Evaluating the efficacy of vilazodone in achieving remission in patients with major depressive disorder: post-hoc analyses of a phase IV trial

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The aim of this study was to evaluate the efficacy of vilazodone using different definitions of remission. Post-hoc analyses were carried out using data from an 8-week, multicenter, randomized, double-blind, placebo-controlled trial of vilazodone 40 mg/day in adults with major depressive disorder (NCT01473394). The primary efficacy endpoint was a mean change in the Montgomery–Åsberg Depression Rating Scale (MADRS) total score; additional measures included the Clinical Global Impressions-Severity (CGI-S) and Hamilton Rating Scale for Anxiety (HAMA) scores. In addition to treatment response (MADRS ≥ 50% improvement), post-hoc analyses were carried out for remission of depressive symptoms [MADRS score ≤ 10; MADRS ≤ 5 (complete remission)], anxiety symptoms (HAMA ≤ 7), and combined depression and anxiety symptoms (MADRS/HAMA ≤ 10/ ≤ 7), as well as for overall symptom severity (CGI-S = 1). Odds ratios (ORs) and numbers needed to treat (NNTs) were also calculated. Significant outcomes were obtained with vilazodone versus placebo for MADRS response (50.6 vs. 33.3%, OR = 2.04, $P < 0.001$, NNT = 6), remission (34.0 vs. 21.8%, OR = 1.82, $P = 0.003$, NNT = 9), and complete remission (18.2 vs. 8.3%, OR = 2.42, $P = 0.002$, NNT = 11). More patients receiving vilazodone rather than placebo also met remission criteria for HAMA (48.8 vs. 35.2%, OR = 1.82, $P = 0.002$, NNT =8), MADRS/HAMA (32.1 vs. 20.4%, OR = 1.83, $P = 0.004$, NNT =9), and CGI-S (24.1 vs. 11.5%, OR = 2.41, $P < 0.001$, NNT =8). Treatment with vilazodone 40 mg/day may help adult patients with major depressive disorder achieve remission of depression and/or anxiety symptoms. ***Int Clin Psychopharmacol*** **30:75–81**

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Introduction

Selective serotonin reuptake inhibitors (SSRIs) are often recommended as first-line therapies in patients with major depressive disorder (MDD; American Psychiatric Association, 2010). It has been postulated, however, that the acute and long-term effects of these drugs may be limited due to autoregulatory feedback mechanisms involving the 5-HT_1 class of serotonergic receptors (Dawson, 2013). One approach to this issue has been the investigation of augmentation therapies, such as the addition of 5-HT_{1A} or 5-HT_{1B} agonists to SSRIs in patients with MDD (Ruf and Bhagwagar, 2009; Kato and Chang, 2013). Another approach has been the development of medications with additional mechanisms of action, such as vilazodone, an SSRI and partial 5-HT_{1A} receptor agonist that is currently approved for the treatment of MDD in adults (Forest Laboratories Inc., 2014). In addition to potentially improving the antidepressant effects, targeting 5-HT_{1A} receptors may help reduce the anxiety symptoms that are often associated with MDD (Rao and Zisook, 2009). Therefore, the role of the 5-HT_{1A} receptor in the treatment of depression and anxiety symptoms associated with mood disorders continues to be explored (Popova and Naumenko, 2013).

The efficacy of vilazodone in the treatment of MDD was established in two 8-week, phase III pivotal trials (Rickels *et al.*, 2009; Khan *et al.*, 2011), both of which used change from baseline in the Montgomery–Åsberg Depression Rating Scale (MADRS) total score as the primary efficacy outcome. Both studies showed a significant mean decreases with vilazodone in this primary outcome measure, indicating improvements in depressive symptomatology. Significant improvements in depression-related anxiety symptoms and overall disease severity were also found, on the basis of the mean change in the Hamilton Rating Scale for Anxiety (HAMA) total score and the Clinical Global Impressions-Severity (CGI-S) score, respectively. These findings from the pivotal studies were further supported by the results from a more recent phase IV clinical trial (NCT01473394;

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Croft *et al.*, 2014) in which patients were randomized to 40 mg/day vilazodone or placebo for 8 weeks of double-blind treatment. Compared with placebo, vilazodone-treated patients in this trial also experienced significantly greater mean improvements from baseline in MADRS total, HAMA total, and CGI-S scores.

Although significantly greater reductions compared with placebo on depression rating scales is an important criterion for establishing antidepressant efficacy, the goal of treatment is for patients to achieve clinically meaningful outcomes. Symptom remission is an important outcome in depression treatment and is associated with improved psychosocial functioning, lower risk of relapse and recurrence, and reduced healthcare utilization among patients with MDD (Thase *et al.*, 2002; Rush *et al.*, 2006). Remission is generally considered a fundamental goal of treatment, and several months of antidepressant therapy may be needed for a patient to achieve remission (Sobocki *et al.*, 2006). However, longitudinal studies with standard-of-care antidepressant treatment have found that early remission (i.e. 6–8 weeks) in MDD patients is associated with greater reduction in overall symptom severity, fewer residual symptoms, and greater likelihood of long-term remission (6–12 months; Roca *et al.*, 2011; Ciudad *et al.*, 2012).

Previous pooled analyses of the data from the two pivotal phase III trials showed that vilazodone-treated patients had significantly higher rates of remission, defined as MADRS total score <10 (Citrome, 2012) or ≤10 (Khan *et al.*, 2014) at week 8 relative to placebo-treated patients. A post-hoc analysis of data from the phase IV vilazodone trial was conducted to further evaluate symptom remission. Several different measures were used in this post-hoc analysis, guided by the concept of no or minimal disease-related symptoms typically used to define remission in MDD clinical trials (Rush *et al.*, 2006; Sobocki *et al.*, 2006). On the basis of the efficacy assessments included in the phase IV trial, the outcomes evaluated in this post-hoc analysis were remission of depressive symptoms (MADRS, Montgomery and Asberg, 1979), anxiety symptoms (HAMA, Hamilton, 1959), or a combination of both (MADRS/HAMA), as well as the overall disease burden (CGI-S). The results of this report are intended to provide additional information about the effects of vilazodone in adult patients with MDD.

Methods

This study was conducted in full compliance with the Food and Drug Administration guidelines for Good Clinical Practice and in accordance with the principles of the Declaration of Helsinki. The protocol was approved by institutional review boards; all patients provided written informed consent. Detailed methods for this multicenter, randomized, double-blind, placebo-controlled, parallel-group study have been published previously (Croft *et al.*, 2014). Key highlights of these methods are summarized below.

Study design

The study was conducted at 14 centers in the USA. It included male and female outpatients, between 18 and 70 years of age, who met the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. – text revision (DSM-IV-TR) criteria for MDD. Patients were required to have an ongoing major depressive episode (≥8 to ≤12 months), a BMI between 18 and 40 kg/m^2, and a MADRS total score of at least 26. Typical exclusion criteria for antidepressant clinical trials were applied, including the presence of DSM-IV-TR Axis I disorders other than MDD, significant psychiatric diagnoses (e.g. bipolar, obsessive–compulsive, psychotic, or cognitive disorder), substance abuse/dependence, and suicide risk. Patients with secondary comorbid generalized anxiety disorder (GAD), social anxiety disorder, and/or specific phobias were allowed to participate in the study. Treatment-related exclusion criteria were: nonresponse to at least two antidepressants, intolerance or hypersensitivity to vilazodone, serotonin–norepinephrine reuptake inhibitors, or SSRIs, use of psychoactive drugs (e.g. antipsychotics, antidepressants, benzodiazepines), and recent substance abuse or dependence.

After a no-drug screening period (1–4 weeks), eligible patients were randomized (1 : 1) to receive 8 weeks of double-blind treatment with placebo or vilazodone 40 mg/day, followed by a 1-week double-blind down-taper period. Vilazodone was initiated at 10 mg/day (week 1), increased to 20 mg/day (week 2), and then increased to a final stable dose of 40 mg/day (weeks 3–8). Patients were instructed to take all study drugs once daily with food. Blinding was established using computer-generated randomization codes. All investigators and patients remained blind during the treatment and taper periods.

Efficacy assessments

The prospectively defined primary efficacy endpoint for this study was the change from baseline in MADRS total score. Other predefined efficacy outcomes in this study included changes from baseline to week 8 in the CGI-S score (secondary endpoint) and the HAMA total score. MDD symptom response, defined as at least 50% improvement from baseline in MADRS total score, was also included as an efficacy outcome.

The effects of vilazodone on remission were evaluated in post-hoc analyses. Remission of depressive symptoms was defined as a MADRS total score of 10 or less, with 'complete remission' defined as a MADRS total score of 5 or less. Remission of anxiety symptoms was defined as a HAMA total score of 7 or less; the number of patients meeting the criteria for both MADRS and HAMA remission (MADRS total score ≤10 and HAMA total

Table 1 Patient demographics (ITT population)

	Placebo ($n = 252$)	Vilazodone ($n = 253$)
Age [mean (SD)] (years)	41.0 (13.2)	39.2 (12.8)
Women [*n* (%)]	142 (56.3)	130 (51.4)
Race [*n* (%)]		
White	167 (66.3)	173 (68.4)
Black/African–American	70 (27.8)	51 (20.2)
Other	15 (5.9)	29 (11.4)
BMI [mean (SD)] (kg/m^2)	29.1 (5.5)	28.4 (5.5)

ITT, intent to treat.

score ≤ 7, respectively) was also measured. Global disease remission was defined by a CGI-S score of 1 (normal, not at all ill) at week 8.

Statistical analyses

Efficacy analyses were based on the intent-to-treat (ITT) population, which included all randomized patients who received one or more dose of the study drug and had at least one postbaseline assessment (MADRS, HAMA, or CGI-S, depending on the analysis). Changes from baseline to the end of double-blind treatment were analyzed using a mixed-effects model for repeated measures with treatment group, study center, visit, and the treatment-group-by-visit interaction as fixed effects and baseline value and the baseline-value-by-visit interaction as covariates.

Response and remission rates at the end of treatment were analyzed through a logistic regression model with treatment group and baseline value as explanatory variables, with missing values imput using last observation carried forward. Response and remission by study visit were analyzed on the basis of observed cases and a generalized linear mixed model based on a logit link function, with a random intercept and fixed terms of treatment group, visit, treatment-by-visit interaction, and baseline value. If the generalized linear mixed model did not converge, a logistic regression model with treatment group and baseline value as explanatory variables was used on the basis of the last observation carried forward approach. Odds ratios (ORs) with 95% CIs are presented for response and remission. Numbers needed to treat (NNTs) to observe one additional favorable response or remission outcome (at end of treatment and at each study visit) were calculated on the basis of the observed risk differences between vilazodone and placebo, with 95% confidence intervals (CIs) reported if the boundaries were finite.

Results

Patients

A total of 505 patients were included in the ITT population; demographics were similar between treatment groups (Table 1). In the ITT population, the majority of patients were women (53.9%), white (67.3%), and between 30 and 60 years of age (66.5%; mean age, 40.1 years). More than 80% of the patients in this population completed the study, with similar completion rates for placebo (82.5%) and vilazodone (83.8%).

Efficacy outcomes

After 8 weeks of treatment, patients randomized to vilazodone 40 mg/day compared with placebo had significantly greater improvement in depressive symptoms (MADRS total score), anxiety symptoms (HAMA total score), and global disease severity (CGI-S score; all Ps < 0.001 vs. placebo; Table 2). The percentage of patients achieving response, defined as at least 50% improvement from baseline in MADRS total score, was significantly higher in the vilazodone group (50.6 vs. 33.3% for placebo, $P < 0.001$), corresponding to an NNT of 6 (Table 3). The odds of patients treated with vilazodone achieving MADRS response were 2.0 times the odds for those treated with placebo (Fig. 1).

Remission rates at the end of double-blind treatment were significantly higher among vilazodone-treated patients on all the measures included in this post-hoc analysis, with NNTs ranging from 8 to 11 (Table 3). Patients had 2.4 times greater odds of achieving complete remission of depressive symptoms (defined as MADRS total score ≤ 5) or global symptom remission (CGI-S score ≤ 1) with vilazodone versus placebo (Fig. 1). For the remaining remission criteria, ORs were 1.8 for vilazodone versus placebo.

Significant differences in response and remission rates were detected for vilazodone-treated patients relative to placebo-treated patients by week 6 (Fig. 2). For MADRS response, significant differences between vilazodone and placebo were found at weeks 6 and 8 of double-blind treatment, with NNTs of 6 and 5, respectively. A trend favoring vilazodone was observed at week 4 of the response analysis ($P = 0.09$), with an NNT of 13. For MADRS remission, significant between-group differences were also found at weeks 6 and 8, with NNTs of 7 and 8, respectively.

Discussion

In a randomized, double-blind, placebo-controlled, phase IV trial, patients who underwent 8 weeks of treatment with vilazodone 40 mg/day were found to have significant mean reductions relative to placebo in MADRS total, HAMA total, and CGI-S scores, indicating improvements across depressive and anxiety symptoms. However, as these average score changes do not necessarily indicate whether response or remission took place, analyzing the proportion of individual patients who achieve remission may provide a more comprehensive clinical context for the effects of antidepressant treatment. Therefore, post-hoc analyses of data from this phase IV trial were carried out using several definitions of remission. Overall, the results of these analyses showed that vilazodone-treated patients experienced remission, with significant

Table 2 Mean score changes from baseline to week 8 in efficacy measures (MMRM)[a]

	Placebo		Vilazodone			
	Mean baseline (SD)	LSM change (SE)	Mean baseline (SD)	LSM change (SE)	LSM difference (95% CI)	*P*
MADRS total	30.9 (3.3)	−11.0 (0.65)	30.6 (3.2)	−16.1 (0.64)	−5.12 (−6.89 to −3.35)	<0.001
HAMA total	15.4 (4.6)	−5.0 (0.36)	15.2 (4.7)	−7.1 (0.36)	−2.12 (−3.10 to −1.14)	<0.001
CGI-S	4.4 (0.5)	−1.2 (0.08)	4.3 (0.5)	−1.8 (0.08)	−0.62 (−0.85 to −0.40)	<0.001

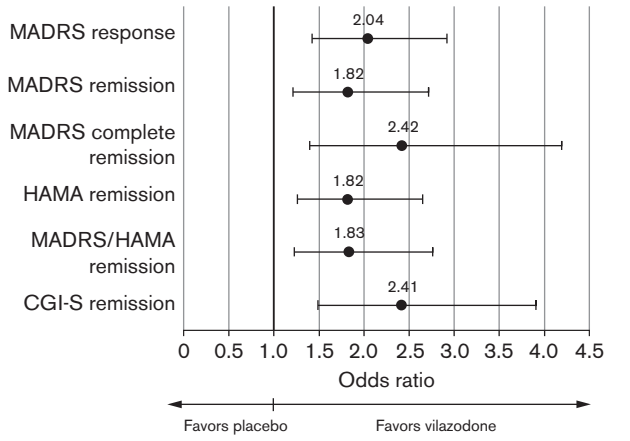
CGI-S, Clinical Global Impressions-Severity; CI, confidence interval; HAMA, Hamilton Rating Scale for Anxiety; LSM, least squares mean; MADRS, Montgomery–Åsberg Depression Rating; MMRM, mixed-effects model for repeated measures.
[a]Data have been previously published and are presented here with permission from *The Journal of Clinical Psychiatry* (Croft *et al.*, 2014).

Table 3 Response and remission rates at end of double-blind treatment

	Placebo [*n*/*N* (%)][a]	Vilazodone [*n*/*N* (%)][a]	Risk difference	NNT (95% CI)	*P*[b]
MADRS response, ≥50% improvement	84/252 (33.3)	128/253 (50.6)	0.173	6 (4–12)	<0.001
MADRS remission, total score ≤10	55/252 (21.8)	86/253 (34.0)	0.122	9 (6–23)	0.003
MADRS complete remission, total score ≤5	21/252 (8.3)	46/253 (18.2)	0.099	11 (7–26)	0.002
HAMA remission, total score ≤7	88/250 (35.2)	123/252 (48.8)	0.136	8 (5–20)	0.002
MADRS/HAMA remission, total scores ≤10/≤7	51/250 (20.4)	81/252 (32.1)	0.117	9 (6–25)	0.004
CGI-S remission, score of 1	29/252 (11.5)	61/253 (24.1)	0.126	8 (6–17)	<0.001

CGI-S, Clinical Global Impressions-Severity; CI, confidence interval; HAMA, Hamilton Anxiety Rating Scale; MADRS, Montgomery–Åsberg Depression Rating; NNT, number needed to treat.
[a]*n* represents the number of patients meeting response or remission criterion. *N* represents the number of patients with a valid assessment at Week 8 (for study completers) or at the last study visit (for patients who discontinued).
[b]*P*-values were obtained for odds ratios through a logistic regression model with treatment group as a factor and baseline value as a covariate.

Fig. 1



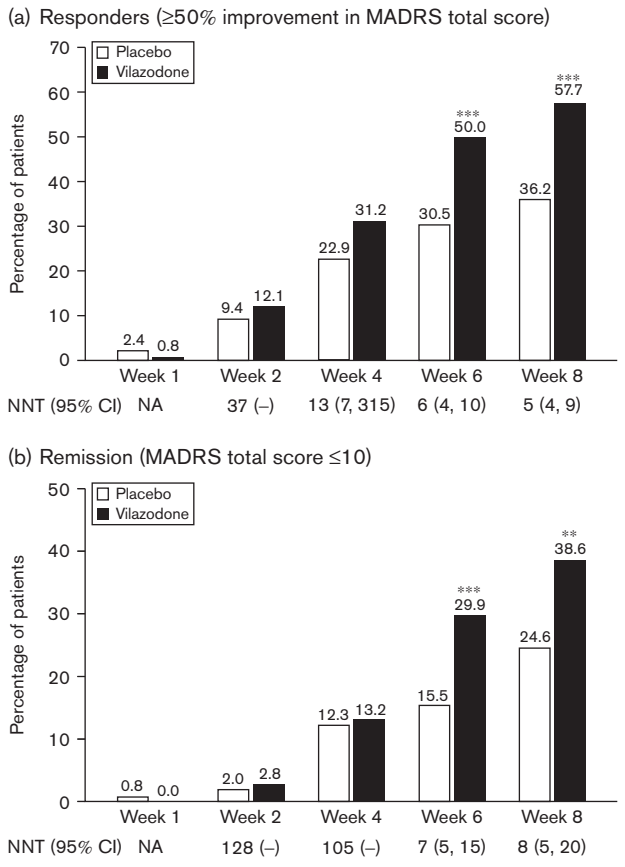
Treatment response and remission, odds ratios with 95% confidence intervals. CGI-S, Clinical Global Impressions-Severity; HAMA, Hamilton Rating Scale for Anxiety; MADRS, Montgomery-Åsberg Depression Rating Scale.

differences from placebo in outcomes that measured depressive symptoms, anxiety symptoms, and overall disease severity (all Ps < 0.01).

Depression symptom remission was defined as a MADRS total score of up to 10 at week 8, which, like the Hamilton Rating Scale for Depression (HAMD, cutoff of ≤7), represents 1 SD from the mean score in healthy controls (Zimmerman *et al.*, 2004). As defined in other MDD studies (Wade *et al.*, 2009; Montgomery *et al.*, 2014), a more stringent cutoff MADRS total score of up to 5 was also used to identify patients with complete remission. The HAMA total score of up to 7 has been used as a definition of remission for anxiety disorders (e.g. GAD) to indicate no or minimal levels of anxiety symptoms (Doyle and Pollack, 2003). The CGI-S is a global measure that allows clinicians to take into account various factors that may affect overall disease severity, including symptom intensity, quality of life, comorbidities, patient distress, and functional impairment. As a single-item measure that uses simple responses, the CGI-S may be a more efficient instrument to use in clinical settings compared with either MADRS or HAMA. A CGI-S score of 1 is defined as 'normal, not ill at all' and is commonly used as a threshold of remission in depression (Riedel *et al.*, 2010). On the basis of the percentage of patients in both treatment arms who met these different criteria, the most stringent outcome measures appear to have been MADRS complete remission (vilazodone, 18.2%; placebo, 8.3%; P=0.002) and CGI-S remission (vilazodone, 24.1%; placebo, 11.5%; P<0.001). Notably, however, these two measures also had the highest ORs for vilazodone versus placebo (2.4 each), suggesting that, although the remission rates may have been numerically low, the treatment effects of vilazodone on symptom resolution were robust. These results also suggest that placebo effects may be smaller when such stringent measures are used.

In this analysis, the NNT represents the number of patients who would require treatment with vilazodone to observe one additional responder/remitter compared with placebo. An NNT of up to 10, which represents an absolute risk difference of 10% or greater between treatment groups, is generally considered to indicate a

Fig. 2



Rates of (a) response and (b) remission at study visits, on the basis of observed cases. The 95% confidence interval is not presented if the boundaries are not finite. $^{**}P < 0.01$; $^{***}P < 0.001$ for vilazodone versus placebo. CI, confidence interval; MADRS, Montgomery–Åsberg Depression Rating; NA, not applicable (due to larger improvement in the placebo group); NNT, number needed to treat.

clinically relevant advantage for an antidepressant therapy (Montgomery and Moller, 2009; Citrome and Ketter, 2013). For MADRS response (≥50% improvement) and remission (total score ≤ 10), the risk differences between vilazodone and placebo were 17.3 and 12.2%, respectively, which corresponded to NNTs of 6 and 9. The NNTs for the remaining remission outcomes ranged from 8 (CGI-S, HAMA) to 11 (MADRS complete remission), suggesting that there were clinically relevant treatment effects across these measures.

The results presented in this report are consistent with those of earlier post-hoc pooled analyses of the two pivotal trials that showed statistically significant response and remission rates in vilazodone patients relative to placebo patients (Citrome, 2012; Khan *et al.*, 2014). Pooling data increases the statistical power, which enhances sensitivity to detect treatment effects, but may also overpower an analysis and yield results that are statistically significant because of a larger sample size rather than a greater magnitude of treatment effect. This post-hoc analysis of data from the phase IV vilazodone trial supports the results of the pooled analyses from those two trials; the NNTs for response and remission in this study were comparable, albeit better than those seen in the previous pooled analyses (response NNTs, 8–9; remission NNTs, 14–15; Citrome, 2012; Khan *et al.*, 2014). No definitive explanation can be given for this discrepancy among the trials without further analyses of factors that might affect response or remission, such as socioeconomic status, symptom type and severity, and/or comorbid medical conditions (Papakostas and Fava, 2008; Jain *et al.*, 2013). Although study designs were generally similar across the trials, there are some differences that may be notable. For example, this trial only allowed patients with a secondary diagnosis of GAD, whereas the pivotal trials allowed patients with comorbid primary GAD.

Statistically significant between-group differences were detected by week 6 for response (placebo, 30.5%; vilazodone 50.0%; $P < 0.001$; NNT = 6) and remission (placebo, 15.5%; vilazodone, 29.9%; $P < 0.001$; NNT = 7). Although it is generally acknowledged that remission may require prolonged therapy and that higher remission rates can be achieved with a longer treatment duration (Schatzberg, 1999), the 8-week outcomes found with vilazodone may also have important clinical implications. In a prospective, longitudinal, multicenter study of adult outpatients with MDD who were treated with antidepressants, 38.2% had an early response (≥50% improvement in HAMD total score at week 6) and 20.5% had early remission (HAMD total score ≤ 7 at week 6) (Ciudad *et al.*, 2012). A 'good outcome' in this longitudinal study, defined as remission that was achieved by 6 months of treatment and was sustained until 12 months, was found in 76.1% of early responders (OR = 4.14 vs. nonearly responders) and 81.1% of early remitters (OR = 4.72 vs. nonearly remitters). Early response and remission in this study were also associated with active employment, absence of physical comorbidities, and improved functioning. In another prospective, clinic-based study that defined remission on the basis of the Self-Rated Inventory of Depressive Symptomatology (Roca *et al.*, 2011), outpatients with MDD who remitted after 6–8 weeks of treatment had significantly fewer residual symptoms and significantly greater improvement in global severity than patients who required 16–20 weeks of treatment to achieve remission.

Findings from these observational studies cannot be directly translated to the current study population in which significant rates of response and remission were found in vilazodone-treated patients after 6 weeks of treatment. However, they do suggest that with ongoing vilazodone treatment, these patients may have continued to experience favorable clinical outcomes. Moreover, the results of post-hoc analyses of the data from this phase IV

trial are consistent with the results for sustained response, which was included as a secondary efficacy measure along with change in CGI-S score (Croft *et al.*, 2014). Sustained response was defined as MADRS total score of 12 or less for at least the last two consecutive visits during the double-blind treatment period. The percentage of patients who had a sustained response (placebo, 17.1%; vilazodone, 27.3%; $P < 0.05$) was similar to the remission rates at week 6 (MADRS total score ≤ 10: placebo, 15.5%; vilazodone, 29.9%; $P < 0.001$).

A limitation of this post-hoc analysis is that it is based on data from an 8-week clinical trial that was not designed nor statistically powered to evaluate remission. Because vilazodone was titrated, exposure to the full therapeutic dose was limited to 6 weeks, making this study difficult to indirectly compare with studies on antidepressants in which exposure times could be longer (and thus with more opportunities for response and remission to occur). In addition, although safety and tolerability were not analyzed for this report, these issues should also be considered when evaluating the potential merits of vilazodone treatment. However, details on the number needed to harm, which can be used to describe key tolerability outcomes, have been published elsewhere (Citrome, 2012). Finally, although this phase IV trial was useful for supporting the results of the prior pivotal studies, it did not include any active comparators that could further clarify the clinical relevance of this medication.

Conclusion

Remission of depression and anxiety symptoms is an important treatment goal in patients with MDD. On the basis of post-hoc analyses of data from a recent phase IV trial using several different remission measures, statistically significant outcomes were found for vilazodone 40 mg/day versus placebo. The NNTs for these measures ranged from 8 to 11, indicating clinically meaningful treatment effects for symptoms of depression and MDD-associated anxiety, as well as for improving overall disease burden.

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Conflicts of interest

Dr Citrome has engaged in collaborative research with or received consulting/speaking fees from: Alexza, Alkermes, AstraZeneca, Avanir, Bristol-Myers Squibb, Eli Lilly and Company, Envivo, Forest Laboratories, Genentech, Janssen, Lundbeck, Merck, Mylan, Novartis, Noven, Otsuka, Pfizer, Reckitt Benckiser, Reviva, Shire, Sunovion, Takeda, and Valeant. He owns small numbers of common-stock shares in Bristol-Myers Squibb, Eli Lilly, Johnson & Johnson, Merck, and Pfizer. Carl Gommoll and Drs Tang, Nunez, and Mathews are full-time employees of Forest Research Institute, a subsidiary of Actavis plc.

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