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Vilazodone in the treatment of major depressive disorder: efficacy across symptoms and severity of depression

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Vilazodone is a potent selective serotonin reuptake inhibitor and serotonin 1A receptor partial agonist approved for the treatment of major depressive disorder in adults. To assess the efficacy of vilazodone across a range of symptoms and severities of depression, data from two phase III, 8-week, randomized, double-blind, placebo-controlled trials were pooled for analysis. Overall improvement in depressive symptoms measured using the Montgomery–Åsberg Depression Rating Scale (MADRS) and the 17-item Hamilton Depression Rating Scale was statistically significant ($P<0.05$) for vilazodone treatment compared with placebo as early as Week 1 and continued throughout double-blind treatment. Vilazodone treatment compared with placebo showed significant improvement on all 10 individual MADRS symptom items at end of treatment ($P<0.01$). Rates of response and remission were significantly greater in the vilazodone group relative to the placebo group, with numbers needed to treat ranging from eight to nine for response and 12–17 for remission. Between-group treatment differences in MADRS and the other outcome measures were similar among all depression subgroups, with no consistent pattern associated with depression severity. These findings support the efficacy of vilazodone across a broad range of depressive symptoms and severities for the treatment of major depressive disorder. *Int Clin Psychopharmacol* 29:86–92 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Major depressive disorder (MDD) is a chronic and debilitating disorder with high rates of medical and psychiatric comorbidity, functional impairment, and significant personal and societal costs (Greenberg *et al.*, 2003; Egede, 2007; Katon *et al.*, 2007; Daly *et al.*, 2010). The heterogeneous symptoms of MDD include sad mood, loss of interest, sleep disturbance, change in appetite, lack of energy, difficulty concentrating, and psychomotor agitation (American Psychiatric Association, 2000). Depression can be characterized as mild, moderate, or severe on the basis of symptom severity, functional impairment, and level of patient distress. Typically, depression severity in clinical trials is categorized by a cutoff score on a depression rating scale such as the Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979) or Hamilton Depression Rating Scale (HAMD; Hamilton, 1960); threshold scores greater than 28–30 on MADRS or greater than 25–28 on the 17-item HAMD ($HAMD_{17}$) are commonly, but somewhat arbitrarily, used to define severe depression (Nemeroff, 2007). Approximately one-third of patients with MDD are severely depressed (Thase, 2000); patients with severe depression tend to have a prolonged course of illness, higher rates of morbidity and mortality, less likelihood of spontaneous remission, and recurrent episodes with early relapse (Thase, 2000; Nemeroff, 2007).

Many patients do not fully respond to initial pharmacologic treatment and experience residual depressive symptoms with a poorer long-term prognosis (Zajecka, 2003). Fewer than half of the patients typically attain response ($\geq 50\%$ improvement) or remission (full resolution of symptoms) during initial treatment. In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, a large multicenter study on antidepressant treatments conducted in 'real-world' clinical settings, patients who received the selective serotonin reuptake inhibitor (SSRI), citalopram, during the initial treatment step had a 47% response rate and a 33% remission rate after 14 weeks of treatment (Trivedi *et al.*, 2006). In addition, among fully remitted patients, 90% still had at least one residual symptom of depression, with the number of residual symptoms being associated with a higher probability of relapse (Nierenberg *et al.*, 2010). These findings point to the need for additional treatment options that offer broad efficacy across diverse MDD populations.

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Initial reports of possible synergy between drugs that affect SSRIs and serotonin 1A (5-HT_{1A}) receptors were published in three case studies on treatment-resistant depression in 1991 (Bakish, 1991). Vilazodone, a potent SSRI and 5-HT_{1A} receptor partial agonist, was approved by the US Food and Drug Administration in 2011 for the treatment of MDD in adults. Preclinical evidence has suggested that the partial agonism of vilazodone at the 5-HT_{1A} receptor may increase endogenous serotonin levels more than an SSRI alone (Hughes *et al.*, 2005). The efficacy of vilazodone for the treatment of MDD was shown in two phase III, 8-week, randomized, double-blind, placebo-controlled trials (NCT00683592 and NCT00285376; Rickels *et al.*, 2009; Khan *et al.*, 2011). In both trials, significant improvement versus placebo was observed on the primary efficacy measure, MADRS total score change from baseline to the end of treatment. Vilazodone was generally well tolerated in both studies; diarrhea and nausea, the most common adverse events, were predominantly mild or moderate in intensity, tended to occur early and were transient, and resulted in few discontinuations from treatment (Liebowitz *et al.*, 2011).

Improvement was also observed in the individual trials by significant differences in favor of vilazodone versus placebo on the $HAMD_{17}$, the Hamilton Anxiety Rating Scale (HAMA; Hamilton, 1959), and the Clinical Global Impressions-Severity (CGI-S) and Clinical Global Impressions-Improvement (CGI-I) Scales (Guy, 1976). The long-term safety and tolerability of vilazodone were supported by a 1-year open-label study (NCT00644358; Robinson *et al.*, 2011). To assess the efficacy of vilazodone across a range of depressive symptoms and severities, data from the two phase III, 8-week, randomized, double-blind, placebo-controlled trials were combined and analyzed.

Methods

Data from two 8-week, randomized, double-blind, placebo-controlled, multicenter studies (Rickels *et al.*, 2009; Khan *et al.*, 2011) on the use of 40 mg/day vilazodone for the treatment of MDD in adults were pooled for this analysis. The studies by Rickels *et al.* (2009) and Khan *et al.* (2011) were conducted at 10 and 15 US sites, respectively, in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The final study protocols were approved by appropriate ethics committees; all patients provided written informed consent. Details of study designs and statistical methods have been reported previously (Rickels *et al.*, 2009; Khan *et al.*, 2011). After washout and screening, patients were randomized (1 : 1) to receive vilazodone or placebo for 8 weeks of double-blind treatment. The dosage of vilazodone was increased to the 40-mg target dose (given once daily with food) on a fixed-dose schedule of 10 mg for 7 days, followed by 20 mg for 7 days, and 40 mg for the remainder of the studies. Efficacy was assessed at baseline (Week 0) and at Weeks 1, 2, 4, 6, and 8/end of treatment (EOT).

Inclusion and exclusion criteria

Eligible patients were 18–70 years of age, with a diagnosis of single-episode or recurrent MDD according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., text revision criteria (American Psychiatric Association, 2000); the diagnosis was confirmed by Mini-International Neuropsychiatric Interview (MINI; Sheehan *et al.*, 1998). Patients had a major depressive episode at least 4 weeks, but less than 2 years, in duration, a $HAMD_{17}$ score of 22 or higher, and a $HAMD_{17}$ item 1 (depressed mood) score of 2 or higher.

Patients were excluded if they had an Axis I disorder other than MDD; patients with generalized anxiety disorder, social phobia, or simple phobia were allowed for inclusion. Additional exclusion criteria included a history of schizophrenia, schizoaffective disorder, and bipolar I or II disorder; substance abuse (prior 3 months) or dependence (prior 6 months); or MDD with postpartum onset, psychotic features, or a seasonal pattern. Patients with significant comorbid medical or physical conditions that might interfere with trial participation were also excluded at the investigator's discretion.

Efficacy assessments

Post-hoc analyses of pooled data included evaluation of change from baseline to EOT in MADRS total and individual symptom ratings, and in $HAMD_{17}$, HAMA, CGI-S, and CGI-I scores at each study visit. EOT response (MADRS or $HAMD_{17} \geq 50\%$ decrease from baseline) and remission (MADRS total score ≤ 10 or HAMD score ≤ 7) were assessed and the respective numbers needed to treat (NNTs) were calculated.

Statistical analyses

The intent-to-treat (ITT) population consisted of all patients in the safety population (randomized patients receiving study drug) who underwent postbaseline MADRS assessment. Patients were stratified by baseline MADRS scores into three severity subgroups: moderate (MADRS < 30), moderate-to-severe ($30 \leq$ MADRS < 35), and severe (MADRS ≥ 35) depression subgroups.

All analyses were based on the ITT dataset using the last observation carried forward approach to impute missing data. Treatment group differences were based on the least squares mean difference and 95% confidence intervals. Continuous efficacy variables were analyzed using an analysis of covariance model with treatment group and pooled study center as factors, and the corresponding baseline efficacy score as a covariate (baseline CGI-S score was used as an explanatory variable for the analysis of the CGI-I score). Categorical efficacy variables were analyzed using a logistic regression model with treatment group and study ID as explanatory variables. All statistical

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Table 1 Pooled baseline demographics and disease characteristics

	All patients		Moderate (MADRS < 30)		Moderate to severe (30 ≤ MADRS < 35)		Severe (MADRS ≥ 35)	
Demographic characteristics (safety population)	Placebo (n = 433)	VLZ (n = 436)	Placebo (n = 143)	VLZ (n = 130)	Placebo (n = 205)	VLZ (n = 220)	Placebo (n = 85)	VLZ (n = 86)
Women (%)	58	61	58	56	62	63	47	64
White (%)	80	83	83	91	79	83	78	70
Age [mean (SD)]	41.3 (12.6)	40.6 (12.2)	41.2 (12.7)	42.0 (12.4)	41.7 (12.5)	39.8 (12.2)	40.7 (12.8)	40.7 (11.9)
Current depressive episode ≤ 12 months (%)	84	79	84	83	85	79	81	72
Baseline scores (ITT population) [mean (SD)]	Placebo (n = 432)	VLZ (n = 431)	Placebo (n = 143)	VLZ (n = 128)	Placebo (n = 204)	VLZ (n = 217)	Placebo (n = 85)	VLZ (n = 86)
MADRS	31.4 (3.8)	31.4 (3.7)	27.2 (1.6)	27.0 (1.9)	32.0 (1.4)	31.9 (1.3)	36.9 (1.9)	36.6 (1.9)
$HAMD_{17}$	25.1 (2.5)	24.9 (2.4)	23.9 (1.6)	23.3 (1.5)	24.9 (2.2)	25.0 (2.0)	27.6 (2.7)	27.1 (2.7)
CGI-S	4.5 (0.5)	4.5 (0.5)	4.2 (0.4)	4.2 (0.4)	4.6 (0.6)	4.5 (0.5)	4.8 (0.4)	4.8 (0.4)
HAMA	18.3 (5.5)	18.2 (5.2)	16.9 (4.7)	16.4 (4.4)	17.7 (5.3)	18.2 (5.1)	22.1 (5.9)	20.7 (5.5)

CGI-S, Clinical Global Impressions-Severity; HAMA, Hamilton Rating Scale for Anxiety; HAMD, Hamilton Rating Scale for Depression; ITT, intent-to-treat; MADRS, Montgomery–Åsberg Depression Rating Scale; VLZ, vilazodone.

comparisons were two sided and generated nominal P-values without adjustment for multiplicity.

Results

Patient disposition

A total of 891 patients were randomized to receive vilazodone (n = 445) or placebo (n = 446). The safety population consisted of 869 patients receiving the study drug (placebo = 433; vilazodone = 436); 863 of these patients (placebo = 432; vilazodone = 431) underwent post-baseline MADRS assessment (ITT population). Overall, 349 (80.6%) patients in the placebo group and 345 (79.1%) patients in the vilazodone group completed treatment.

Baseline demographics and clinical characteristics

Patient baseline demographics and clinical characteristics are presented in Table 1. Approximately one-third of patients were experiencing a first lifetime MDD episode and most patients had a current depressive episode of 12 months or less. The mean baseline MADRS score was 31.4, indicative of a patient population with baseline depression symptoms that were in the moderate-to-severe depression range.

At baseline, 31% of patients had moderate depression (MADRS < 30), 49% had moderate-to-severe depression (30 ≤ MADRS < 35), and 20% had severe depression (MADRS ≥ 35). Baseline demographic characteristics were similar across depression severity subgroups. A slightly higher percentage of patients with a current MDD episode duration of greater than 12 months were in the severe depression subgroup (23%) compared with the moderate (17%) or moderate-to-severe (18%) depression subgroups. The mean MADRS, $HAMD_{17}$, CGI-S, and HAMA scores generally increased with increasing depression severity (Table 1).

Efficacy

In the pooled analysis, least squares mean improvement from baseline to EOT in MADRS was significantly greater ($P < 0.0001$) for patients treated with vilazodone compared with placebo (Table 2). Statistically significant differences favoring vilazodone over placebo were evident at the earliest measurement after baseline (Week 1) and continued throughout double-blind treatment ($P < 0.01$, all weeks).

Table 2 Change from baseline to end of treatment in efficacy assessments[a]

	LSM (SE)			
Measure	Placebo (n = 432)	VLZ (n = 431)	LSMD (95% CI)	P-value[b]
MADRS	−10.3 (0.6)	−13.0 (0.6)	−2.8 (−4.1, −1.4)	<0.0001
$HAMD_{17}$	−8.9 (0.5)	−10.5 (0.5)	−1.7 (−2.7, −0.6)	0.0015
CGI-I[c]	2.9 (0.1)	2.6 (0.1)	−0.3 (−0.5, −0.2)	<0.0001
CGI-S	−1.0 (0.1)	−1.4 (0.1)	−0.4 (−0.6, −0.2)	<0.0001
HAMA	−5.4 (0.4)	−6.6 (0.4)	−1.2 (−2.0, −0.4)	0.0047

CGI-I, Clinical Global Impressions-Improvement; CGI-S, CGI-Severity; CI, confidence interval; HAMA, Hamilton Rating Scale for Anxiety; HAMD, Hamilton Rating Scale for Depression; ITT, intent-to-treat; LOCF, last observation carried forward; LSM, least squares mean; LSMD, least squares mean difference; MADRS, Montgomery–Åsberg Depression Rating Scale; VLZ, vilazodone.
[a]Pooled ITT population; LOCF.
[b]P-value for VLZ versus placebo.
[c]CGI-I reported as LSM score (SE) at Week 8.

Significant treatment differences from baseline to EOT favoring vilazodone over placebo were also observed for $HAMD_{17}$ ($P < 0.05$) and CGI-S ($P < 0.01$; Table 2); separation from placebo occurred as early as Week 1 and continued throughout treatment. Improvement in HAMA scores was also significantly greater ($P < 0.01$) for vilazodone versus placebo beginning at Week 6 until EOT. CGI-I favored vilazodone over placebo at all postbaseline visits ($P < 0.01$) and at EOT ($P < 0.0001$; Table 2).

Montgomery–Åsberg Depression Rating Scale individual depressive symptoms analysis

Analyses of MADRS single items examined treatment effects of vilazodone on individual symptoms of depression. Vilazodone treatment compared with placebo treatment

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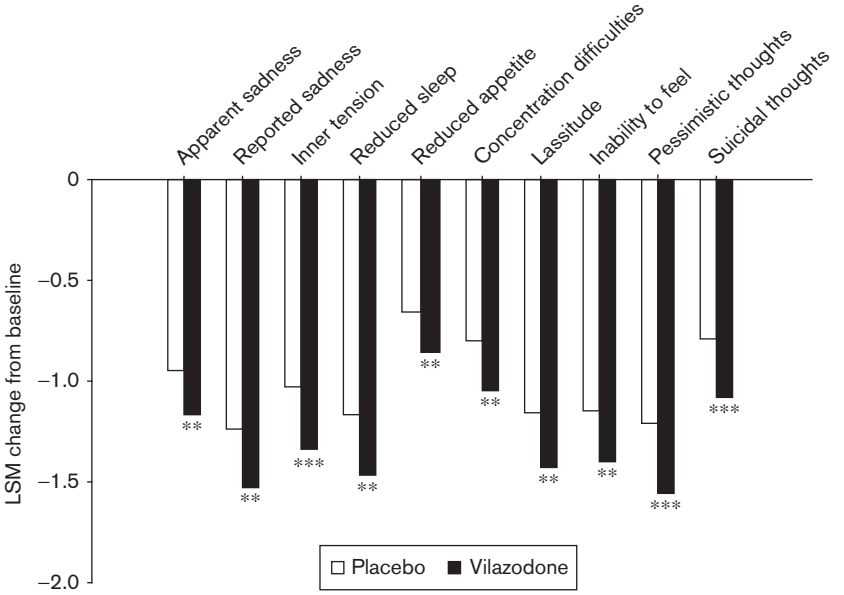
Fig. 1



Least squares mean change in MADRS single items at the end of treatment. Pooled ITT population; LOCF. $^{**}P<0.01$ versus placebo; $^{***}P<0.001$ versus placebo. ITT, intent-to-treat; LOCF, last observation carried forward; LSM, least squares mean; MADRS, Montgomery–Åsberg Depression Rating Scale.

resulted in significant improvement ($P < 0.01$) in each of the 10 MADRS symptoms of depression (Fig. 1).

Depression severity subgroup analyses

For each depression severity subgroup, MADRS total score improvement from baseline to EOT was significantly greater for vilazodone treatment relative to placebo, with no apparent trend toward greater improvement with increasing baseline depression severity (Table 3). With regard to the secondary efficacy measures, the pattern of improvement indicated by between-group differences across severity subgroups for vilazodone relative to placebo was similar to that observed for the primary MADRS outcome measure (Table 3).

Clinical relevance

Vilazodone-treated patients compared with placebo-treated patients had significantly higher response and remission rates at EOT on the basis of both MADRS and $HAMD_{17}$ criteria (Fig. 2). The NNTs (95% confidence interval) for response were eight (5–17) for MADRS and nine (6–21) for $HAMD_{17}$; for remission, the NNTs were 12 (7–37) for MADRS and 17 (9–295) for $HAMD_{17}$.

Discussion

Findings from the pooled analyses of data from two positive, 8-week, placebo-controlled, randomized, double-blind trials show a consistent pattern of efficacy for 40 mg vilazodone compared with placebo across a range of depression symptoms and severities. The 2.8-point mean difference in MADRS score at EOT favoring vilazodone over placebo is indicative of clinically relevant improvement in depression (Montgomery and Moller, 2009). Statistically significant and clinically relevant improvements in MADRS total score at Week 8 were observed with vilazodone compared with placebo regardless of the severity of baseline depression symptoms. The MADRS treatment advantage for vilazodone versus placebo (least squares mean difference) was greater than 2 for all severity subgroups, supporting the clinical relevance of treatment across the range of depression severities (Montgomery and Moller, 2009). Between-group treatment differences were generally similar for other efficacy outcome measures across the range of depression severity subsets, with no apparent trends among subgroups. Although a prior meta-analysis has suggested that antidepressant treatment is most efficacious in patients with the most severe symptoms (Kirsch *et al.*, 2008), the results of these analyses support the therapeutic benefit of vilazodone across a spectrum of depression severities. A retrospective analysis of randomized placebo-controlled trials conducted in 2012 concurred with our results, finding significant antidepressant efficacy for patients with mild–moderate MDD (Stewart *et al.*, 2012).

Depression symptom improvement, as measured by both MADRS total score and $HAMD_{17}$, was apparent for vilazodone treatment compared with placebo by the first postbaseline assessment (Week 1) and continued

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Table 3 Additional efficacy assessments by baseline depression severity subgroup at the end of treatment[a]

	Moderate (MADRS<30)		Moderate to severe (30 ≤ MADRS<35)		Severe (MADRS ≥ 35)	
	Placebo (n=143)	VLZ (n=130)	Placebo (n=205)	VLZ (n=220)	Placebo (n=85)	VLZ (n=86)
MADRS						
LSM change (SE)	−10.7 (1.1)	−13.6 (1.1)	−10.0 (1.1)	−12.3 (1.1)	−10.8 (1.6)	−14.9 (1.5)
LSMD (95% CI)	−2.9 (−5.0, −0.9)**		−2.3 (−4.4, −0.2)*		−4.1 (−7.4, −0.7)*	
$HAMD_{17}$						
LSM change (SE)	−10.6 (0.9)	−12.1 (0.9)	−8.4 (0.8)	−10.0 (0.8)	−8.5 (1.2)	−10.8 (1.1)
LSMD (95% CI)	−1.6 (−3.3, 0.1)		−1.6 (−3.2, −0.1)*		−2.4 (−4.8, 0.1)	
CGI-S						
LSM change (SE)	−1.3 (0.1)	−1.7 (0.1)	−0.9 (0.1)	−1.3 (0.1)	−1.1 (0.2)	−1.6 (0.2)
LSMD (95% CI)	−0.4 (−0.7, −0.1)**		−0.4 (−0.6, −0.1)**		−0.4 (−0.8, 0.0)	
HAMA						
LSM change (SE)	−6.6 (0.7)	−7.6 (0.7)	−5.0 (0.7)	−6.3 (0.7)	−5.7 (1.0)	−7.4 (1.0)
LSMD (95% CI)	−1.1 (−2.4, 0.3)		−1.3 (−2.5, −0.0)*		−1.7 (−3.8, 0.5)	
CGI-I						
LSM score (SE)	2.6 (0.1)	2.2 (0.1)	3.0 (0.1)	2.7 (0.1)	2.9 (0.2)	2.6 (0.2)
LSMD (95% CI)	−0.4 (−0.7, −0.2)**		−0.3 (−0.5, −0.1)*		−0.3 (−0.7, 0.0)	

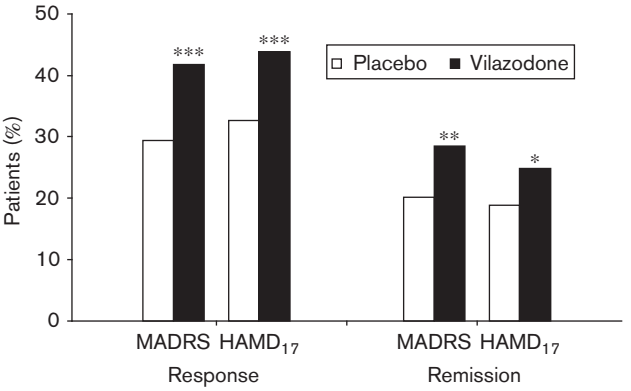
CGI-I, Clinical Global Impressions-Improvement; CGI-S, CGI-Severity; CI, confidence interval; HAMA, Hamilton Rating Scale for Anxiety; HAMD, Hamilton Rating Scale for Depression; ITT, intent-to-treat; LOCF, last observation carried forward; LSM, least squares mean; LSMD, least squares mean difference; MADRS, Montgomery–Åsberg Depression Rating Scale; VLZ, vilazodone.
[a]Pooled ITT population; LOCF.
*P<0.05 versus placebo.
**P<0.01 versus placebo.

throughout treatment across a range of depression severities. Patients who experience clinically meaningful improvement (i.e. ≥ 20% improvement from baseline) in depressive symptoms in the first 2 weeks of treatment have a greater likelihood of stable treatment response and remission of symptoms (Szegedi *et al.*, 2009). Early improvement (e.g. within 2 weeks) may enhance treatment compliance and lessen relapse or recurrence (Demyttenaere *et al.*, 2001; Taylor *et al.*, 2006; Szegedi *et al.*, 2009). The results of these analyses are interesting considering that vilazodone treatment compared with placebo treatment led to a statistically significant improvement in depressive symptoms as early as the first week of treatment despite the fact that patients did not attain full therapeutic dosage of vilazodone until Week 3 of the 8-week double-blind treatment period.

Vilazodone treatment compared with placebo treatment led to a statistically significant improvement in all 10 individual MADRS symptom items. The improvement in the 'suicidal thoughts' item was unanticipated because patients with suicidal ideation, recent suicidal attempt, or suicidal risk were excluded from the trials. Efficacy across a broad range of depression symptoms may lessen the likelihood of residual symptoms, which is associated with a risk for relapse, greater psychosocial impairment, and reduced quality of life (Menza *et al.*, 2003).

Vilazodone compared with placebo also significantly improved overall anxiety symptoms on the basis of HAMA scores. It is possible that the combined property of serotonin reuptake inhibition and 5-HT_{1A} partial agonism of vilazodone leads to a broader antidepressant efficacy with enhanced anxiolytic efficacy in MDD patients compared with serotonin reuptake inhibition alone (Blier and Ward, 2003; Sussman, 2003; Papakostas *et al.*, 2007).

Fig. 2



Response and remission rates at the end of treatment. Pooled ITT population; LOCF. *P<0.05, **P<0.01, ***P<0.001. Response is defined as a decrease of 50% or greater from baseline to end of treatment in MADRS or $HAMD_{17}$ total score. Remission is defined as an end-of-treatment MADRS total score ≤ 10 or $HAMD_{17}$ score ≤ 7. $HAMD_{17}$, 17-item Hamilton Depression Rating Scale; ITT, intent-to-treat; LOCF, last observation carried forward; MADRS, Montgomery–Åsberg Depression Rating Scale.

The clinical relevance of improvement in depression symptoms with vilazodone was shown by an absolute treatment difference of greater than 10% compared with placebo on all response rate criteria (Montgomery and Moller, 2009). NNT values for response of eight and nine further suggest the clinical relevance of these data as an NNT of less than 10 represents the threshold for demonstrating clinically relevant response to antidepressant treatment (Cipriani *et al.*, 2006).

Remission to an asymptomatic state is considered by many to be the ultimate standard of efficacy for antidepressant

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drugs in depressive disorders. In these analyses, absolute differences in remission rates for vilazodone versus placebo ranged from 6 to 9%, corresponding to NNTs of 12–17 for remission. A recent review of vilazodone that used a MADRS total score of less than 10 as the remission criterion reported remission rates of 25.4% for vilazodone and 18.1% for placebo, with an NNT of 14 (Citrome, 2012). MADRS remission rates in our analysis (MADRS total score ≤ 10), 28.6% for vilazodone and 20.1% for placebo (NNT = 12), were slightly higher than the rates observed in the study by Citrome (2012) (MADRS total score < 10). This may reflect the slightly less stringent but more common definition of remission used in our analysis (Zimmerman *et al.*, 2004), in which patients with a MADRS total score of 10, as opposed to a maximum score of 9, are categorized as remitters. In addition, it is possible that the 8-week duration of the trials may have been insufficient for some patients to attain remission of symptoms, and more patients might have remitted with longer treatment; this may be especially true for the more severely depressed patients with high baseline MADRS scores (Schatzberg, 1999).

The two clinical trials with almost identical study designs and patient populations facilitate the pooling of data for increased statistical power to assess additional treatment effects of clinical interest, and provide more precise estimates with large enough sample sizes for subgroup analyses. Limitations of these analyses include lack of head-to-head comparison with other antidepressants and more stringent entry criteria that may limit generalizability. In addition, the cutoff score used to denote severe depression in this analysis (MADRS ≥ 35) is more stringent than the score often used in clinical trials (MADRS ≥ 30; Nemeroff, 2007), resulting in a sample size that may be insufficient to detect significant treatment differences in the subgroup designated as severely depressed. Finally, these analyses were carried out *post hoc* and did not correct for multiple comparisons.

Vilazodone treatment was significantly superior to placebo treatment on all efficacy outcome measures, with consistent efficacy across a range of depression severities in MDD patients. Clinically relevant advantages of vilazodone treatment over placebo treatment were evident in overall measures of depression, individual depressive symptoms, and antidepressant response and remission rates.

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Conflicts of interest

Dr Khan is the Medical Director of the Northwest Clinical Research Center (NWCRC). NWCRC was an investigative site for the vilazodone phase III studies randomizing 241 patients. He has served as an uncompensated advisor to Forest Research and is not compensated for his role as author of medical manuscripts. Dr Khan is also the Medical Director of Columbia Northwest Pharmaceuticals, which owns intellectual property rights for potential therapies for central nervous system disorders and other medical conditions. Dr Sambunaris has received consultant and speaking fees from Forest Research Institute Inc., as well as Takeda Pharmaceuticals and Mylan Pharmaceuticals. Angelo Sambunaris has received research support from Alkermes, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, BrainCells, CeNeRx, Cephalon, Forest Pharmaceuticals, GlaxoSmithKline, Jazz, Johnson & Johnson Labopharm, Lilly, Lundbeck, MediciNova, Merck, Neurocrine, Novartis, Otsuka, Pfizer, Roche, Sanofi-Aventis, Sepracor/Sunovion, Shire, and Takeda. He has also served as a speaker for Forest Pharmaceuticals and as a consultant for Forest, Mylan, and Takeda. He was also a principal investigator in both vilazodone phase III studies. Dr Edwards is a full-time employee of Forest Laboratories Inc. Dr Ruth is an employee of Prescott Medical Communications Group, a contractor for Forest Research Institute. Dr Robinson has served as a consultant to Forest Laboratories, PGxHealth, Dey Pharmaceuticals, Mylan Pharmaceuticals, and Ironwood Pharmaceuticals. This study was funded by PGxHealth LLC, a subsidiary of Clinical Data Inc. (acquired by Forest Laboratories Inc.). PGxHealth LLC and Forest Laboratories Inc. were involved in the study design; collection, analysis, and interpretation of data; writing of the report; and decision to submit the paper for publication. Editorial assistance was provided by Prescott Medical Communications and was funded by Forest Laboratories Inc.

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