rating Scale (HAMD17) total score ≤17. Patients had normal physical examination, laboratory, and electrocardiogram (ECG) findings, or abnormal results that were judged to be not clinically significant; females of childbearing potential had a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test.

Patients were excluded for a DSM-IV-TR-based Axis I diagnosis other than GAD within 6 months of screening; secondary diagnoses of comorbid social anxiety disorder, and/or specific phobias were allowed. Additional exclusion criteria included a lifetime diagnostic history of various psychiatric disorders (e.g., bipolar disorder, depressive episode with psychotic/catatonic features, psychotic disorder, substance abuse, cognitive disorders); suicide risk (including suicide attempt within 1 year); nonresponse to ≥2 adequate treatment trials of antidepressants (≥8 weeks of treatment at an adequate dose based on approved package insert recommendations) for the treatment of GAD; and intolerance/hypersensitivity to vilazodone, SNRIs, or SSRIs. Psychoactive drugs and required concomitant treatment with prohibited medications were barred; eszopiclone, zopiclone, zaleplon, or zolpidem could be continued for insomnia. Patients with medical conditions that could interfere with study conduct, confound the interpretation of results, or endanger patient well-being were excluded.

EFFICACY AND SAFETY ASSESSMENTS

Efficacy was assessed by the HAMA (weeks −1 [screening], 0 [baseline], 1, 2, 4, 6, 8), Sheehan Disability Scale (SDS)[16] (weeks 0, 2, 4, 6, 8), HAMD17 (weeks −1, 0, 8), CGI-S (all weeks), and CGI-Improvement (CGI-I)[16] (weeks 1, 2, 4, 6, 8). Safety was assessed by AE reports (patients were asked a nonleading question to elicit reporting of any AEs that had occurred since the previous visit), physical examination, clinical laboratory and vital sign measures, ECGs, the Columbia-Suicide Severity Rating Scale (C-SSRS) [17] (all weeks and down-taper), and Changes in Sexual Functioning Questionnaire (CSFQ) [18] (weeks 0, 4, 8).

Depression and Anxiety
STATISTICAL ANALYSES

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

The primary efficacy parameter, change from baseline to week 8 in HAMA total score, was analyzed using the predefined mixed-effect model for repeated measures (MMRM) with treatment group, study center, visit, and treatment-group-by-visit interaction as fixed effects and the baseline value and baseline-value-by-visit interaction as covariates. An unstructured covariance matrix was used for modeling the covariance of within-patient scores; the Kenward-Roger approximation was used to estimate denominator degrees of freedom using the observed cases (OC) approach without imputation of missing values. Two prespecified sensitivity analyses were performed on the primary efficacy parameter: a pattern-mixture model (PMM) approach based on nonfuture-dependent missing value restrictions[19] and a last observation carried forward (LOCF) approach. Both approaches were based on an analysis of covariance (ANCOVA) model using treatment group and study center as factors and baseline HAMA total score as a covariate.

The secondary efficacy parameter, change from baseline to week 8 in SDS total score, was analyzed using an MMRM approach; a prespecified LOCF sensitivity analysis was also conducted. SDS total score was based on a modified ITT population and was calculated as the sum of the individual domain items (Work/School, Social Life, Family Life) based on a modified ITT population and was calculated as the sum of the individual domain items (Work/School, Social Life, Family Life) determined by the CG-I-S subscales. The severity of suicidal ideation and behavior was monitored by the C-SSRS. Patient-rated change in sexual behavior was monitored by the C-SSRS. Patient-rated change in sexual behavior was monitored by the C-SSRS. Patient-rated change in sexual behavior was monitored by the C-SSRS.

RESULTS

PATIENT DISPOSITION AND DEMOGRAPHIC CHARACTERISTICS

Six hundred eighty patients were randomized to double-blind treatment; 667 and 673 patients were included in the ITT and safety populations, respectively (Table 1). There were higher rates of discontinuation in the vilazodone 40-mg/day group (29%) than in the placebo (19%) and 20-mg/day (23%) groups. AEs were the most frequent reason for discontinuation in all groups; the rate of discontinuation due to AEs was higher for vilazodone 40 mg/day than placebo (P < .05 [Fisher exact test]). Demographics and other patient characteristics were similar among groups (Table 2); mean age was 40.2 years, 65% of patients were women, and 76% were White. Most patients reported a long duration of illness with GAD; approximately 17% of patients had received previous GAD treatment and almost half reported nonresponse (Table 2).

Mean baseline scores were similar among groups on most efficacy measures. HAMA Anxious Mood baseline score distribution was significantly different for vilazodone 20 mg/day versus placebo (P = .0339); mean baseline SDS Work/School score was significantly higher for vilazodone 20 mg/day versus placebo (P = .0482), suggesting greater baseline functional impairment in this domain for this vilazodone group. CGI-S baseline scores showed that the majority of patients in the placebo and vilazodone 20- and 40-mg/day groups, respectively, were moderately ill (75%, 69%, 74%) and had severe symptoms on the HAMA Anxious Mood (70%, 72%, 67%) and Tension (63%, 69%, 63%) items. Mean HAMD17 baseline scores were approximately 13 in each group, indicating a non- or mildly depressed patient population.[21]

ANALYSIS OF EFFICACY

The least squares mean difference (LSMD) in change from baseline to week 8 in HAMA total score was statistically significant for vilazodone 40 mg/day versus placebo.
TABLE 2. Demographic characteristics and GAD history (safety population)

| Characteristics                  | Placebo, n = 221 | 20 mg/day, n = 227 | 40 mg/day, n = 225 |
|----------------------------------|------------------|-------------------|-------------------|
| Age, mean (SD), years            | 40.0 (13.7)      | 40.6 (13.7)       | 39.9 (13.3)       |
| Women, n (%)                     | 143 (64.7)       | 149 (65.6)        | 142 (63.1)        |
| Race, n (%)                      |                  |                   |                   |
| White                            | 174 (78.7)       | 167 (73.6)        | 167 (74.2)        |
| Black or African American        | 35 (15.8)        | 50 (22.0)         | 46 (20.4)         |
| Asian                            | 4 (1.8)          | 3 (1.3)           | 5 (2.2)           |
| Other                            | 8 (3.6)          | 7 (3.0)           | 7 (3.1)           |
| Body weight, mean (SD), kg       | 80.2 (16.8)      | 81.0 (17.3)       | 80.8 (19.0)       |
| BMI, mean (SD), kg/m²            | 28.3 (5.3)       | 28.3 (5.4)        | 28.0 (5.5)        |
| GAD history                      |                  |                   |                   |
| Duration of GAD, mean (SD), years| 13.90 (13.25)   | 13.94 (13.29)     | 12.84 (12.03)     |
| Age at GAD onset, mean (SD), years| 26.1 (14.4)   | 26.7 (14.2)       | 27.1 (14.5)       |
| Previous treatment for Yes       | 38 (17.2)        | 39 (17.2)         | 40 (17.8)         |
| GAD No                           | 183 (82.8)       | 188 (82.8)        | 185 (82.2)        |
| Nonresponders to previous treatment a | 20 (53)           | 17 (44)           | 18 (45)           |

*Percentage based on number of patients with previous treatment.

BMI, body mass index; GAD, generalized anxiety disorder.

Using the predefined MMRM primary analysis (adjusted for multiple comparisons: \( P = .0312 \)) (Table 3); the difference in HAMA total score for vilazodone 20 mg/day versus placebo was not statistically significant. The statistically significant difference in HAMA total score for vilazodone 40 mg/day versus placebo was seen as early as week 2 and it persisted for the remainder of the study (Fig. 1). PMM sensitivity analysis supported the primary results for vilazodone 40 mg/day versus placebo (results not shown); the LOCF analysis did not show a statistically significant difference for either vilazodone dose versus placebo.

Using the predefined MMRM analysis, the LSMD in change from baseline to week 8 in SDS total score was not statistically significant for either vilazodone group versus placebo when adjusted for multiple comparisons (Table 3); a significant difference versus placebo was noted for vilazodone 40 mg/day without adjustment for multiplicity (\( P = .0349 \)). In the sensitivity analysis, the differences between vilazodone 20 or 40 mg/day

TABLE 3. Primary and secondary efficacy outcomes (ITT population)

| Efficacy measure                  | Placebo, n = 221 | 20 mg/day, n = 227 | 40 mg/day, n = 225 |
|-----------------------------------|------------------|-------------------|-------------------|
| HAMA total score (primary efficacy) |                  |                   |                   |
| Baseline, mean (SD)               | 24.4 (3.5)       | 24.7 (3.8)        | 24.4 (3.5)        |
| MMRM Change from baseline to week 8, LS mean (SE) | –11.68 (0.52) | –12.95 (0.53)    | –13.48 (0.55)    |
| LSMD (95% CI)                     | –1.27 (–2.71, 0.17) | –1.80 (–3.26, –0.34) |
| \( P \)-value                     | .0830            | .0156             | .0156             |
| Adjusted \( P \)-value a          |                  |                   |                   |
| LOCF Change from baseline to week 8, LS mean (SE) | –10.83 (0.52) | –11.70 (0.51)    | –11.91 (0.52)    |
| LSMD (95% CI)                     | –0.87 (–2.42, 0.50) | –1.08 (–2.45, 0.29) |
| \( P \)-value b                   | .2136            | .1213             | .1213             |
| SDS total score (secondary efficacy) c |                  |                   |                   |
| Baseline, mean (SD)               | 15.8 (6.1)       | 16.7 (5.9)        | 15.7 (5.9)        |
| MMRM Change from baseline to week 8, LS mean (SE) | –7.41 (0.51) | –8.77 (0.51)     | –8.93 (0.53)     |
| LSMD (95% CI)                     | –1.37 (–2.75, 0.02) | –1.52 (–2.94, –0.11) |
| \( P \)-value                     | .0536            | .0349             | .0349             |
| Adjusted \( P \)-value a          |                  |                   |                   |
| LOCF Change from baseline to week 8, LS mean (SE) | –7.10 (0.51) | –8.21 (0.50)     | –7.93 (0.50)     |
| LSMD (95% CI)                     | –1.11 (–2.44, 0.21) | –0.83 (–2.16, 0.50) |
| \( P \)-value b                   | .0999            | .2200             | .2200             |

*Adjusted \( P \)-values were obtained from the matched parallel gatekeeping procedure.

Based on an ANCOVA model.

SDS total score based on a modified ITT population and calculated as the sum of the three subscales.

CI, confidence interval; HAMA, Hamilton Rating Scale for Anxiety; LOCF, last observation carried forward; LS, least squares; LSMD, least squares mean difference; MMRM, mixed-effects model for repeated measures; SE, standard error; SDS, Sheehan Disability Scale.

Depression and Anxiety
and placebo were not statistically significant using the ANCOVA with LOCF approach.

Additional efficacy parameters are presented in Table 4. Improvement from baseline was statistically significant in favor of vilazodone 40 mg/day versus placebo on the HAMA Total score and CGI-I score at week 8, change in the HAMA Ten-sion item, and CGI-I response rates were statistically significant for both vilazodone 20 and 40 mg/day versus placebo.

SAFETY AND TOLERABILITY

Extent of Exposure. For the placebo and vilazodone 20- and 40-mg/day groups, mean duration of treatment was 51, 48, and 45 days, respectively; patient years of exposure (total treatment duration in days divided by 365.25) were 30.6, 30.0, and 28.0, respectively.

Adverse Events. An overall summary of AEs is presented in Table 5. The incidence of treatment-emergent AEs (TEAEs) was similar in the vilazodone 20- and 40-mg/day groups (~71%) and slightly lower in the placebo group (62%). TEAEs reported at ≥5% in either vilazodone group and at least twice the rate of placebo were nausea, diarrhea, dizziness, vomiting, and fatigue. Discontinuation due to AEs was more frequent with vilazodone 40 mg/d than placebo (P < .05); nausea and headache were the most frequent AEs leading to discontinuation. Approximately, 97% of TEAEs in each group were considered by the investigator to be mild or moderate in severity; TEAEs were considered related to treatment in 54%, 69%, and 71% of placebo and vilazodone 20- and 40-mg/day patients, respectively.

Serious AEs (SAEs) were reported by two patients (hematoma [one placebo patient]; suicidal ideation [one vilazodone 20-mg/day patient]); neither event was considered related to treatment and both patients discontinued. The incidence of newly emergent AEs during down-taper was similar in all treatment groups.

Clinical Laboratory, Vital Sign, ECG Evaluation. Mean changes from baseline to the end of double-blind treatment were generally small and similar among groups for most laboratory parameters and vital signs. Changes in liver enzyme/function parameters were small and similar across groups and 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).

Potentially clinically significant (PCS) laboratory and vital sign values were generally low and similar for placebo and vilazodone. The most frequently reported PCS changes in metabolic parameters were for total cholesterol (>1.1 × ULN) and triglycerides (>1.2 × ULN), which occurred with similar frequency in the placebo and vilazodone 20- and 40-mg groups (total cholesterol: 11%, 13%, 16%; triglycerides: 16%, 11%, 12%, respectively). PCS change in high serum glucose (>1.2 × ULN) was more frequent with vilazodone 40 mg/day (6%) than placebo (2%) and vilazodone 20 mg/day (2%); PCS changes in creatine kinase (>1.5 × ULN) were similar across treatment groups (6–8%).

Orthostatic hypotension (≥20 mmHg reduction in systolic BP or ≥10 mmHg reduction in diastolic BP while changing from a supine to standing position) was reported in 14 (6%) placebo, 24 (11%) vilazodone 20-mg/day, and 11 (5%) vilazodone 40-mg/day patients; no related AE pattern was noted. Mean changes in body weight were low for placebo (0.12 kg), and vilazodone 20-mg/day (0.36 kg) and 40-mg/day (0.39 kg) patients; PCS weight increase (>7%) was low in each group (1%, 2%, 1%, respectively). No patient had a QTc Bazett (QTcB) or QTc Fridericia (QTcF) interval increase >500 ms.

Suicidality and Suicide-Related AEs. During the study, C-SSRS–based suicidal ideation was more common in placebo patients (22 [10%]) than in vilazodone 20-mg/day (15 [7%]) or 40-mg/day (15 [7%]) patients, and no suicidal behavior was reported. TEAEs of suicidal ideation were reported in one vilazodone 20-mg/day patient (severe; resulted in discontinuation from the study) and one vilazodone 40-mg/day patient (nonserious; resolved on treatment). Neither event was considered related to treatment.

Sexual Functioning. At the end of double-blind treatment, systematic assessment of sexual functioning using the CSFQ showed small and similar mean score changes in the placebo (1.6), and vilazodone 20-mg/day (1.3) and 40-mg/day (1.5) groups; in these treatment

Figure 1. HAMA total score mean change from baseline (MRRM, ITT population). The least squares mean change from baseline in HAMA total score was significantly greater for vilazodone 40 mg/day versus placebo beginning at week 2; the significant difference persisted throughout double-blind treatment. P-values shown are for vilazodone 40 mg/day versus placebo and were not adjusted for multiplicity. Vilazodone 20 mg/day was not statistically different versus placebo at any visit.

Depression and Anxiety
| Additional efficacy outcomes (MMRM) | Placebo, $n = 221$ | Vilazodone 20 mg/day, $n = 223$ | Vilazodone 40 mg/day, $n = 223$ |
|------------------------------------|-------------------|------------------------|------------------------|
| **HAMA Psychic Anxiety Subscale**  |                   |                        |                        |
| Baseline, mean (SD)                | 14.2 (2.1)        | 14.3 (2.3)             | 14.2 (2.2)             |
| Change from baseline to week 8, LS mean (SE) | $-6.62 (0.31)$  | $-7.37 (0.31)$         | $-7.65 (0.32)$         |
| LSMD (95% CI)                      |                  | $-0.75 (-1.59, 0.10)$  | $-1.03 (-1.89, -0.17)$ |
| $P$-value                          |                  | .0825                  | .0184                  |
| **HAMA Somatic Anxiety Subscale**  |                   |                        |                        |
| Baseline, mean (SD)                | 10.2 (2.8)        | 10.4 (2.9)             | 10.2 (3.0)             |
| Change from baseline to week 8, LS mean (SE) | $-5.07 (0.26)$  | $-5.61 (0.26)$         | $-5.86 (0.27)$         |
| LSMD (95% CI)                      |                  | $-0.54 (-1.24, 0.17)$  | $-0.79 (-1.51, -0.08)$ |
| $P$-value                          |                  | .1349                  | .0101                  |
| **HAMA Anxious Mood item**         |                   |                        |                        |
| Baseline, mean (SD)                | 2.8 (0.49)        | 2.9 (0.51)             | 2.8 (0.53)             |
| Change from baseline to week 8, LS mean (SE) | $-1.26 (0.07)$  | $-1.41 (0.07)$         | $-1.44 (0.07)$         |
| LSMD (95% CI)                      |                  | $-0.15 (-0.33, 0.04)$  | $-0.18 (-0.37, 0.01)$  |
| $P$-value                          |                  | .1320                  | .0706                  |
| **HAMA Tension item**              |                   |                        |                        |
| Baseline, mean (SD)                | 2.7 (0.53)        | 2.8 (0.52)             | 2.7 (0.55)             |
| Change from baseline to week 8, LS mean (SE) | $-1.24 (0.07)$  | $-1.49 (0.07)$         | $-1.50 (0.07)$         |
| LSMD (95% CI)                      |                  | $-0.24 (-0.43, -0.05)$ | $-0.25 (-0.45, -0.06)$ |
| $P$-value                          |                  | .0146                  | .0111                  |
| **SDS Work/School item**           |                   |                        |                        |
| Baseline, mean (SD)                | 4.9 (2.5)         | 5.4 (2.4)*             | 5.0 (2.3)              |
| Change from baseline to week 8, LS mean (SE) | $-2.41 (0.19)$  | $-2.83 (0.19)$         | $-2.76 (0.20)$         |
| LSMD (95% CI)                      |                  | $-0.42 (-0.94, 0.01)$  | $-0.34 (-0.87, 0.19)$  |
| $P$-value                          |                  | .2035                  | .1111                  |
| **SDS Social Life item**           |                   |                        |                        |
| Baseline, mean (SD)                | 5.5 (2.5)         | 5.8 (2.3)              | 5.7 (2.3)              |
| Change from baseline to week 8, LS mean (SE) | $-2.69 (0.18)$  | $-2.96 (0.18)$         | $-3.34 (0.18)$         |
| LSMD (95% CI)                      |                  | $-0.28 (-0.75, 0.20)$  | $-0.65 (-1.13, -0.17)$ |
| $P$-value                          |                  | .0533                  | .0086                  |
| **SDS Family Life item**           |                   |                        |                        |
| Baseline, mean (SD)                | 5.2 (2.4)         | 5.4 (2.4)              | 5.2 (2.4)              |
| Change from baseline to week 8, LS mean (SE) | $-2.36 (0.17)$  | $-2.78 (0.17)$         | $-2.98 (0.18)$         |
| LSMD (95% CI)                      |                  | $-0.41 (-0.88, 0.05)$  | $-0.62 (-1.10, -0.15)$ |
| $P$-value                          |                  | .0157                  | .0103                  |
| **CGI-S**                          |                   |                        |                        |
| Baseline, mean (SD)                | 4.3 (0.5)         | 4.4 (0.6)              | 4.3 (0.5)              |
| Change from baseline to week 8, LS mean (SE) | $-1.40 (0.08)$  | $-1.61 (0.08)$         | $-1.69 (0.09)$         |
| LSMD (95% CI)                      |                  | $-0.21 (-0.43, 0.02)$  | $-0.29 (-0.52, -0.06)$ |
| $P$-value                          |                  | .0749                  | .0148                  |
| **CGI-I**                          |                   |                        |                        |
| Score at week 8, mean (SE)         | 2.4 (0.08)        | 2.2 (0.08)             | 2.1 (0.08)             |
| $P$-value                          |                  | .0157                  | .0053                  |
| **HAMD$_{17}$ total score**        |                   |                        |                        |
| Baseline, mean (SD)                | 13.0 (2.5)        | 12.8 (2.5)             | 12.9 (2.5)             |
| Change from baseline to week 8, LS mean (SE) | $-4.67 (0.37)$  | $-4.84 (0.38)$         | $-5.56 (0.39)$         |
| LSMD (95% CI)                      |                  | $-0.17 (-1.15, 0.81)$  | $-0.88 (-1.89, 0.13)$  |
| $P$-value                          |                  | .7359                  | .0863                  |

Response (GLMM)

| HAMA responders at week 8 (%; ≥50% improvement from baseline) | 48.1 | 53.9 | 62.1 |
| OR (95% CI) | 1.458 (0.780, 2.728) | 2.141 (1.115, 4.109) |
| $P$-value | .0530 | .0222 |

| CGI-I responders at week 8 (%; CGI-I ≤2) | 54.1 | 64.0 | 65.2 |
| OR (95% CI) | 1.944 (1.019, 3.709) | 1.964 (1.011, 3.815) |
| $P$-value | .0436 | .0463 |

Statistical significance for additional efficacy parameters was nominal without adjustment for multiplicity. *$P < .05$ versus placebo.

*Based on the number of patients with an SDS analysis value at baseline and week 8 (Work/School: placebo = 145; vilazodone 20 mg = 141; vilazodone 40 mg = 129; Social Life and Family Life: placebo = 185, vilazodone 20 mg = 178, vilazodone 40 mg = 161).

CGI-I, Clinical Global Impressions-Improvement; CGI-S, Clinical Global Impressions-Severity; CI, confidence interval; HAMA, Hamilton Rating Scale for Anxiety; HAMD$_{17}$, Hamilton Depression Rating Scale; GLMM, generalized linear mixed model; LS, least squares; LSMD, least squares mean difference; MMRM, mixed-effects model for repeated measures; SE, standard error; SDS, Sheehan Disability Scale.

groups, respectively, small mean score increases, indicating improvement on the scale, were seen in male (3.0, 0.6, 1.5) and female (0.9, 1.6, 1.4) patients. AEs related to sexual function were more common in vilazodone- than placebo-treated patients, except for ejaculation delayed, which occurred in one male patient in each treatment group; the most frequently reported sexual function related TEAE was libido decreased (placebo = 2 [0.9%]; vilazodone 20 mg/day = 3 [1.3%]; vilazodone 40 mg/day = 5 [2.2%]). Most sexual function AEs were considered mild or moderate; three male patients discontinued due to sexual AEs (one [0.5%] placebo [libido decreased], one...
TABLE 5. Adverse events (safety population)

| Adverse events summary, n (%) | Placebo, n = 221 | 20 mg/day, n = 227 | 40 mg/day, n = 225 |
|-------------------------------|------------------|-------------------|-------------------|
| Deaths                        | 0                | 0                 | 0                 |
| Patients with ≥1 TEAE         | 138 (62.4)       | 163 (71.8)        | 160 (71.1)        |
| Patients who discontinued due to AE | 11 (5.0)      | 18 (7.9)          | 30 (13.3)         |
| Patients with SAE            | 1 (0.5)          | 1 (0.4)           | 0                 |
| Patients with newly emergent AE<sup>a</sup> | 7 (3.2)      | 9 (4.0)           | 9 (4.0)           |

Common adverse events during double-blind treatment (≥5% in any treatment group)

- Nausea: Placebo 25 (11.3), 20 mg/day 55 (24.2), 40 mg/day 58 (25.8)
- Diarrhea: Placebo 23 (10.4), 20 mg/day 57 (25.1), 40 mg/day 48 (21.3)
- Headache: Placebo 18 (8.1), 20 mg/day 32 (14.1), 40 mg/day 25 (11.1)
- Dizziness: Placebo 8 (3.6), 20 mg/day 12 (5.3), 40 mg/day 21 (9.3)
- Vomiting: Placebo 5 (2.3), 20 mg/day 13 (5.7), 40 mg/day 17 (7.6)
- Fatigue: Placebo 6 (2.7), 20 mg/day 7 (3.1), 40 mg/day 13 (5.8)
- Insomnia: Placebo 11 (5.0), 20 mg/day 12 (5.3), 40 mg/day 13 (5.8)
- Upper respiratory tract infection: Placebo 16 (7.2), 20 mg/day 11 (4.8), 40 mg/day 12 (5.3)
- Dry mouth: Placebo 12 (5.4), 20 mg/day 10 (4.4), 40 mg/day 10 (4.4)

Adverse events leading to discontinuation of ≥2 patients in any group

- Nausea: Placebo 2 (0.9), 20 mg/day 4 (1.8), 40 mg/day 9 (4.0)
- Headache: Placebo 1 (0.5), 20 mg/day 3 (1.3), 40 mg/day 7 (3.1)
- Anxiety: Placebo 1 (0.5), 20 mg/day 1 (0.4), 40 mg/day 3 (1.3)
- Diarrhea: Placebo 1 (0.5), 20 mg/day 3 (1.3), 40 mg/day 3 (1.3)
- Dizziness: Placebo 1 (0.5), 20 mg/day 2 (0.9), 40 mg/day 3 (1.3)
- Vomiting: Placebo 0, 20 mg/day 4 (1.8), 40 mg/day 1 (0.4)
- Hyperhidrosis: Placebo 0, 20 mg/day 2 (0.9), 40 mg/day 0

Coded by preferred term using MedDRA Version 15.1.
<sup>a</sup>Newly emergent AEs occurred during the double-blind down-taper period or within 30 days after the last dose of double-blind study drug. AE, adverse event; TEAE, treatment-emergent adverse event; SAE serious adverse event.

[0.4%] vilazodone 20 mg/day [sexual dysfunction], one [0.4%] vilazodone 40 mg/day [anorgasmia]).

DISCUSSION

This 8-week clinical trial met its primary efficacy endpoint and demonstrated statistically significant improvement in HAMA total score for patients treated with vilazodone 40 mg/day compared with placebo; the difference for the 20-mg/day group versus placebo was not statistically significant. Changes consistent with improvement in anxiety symptoms were observed on most efficacy measures for vilazodone 40-mg/day patients; greater overall improvement in illness versus placebo was suggested by statistically significant differences from placebo on the CGI-I score (vilazodone 20 and 40 mg/day) and CGI-S change (vilazodone 40 mg/day). The proportion of HAMA and CGI-I responders in the vilazodone 40-mg/day group was comparable to other antidepressants in the treatment of GAD.<sup>23</sup>

Since improvement in functional impairment generally lags behind symptomatic improvement in psychiatric disorders such as depression,<sup>23</sup> an 8-week study in GAD may not have been adequate to capture SDS changes. Only patients with assessments on all three individual domains are included in the calculation for SDS total score and in this trial, the differences versus placebo were not statistically significant in either vilazodone group. Statistically significant differences for the vilazodone 40-mg/day group versus placebo were observed on the Social Life (P = .0086) and Family Life (P = .0103) items, indicating improvements in these areas of functional impairment. It may have been more difficult to demonstrate improvement on the Work/School item since patients were less likely to experience these activities than social or family activities. Fewer 8-week assessments were available for placebo and vilazodone 20- and 40-mg/day patients, respectively, on the Work/School item (145, 141, 129) than the Family Life and Social Life items (185, 178, 161 both), suggesting that a smaller sample size may have contributed to difficulty in detecting an efficacy signal.

Vilazodone acts as an SSRI, similar to some antidepressants that are approved for GAD treatment,<sup>24,25</sup> and also possesses partial agonist activity at the 5-HT<sub>1A</sub> receptor similar to buspirone, an approved anxiolytic with demonstrated efficacy in short-term clinical trials in GAD.<sup>26</sup> Buspirone is not recommended as first-line treatment because of its slow onset of action, variable tolerability, and limited benefit in comorbid conditions.<sup>27-29</sup> Acute and chronic administration of vilazodone has produced anxiolytic-like activity in several animal models, with results suggesting that both serotonin reuptake inhibition and partial...
5-HT\textsubscript{1A} receptor agonist activity contributed to the effects (Vilazodone HCl Investigator’s Brochure, 2013). Although vilazodone 40 mg/day was significantly different than placebo on the primary efficacy parameter in this trial, additional investigation is necessary before any specific conclusions can be drawn about the mechanism of action for vilazodone and potential benefits in GAD.

Although our results demonstrated more robust efficacy for the vilazodone 40-mg/day than 20-mg/day dose, this study was not powered to detect a dose response. Other randomized, placebo-controlled, fixed-dose studies of SSRIs and SNRIs have not provided clear evidence of a dose–response relationship in the treatment of GAD. Paroxetine, escitalopram, and duloxetine have demonstrated efficacy versus placebo in GAD studies, but higher dosages were not found to be superior.\textsuperscript{[30–32]} Conversely, venlafaxine XR has demonstrated evidence for dose response in 12-week\textsuperscript{[33]} and 6-month GAD trials.\textsuperscript{[34]}

Due to the waxing and waning course of GAD, it is recommended that treatment continue for at least a year to maximize the probability of remission.\textsuperscript{[35]} Over time, some antidepressant-related AEs, including weight gain, sleep disturbance, and sexual dysfunction, may impair treatment acceptance.\textsuperscript{[32]} In our short-term study, the incidence of these AEs were generally low and resulted in few study discontinuations. Body weight increases were small and similar across groups, and weight-related AEs were reported in only two vilazodone patients; PCS weight gain occurred in \(\leq2\%\) of patients in any group. The incidence of insomnia TEAEs in the placebo (5%) and vilazodone 20-mg/day (5%) and 40-mg/day (6%) groups was lower than the percentage of patients from each group who reported a history of insomnia (16%, 14%, and 13%, respectively).

CSFQ scores indicated that sexual functioning did not worsen with vilazodone treatment during this trial; there were no observed differences using this systematic assessment of sexual function for patients being treated with vilazodone or placebo. However, there were more AEs related to sexual function in the vilazodone group than in the placebo group, suggesting that some treatment-related sexual side effects may have occurred. Of note, no sexual function related TEAE occurred in \(>2\%\) of patients in any group and discontinuations due to sexual function AEs were only reported for one male patient in each treatment group. Knowledge of the sexual function profile of vilazodone is important since sexual dysfunction, a class effect of SSRIs, is considered a particularly unacceptable side effect\textsuperscript{[30]} and it can lead to treatment nonadherence.\textsuperscript{[37]}

Limitations of this study include its short duration, which may have limited assessment of maximum SDS improvement, and lack of an active comparator. No patients with significant depressive symptoms or MDD were enrolled; as such, these findings may not generalize to GAD patients with a broader symptom profile or comorbid MDD.

CONCLUSION

Statistically significant improvements for vilazodone 40 mg/day versus placebo were seen on the primary efficacy measure and on several additional efficacy measures in this clinical trial in patients with GAD; differences from placebo for vilazodone 20 mg/day were not statistically significant on most outcome measures. The safety profile of vilazodone was consistent with findings in studies of patients with MDD and what has been described in the prescribing information; no new safety concerns were identified. Future studies of vilazodone in this population are warranted.

Acknowledgements. Writing assistance and editorial support for the preparation of this manuscript were provided by Carol Brown, MS, of Prescott Medical Communications Group, Chicago, Illinois, a contractor of Forest Research Institute, an affiliate of Actavis, Inc.

Conflicts of interest. Carl Gommoll, Suresh Durgam, and Xiongwen Tang acknowledge a potential conflict of interest as employees of Forest Research Institute, an affiliate of Actavis Inc. Maju Mathews, Giovanna Forero, and Rene Nunez acknowledge a potential conflict of interest as employees of Forest Research Institute, Inc., an affiliate of Actavis Inc., at the time of the study.

During the past 3 years, Michael E. Thase has served as an advisor/consultant for Alkermes, AstraZeneca, Avenir, Aventis (including Allergan, Forest Laboratories, an affiliate of Actavis, Inc., and PGX Health, Inc.), Bristol-Myers Squibb Company, Cerecor, Eli Lilly & Co., Gerson Lehman Group, Guidepoint Global, H. Lundbeck A/S, Johnson & Johnson (including Janssen and Ortho-McNeil Pharmaceuticals), MedAvante Inc., Merck & Co. Inc., Naurex, Nestlé (including PamLab), Neurotechnics, Inc., Novartis, Otsuka, Pamlab, Pfizer, PharmaNeuroboost, Shire US Inc., Supernus Pharmaceuticals, Takeda, and Transcept Pharmaceuticals. During the same period, he has received grant support from Agency for Healthcare Research and Quality, Alkermes, AstraZeneca, Avenir, Eli Lilly and Company, Forest Pharmaceuticals, GlaxoSmithKline, Johnson & Johnson, the National Institute of Mental Health, Novartis, and Otsuka Pharmaceuticals. Dr. Thase’s spouse is an employee of Peloton Advantage, which does business with several pharmaceutical companies.

REFERENCES

1. Wittchen HU, Carter RM, Pfister H, et al. Disabilities and quality of life in pure and comorbid generalized anxiety disorder and major depression in a national survey. Int Clin Psychopharmacol 2000;15:319–328.
2. Buoli M, Caldiroli A, Caletti E, et al. New approaches to the pharmacological management of generalized anxiety disorder. Expert Opin Pharmacother 2013;14:175–184.
3. Khan A, Cutler AJ, Kajdasz DK, et al. A randomized, double-blind, placebo-controlled, 8-week study of vilazodone, a serotonergic agent for the treatment of major depressive disorder. J Clin Psychiatry 2011;72:441–447.

4. Rickels K, Athanasiou M, Robinson DS, et al. Evidence for efficacy and tolerability of vilazodone in the treatment of major depressive disorder: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry 2009;70:326–333.

5. Croft HA, Pomara N, Gommoll C, et al. Efficacy and safety of vilazodone in major depressive disorder: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry 2014;75:e1291–e1298.

6. Mathews M, Gommoll C, Chen D, et al. Efficacy and safety of vilazodone 20 and 40 mg in major depressive disorder: a randomized, double-blind, placebo-controlled trial. Int Clin Psychopharmacol 2015;30:67–74.

7. Robinson DS, Kajdasz DK, Gallipoli S, et al. A 1-year, open-label study assessing the safety and tolerability of vilazodone in patients with major depressive disorder. J Clin Psychopharmacol 2011;31:643–646.

8. Liebowitz M, Croft HA, Kajdasz DK, et al. The safety and tolerability profile of vilazodone, a novel antidepressant for the treatment of major depressive disorder. Psychopharmacol Bull 2011;44:1–19.

9. Hub J, Goebert D, Takeshita J, et al. Treatment of generalized anxiety disorder: a comprehensive review of the literature for psychopharmacologic alternatives to newer antidepressants and benzodiazepines. Prim Care Companion CNS Disord 2011;13(2):e1–e9. Available at http://www.psychiatrist.com/pcp/articlePages/2011/v13n02/08r00709.aspx

10. BuSpar [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2010.

11. Thase ME, Chen D, Edwards J, Ruth A. Efficacy of vilazodone on anxiety symptoms in patients with major depressive disorder. Int Clin Psychopharmacol 2014;29:351–356.

12. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed., text revision. Washington, DC: American Psychiatric Association; 2000.

13. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959:32:50–55.

14. Guy W. The clinician global severity and impression scales. ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: National Institute of Mental Health; 1976:218–222.

15. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62.

16. Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. Int Clin Psychopharmacol 1996;11(Suppl. 3):89–95.

17. Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry 2011;168:1266–1277.

18. Clayton AH, McGarvey EL, Clavet GJ, Piazza L. Comparison of sexual functioning in clinical and nonclinical populations using the Changes in Sexual Functioning Questionnaire (CSFQ). Psychopharmacol Bull 1997;33:747–753.

19. Kenward MG, Molenberghs G, Thijs H. Pattern-mixture models with proper time dependence. Biometrika 2003;90:53–71.

20. Chen X, Luo X, Capizzi T. The application of enhanced parallel gatekeeping strategies. Statist Med 2005;24:1385–1397.

21. Zimmerman M, Martinez JH, Young D, et al. Severity classification on the Hamilton Depression Rating Scale. J Affect Disord 2013;150:384–388.

22. Baldwin DS, Waldman S, Allgulander C. Evidence-based pharmacological treatment of generalized anxiety disorder. Int J Neuropsychopharmacol 2011;14:697–710.

23. Hirschfeld RM, Dunner DL, Keitner G, et al. Does psychosocial functioning improve independent of depressive symptoms? A comparison of nefazodone, psychotherapy, and their combination. Biol Psychiatry 2002;51(2):123–133.

24. Paxil [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2013.

25. Lexapro [package insert]. St. Louis, MO: Forest Pharmaceuticals, Inc; 2014.

26. Chessick CA, Allen MH, Thase M, et al. Azapirones for generalized anxiety disorder. Cochrane Database Syst Rev 2006;3:CD006115.

27. Ballenger JC, Davidson JR, Lecrubier Y, et al. Consensus statement on generalized anxiety disorder from the International Consensus Group on Depression and Anxiety. J Clin Psychiatry 2001;62(Suppl 11):53–58.

28. Bandelow B, Zohar J, Hollander E, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders—first revision. World J Biol Psychiatry 2008;9:248–312.

29. Davidson JR, Zhang W, Connor KM, et al. A psychopharmacological treatment algorithm for generalised anxiety disorder (GAD). J Psychopharmacol 2010;24:3–26.

30. Baldwin DS, Huusom AK, Maehlum E. Escitalopram and paroxetine in the treatment of generalised anxiety disorder: randomised, placebo-controlled, double-blind study. Br J Psychiatry 2006;189:264–272.

31. Koponen H, Allgulander C, Erickson J, et al. Efficacy of duloxetine for the treatment of generalised anxiety disorder: implications for primary care physicians. Prim Care Companion J Clin Psychiatry 2007;9:100–107.

32. Rickels K, Zaninelli R, McCafferty J, et al. Paroxetine treatment of generalized anxiety disorder: a double-blind, placebo-controlled study. Am J Psychiatry 2003;160:749–756.

33. Rickels K, Pollack MH, Sheehan DV, Hasksin JT. Efficacy of extended-release venlafaxine in nondepressed outpatients with generalized anxiety disorder. Am J Psychiatry 2000;157:968–974.

34. Allgulander C, Hackett D, Salinas E. Venlafaxine extended release (ER) in the treatment of generalised anxiety disorder: twenty-four-week placebo-controlled dose-ranging study. Br J Psychiatry 2001;179:15–22.

35. Allgulander C. Generalized anxiety disorder: a review of recent findings. J Exp Clin Med 2012;4:88–91.

36. Hu XH, Bull SA, Hunkeler EM, et al. Incidence and duration of side effects and those rated as bothersome with selective serotonin reuptake inhibitor treatment for depression: patient report versus physician estimate. J Clin Psychiatry 2004;65:959–965.

37. Ashton AK, Jamerson BD, Weinstein W, Wagner C. Antidepressant-related adverse effects impacting treatment compliance: Results of a patient survey. Curr Ther Res Clin Exp 2005;66:96–106.

Depression and Anxiety