

# Efficacy of vilazodone on anxiety symptoms in patients with major depressive disorder

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Anxiety symptoms are prevalent in patients with major depressive disorder. A post-hoc analysis of two phase III trials was conducted to evaluate the efficacy of vilazodone on depression-related anxiety. Using the 17-item Hamilton Depression Rating Scale (HAMD<sub>17</sub>) Anxiety/Somatization subscale, patients were classified as anxious or nonanxious. Improvements in depressive symptoms were based on least squares mean changes in HAMD<sub>17</sub> and Montgomery–Asberg Depression Rating Scale total scores. Anxiety symptoms in the anxious subgroup were evaluated using Hamilton Anxiety Rating Scale (HAMA) total and subscale (Psychic Anxiety, Somatic Anxiety) scores, HAMD<sub>17</sub> Anxiety/Somatization subscale and item (Psychic Anxiety, Somatic Anxiety) scores, and the Montgomery–Asberg Depression Rating Scale Inner Tension item score. Most of the pooled study population [82.0% (708/863)] was classified with anxious depression. After 8 weeks of treatment, least squares mean differences between vilazodone and placebo for changes in HAMA total and HAMD<sub>17</sub> Anxiety/Somatization subscale scores were  $-1.82$  (95% confidence interval  $-2.81$  to  $-0.83$ ;  $P < 0.001$ )

and  $-0.75$  (95% confidence interval  $-1.17$  to  $-0.32$ ;  $P < 0.001$ ), respectively. Statistically significant improvements with vilazodone were also found on all other anxiety-related measures, except the HAMA Somatic Anxiety subscale. Vilazodone may be effective in treating patients with major depressive disorder who exhibit somatic and/or psychic symptoms of anxiety. *Int Clin Psychopharmacol* 29:351–356 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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## Introduction

Approximately one-half of all patients diagnosed with major depressive disorder (MDD) have clinically meaningful levels of anxiety, which complicates clinical management and can affect treatment outcomes (Rao and Zisook, 2009; Wiethoff *et al.*, 2010). Anxious depression is associated with more severe depressive symptoms, greater duration of current episode, suicidal ideation and history of suicide attempt, and more medical comorbidities (Rao and Zisook, 2009). Patients with both depressive and anxiety symptoms are less likely to achieve treatment response or remission (Fava *et al.*, 2008; Kennedy, 2008), more likely to have delayed treatment response (Clayton *et al.*, 1991), and are more likely to report adverse events during antidepressant treatment, including bursts of anxiety or agitation (Fava *et al.*, 2006). Residual anxiety symptoms are also associated with an increased risk of MDD relapse (Ramana *et al.*, 1995; Flint and Rifat, 1997).

Although anxious depression was not historically recognized as a separate diagnostic entity, the recently published *Diagnostic and Statistical Manual of Mental Disorders*,

5th ed. (DSM-V) includes ‘anxious distress’ as a category specifier for patients with depressive disorders (American Psychiatric Association, 2013). The symptoms listed for anxious distress include tenseness, restlessness, difficulty concentrating because of worry, fear that something awful may happen, and feelings of loss of control. Severity is based on the number of symptoms that patients exhibit.

Prior to the release of the DSM-V, clinical studies used several methods to identify patients with mixed depressive and anxiety symptoms (Ionescu *et al.*, 2013). In the Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) study (Fava *et al.*, 2008), anxious depression was defined as patients meeting the DSM-IV-TR (4th ed., text revision) criteria (American Psychiatric Association, 2000a) for MDD and having a score of 7 or greater on the Anxiety/Somatization subscale of the 17-item Hamilton Depression Rating Scale (HAMD<sub>17</sub>) (Hamilton, 1960). Slightly more than half of the STAR\*D patients fulfilled these criteria (53.2%) and, when compared with nonanxious patients, those with anxious depression had poorer treatment outcomes across the first and second levels of therapy.

The availability of a pharmacologic treatment that effectively manages anxious depression would be an

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important development for the therapeutics of MDD. As many of the selective serotonin reuptake inhibitors (SSRIs) have established efficacy for anxiety disorders, they are commonly considered a first-line treatment for anxious depression (Nutt, 2005). For patients who do not respond to SSRIs, alternatives include other newer generation antidepressants, such as the serotonin and norepinephrine reuptake inhibitors, and adjunctive therapy with atypical antipsychotics and benzodiazepines. Adjunctive therapy with the alternate anxiolytic agent buspirone is also sometimes used to treat anxious depression that has not responded adequately to SSRIs (American Psychiatric Association, 2000b). From a mechanistic standpoint, buspirone is a strong 5-HT<sub>1A</sub> partial agonist that is considered to decrease serotonergic autoinhibition by desensitizing 5-HT<sub>1A</sub> autoreceptors (Albert and Francois, 2010). Buspirone also shows moderate affinity at dopamine D<sub>2</sub> receptors and a short half-life (2–3 h for 10–40 mg/day), requiring twice-daily dosing (Bristol-Myers Squibb Company, 2010). The therapeutic potential of combining the actions of an SSRI and a 5-HT<sub>1A</sub> partial agonist is of clinical interest, but the value of such a strategy has not yet been shown conclusively. Several preliminary clinical studies found that adjunctive use of buspirone with an antidepressant agent may help improve symptoms in patients with inadequate response to antidepressant monotherapy (Nelson, 2000; Fleurence *et al.*, 2009). However, the benefits of this adjunctive strategy in patients with anxious depression were not confirmed in the STAR\*D study (Fava *et al.*, 2008), although the results from this study must be interpreted with caution as inadequate response following buspirone augmentation may have been confounded by the study design or the specific pharmacokinetic or pharmacodynamic profile of buspirone.

Vilazodone is a serotonin reuptake inhibitor and 5-HT<sub>1A</sub> receptor partial agonist that was approved by the US Food and Drug Administration (FDA) in January 2011 for the treatment of MDD in adults. Vilazodone potently and selectively inhibits reuptake of serotonin and binds selectively with high affinity to 5-HT<sub>1A</sub> receptors (Forest Laboratories Inc., 2013). With a terminal half-life of ~25 h, vilazodone is administered once daily with food. It has been proposed that because vilazodone combines serotonin reuptake inhibition and a buspirone-like anxiolytic mechanism, it may be a useful treatment option for patients with MDD and symptoms of anxiety. The efficacy and safety of vilazodone have been established by the results of two phase III, 8-week, randomized, double-blind, placebo-controlled trials: NCT00285376 (RCT-1) (Rickels *et al.*, 2009) and NCT00683592 (RCT-2) (Khan *et al.*, 2011). In both trials, change from baseline to week 8 was statistically significant in favor of vilazodone versus placebo on the primary efficacy measure, the Montgomery–Asberg Depression Rating Scale (MADRS) (Montgomery and

Asberg, 1979). Statistically significant improvements were also observed on secondary endpoints including the HAMD<sub>17</sub> and Hamilton Anxiety Rating Scale (HAMA) (Hamilton, 1959). Further support for the safety and tolerability of vilazodone in patients with MDD was demonstrated in a 1-year open-label study (NCT00644358) (Robinson *et al.*, 2011). In all three studies, diarrhea and nausea were the most common treatment-emergent adverse events associated with vilazodone therapy.

To further investigate the clinical benefits of vilazodone in patients with MDD and prominent anxiety symptoms, data from the two phase III vilazodone studies (RCT-1 and RCT-2) were pooled. Post-hoc analyses using the HAMD<sub>17</sub> and MADRS scales were conducted to evaluate changes in depressive symptoms in anxious and nonanxious patients as well as evaluate changes in anxiety symptoms in the anxious subgroup. Several different anxiety-related measures were used to assess both the somatic and the psychic symptoms of anxiety found in patients with MDD.

## Methods

RCT-1 and RCT-2 were carried out at multiple US study centers between 2006 and 2009 in full compliance with FDA guidelines for good clinical practice and the ethical principles of the Declaration of Helsinki. Final study protocols were approved by the appropriate institutional review board for each study site and all patients provided written informed consent before the initiation of any study-specific procedures.

## Study designs

Detailed study design, inclusion and exclusion criteria, and statistical methods from the two pivotal phase III, randomized, double-blind, placebo-controlled, multicenter studies of vilazodone studies have been published (Rickels *et al.*, 2009; Khan *et al.*, 2011). Adult patients with MDD were randomized (1 : 1) to receive vilazodone 40 mg/day or placebo for 8 weeks of double-blind treatment. Patients randomized to active treatment received once-daily vilazodone 10 mg for 7 days, 20 mg for 7 days, and 40 mg for the rest of the study.

## Principal inclusion and exclusion criteria

Adult patients (aged 18–70 years) with MDD (single or recurrent episode) as defined by the DSM-IV-TR were included. Patients were required to have a current major depressive episode of 4 or more weeks' and less than 2 years' duration, a HAMD<sub>17</sub> total score of at least 22, and HAMD<sub>17</sub> item 1 (Depressed Mood) score at least 2. Psychiatric exclusions included an Axis I disorder other than MDD within 6 months of screening (generalized anxiety disorder, social phobia, or simple phobia were allowed), a history of psychotic or bipolar disorders, substance abuse (in the past 3 months) or dependence (in the past 6 months), and serious suicide or homicide risk.

Patients with clinically significant medical conditions that might interfere with study participation were excluded at the discretion of the investigator; patients taking medications with serotonergic mechanisms of action or who had not responded to two or more previous antidepressants from different classes were also excluded.

### Patient subgroups and efficacy assessments

The intent-to-treat population, defined as all randomized patients who received at least one dose of study drug and had at least one postbaseline MADRS total score assessment, was divided into subgroups based on baseline HAMD<sub>17</sub> Anxiety/Somatization subscale scores. The HAMD<sub>17</sub> Anxiety/Somatization subscale comprises six individual items: item 10, Psychic Anxiety; item 11, Somatic Anxiety; item 12, Somatic Symptoms (gastrointestinal); item 13, General Somatic Symptoms; item 15, Hypochondriasis; and item 17, Insight. Patients with a baseline HAMD<sub>17</sub> Anxiety/Somatization subscale score 7 or more were classified as having anxious depression; those with a score less than 7 were classified as having nonanxious depression.

MADRS and HAMD<sub>17</sub> total scores were used to assess the effects of vilazodone on depressive symptoms in both the anxious and the nonanxious subgroups. Since the smaller nonanxious subgroup ( $n=155$ ) did not have prominent symptoms of anxiety, analyses of anxiety-related measures were only carried out in the anxious subgroup ( $n=708$ ). In addition to the HAMA total score, two HAMA-derived subscales were evaluated: the Psychic Anxiety subscale (item 1, Anxious Mood; item 2, Tension; item 3, Fears; item 4, Insomnia; item 5, Intellectual; item 6, Depressed Mood; and item 14, Behavior at Interview) and the Somatic Anxiety subscale [item 7, Somatic (muscular); item 8, Somatic (sensory); item 9, Cardiovascular Symptoms; item 10, Respiratory Symptoms; item 11, Gastrointestinal Symptoms; item 12, Genitourinary Symptoms; and item 13, Autonomic Symptoms]. Changes in anxiety symptoms were also measured using the HAMD<sub>17</sub> Anxiety/Somatization subscale, Psychic Anxiety item (item 10), and Somatic Anxiety item (item 11), as well as the MADRS Inner Tension item (item 3).

### Statistical analyses

Least squares mean (LSM) changes from baseline to week 8 for all post-hoc efficacy parameters were analyzed using a mixed-effects model for repeated measures with treatment group, study, study center, visit, and treatment group by visit interaction as fixed effects and baseline value and baseline value by visit as covariates. An unstructured covariance matrix was used to model the covariance of within-patient scores. The Kenward–Roger approximation was used to estimate denominator degrees of freedom (Kenward and Roger, 1997). Only observed cases of postbaseline scores were used without

imputation of missing values;  $P$  values for the statistical tests in the post-hoc analyses are nominal and not adjusted for multiple comparisons. Treatment effect sizes for vilazodone versus placebo in anxiety-related measures were estimated using Cohen's  $d$  formula.

## Results

### Patient characteristics

Of the 863 patients included in the intent-to-treat population, 708 (82.0%) patients were classified as having anxious depression (HAMD<sub>17</sub> Anxiety/Somatization subscale score  $\geq 7$ ); 155 (18.0%) were classified as non-anxious. For both the anxious and the nonanxious depression subgroups, the demographic characteristics and history of MDD were generally similar between the vilazodone and the placebo treatment groups (Table 1). In the anxious depression subgroup, the mean duration of the current episode was 1 or less year for the majority of patients ( $>75\%$ ); approximately two-thirds of patients reported had a previous depressive episode. The mean baseline HAMD<sub>17</sub> and MADRS total scores met or exceeded the threshold scores commonly used to indicate severe depressive symptomatology (Nemeroff, 2007). The mean baseline HAMA total scores were consistent with those observed in studies of generalized anxiety disorder (Matza *et al.*, 2010).

### Efficacy in depression measures

Mean improvements with vilazodone were found for MADRS and HAMD<sub>17</sub> total scores, with statistically significant differences from placebo in the anxious depression subgroup. LSM differences between vilazodone and placebo [with 95% confidence interval (95% CI)] for changes in the MADRS total score were as

**Table 1 Demographics and baseline characteristics**

	Anxious depression subgroup		Nonanxious depression subgroup	
	Placebo ( $n=357$ )	Vilazodone ( $n=351$ )	Placebo ( $n=75$ )	Vilazodone ( $n=80$ )
Mean age (SD) (years)	40.6 (12.4)	40.4 (12.0)	44.7 (13.0)	41.4 (13.0)
Female [ $n$ (%)]	202 (56.6)	224 (63.8)	48 (64.0)	40 (50.0)
White [ $n$ (%)]	280 (78.4)	282 (80.3)	65 (86.7)	75 (93.8)
Duration of current episode [ $n$ (%)]				
1–12 months	298 (83.5)	277 (78.9)	65 (86.7)	61 (76.3)
> 12 months	59 (16.5)	74 (21.1)	10 (13.3)	19 (23.7)
Recurrent depression [ $n$ (%)]	236 (66.1)	241 (68.7)	54 (72.0)	55 (68.8)
Mean baseline efficacy values (SD)				
HAMA total	18.7 (5.6)	18.7 (5.3)	16.2 (4.7)	15.5 (4.0)
HAMD <sub>17</sub> total	25.5 (2.5)	25.2 (2.4)	23.4 (1.6)	23.4 (1.4)
HAMD <sub>17</sub> Anxiety/Somatization subscale	8.2 (1.2)	8.2 (1.1)	5.7 (0.6)	5.7 (0.6)
MADRS total	31.8 (3.8)	31.7 (3.8)	29.6 (3.3)	30.1 (3.3)

HAMA, Hamilton Anxiety Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; HAMD<sub>17</sub>, 17-item Hamilton Depression Rating Scale; SD, standard deviation.

follows: anxious,  $-3.6$  ( $-5.2$  to  $-2.0$ ;  $P < 0.001$ ); non-anxious,  $-0.9$  ( $-4.6$  to  $2.8$ ;  $P > 0.05$ ). LSM differences for changes in the HAMD<sub>17</sub> total score were as follows: anxious,  $-2.3$  ( $-3.5$  to  $-1.1$ ;  $P < 0.001$ ); nonanxious,  $-0.5$  ( $-3.2$  to  $2.2$ ;  $P > 0.05$ ).

### Efficacy in anxiety-related measures in patients with anxious depression

In the anxious depression subgroup, patients treated with vilazodone showed significantly greater improvements in anxiety-related outcomes than patients receiving placebo. After 8 weeks of treatment, the LSM difference between vilazodone and placebo in the HAMA total score was  $-1.82$  (95% CI  $-2.81$  to  $-0.83$ ;  $P < 0.001$ ). Significant differences between treatment groups were observed by week 6 (Fig. 1a). On the HAMD<sub>17</sub> Anxiety/Somatization subscale, significant mean improvements with vilazodone versus placebo were detected by week 2 (Fig. 1b). At the end of the double-blind treatment, the LSM difference between vilazodone and placebo in the

HAMD<sub>17</sub> Anxiety/Somatization subscale score was  $-0.75$  (95% CI  $-1.17$  to  $-0.32$ ;  $P < 0.001$ ). As estimated by Cohen's  $d$ , the treatment effect size was 0.25 for both the HAMA total and the HAMD<sub>17</sub> Anxiety/Somatization subscale scores.

Statistically significant improvements with vilazodone were also detected on all other anxiety-related measures, except the HAMA Somatic Anxiety subscale (Table 2). The largest treatment effects were observed on the HAMA Psychic Anxiety subscale (0.31) and the MADRS Inner Tension item (0.27).

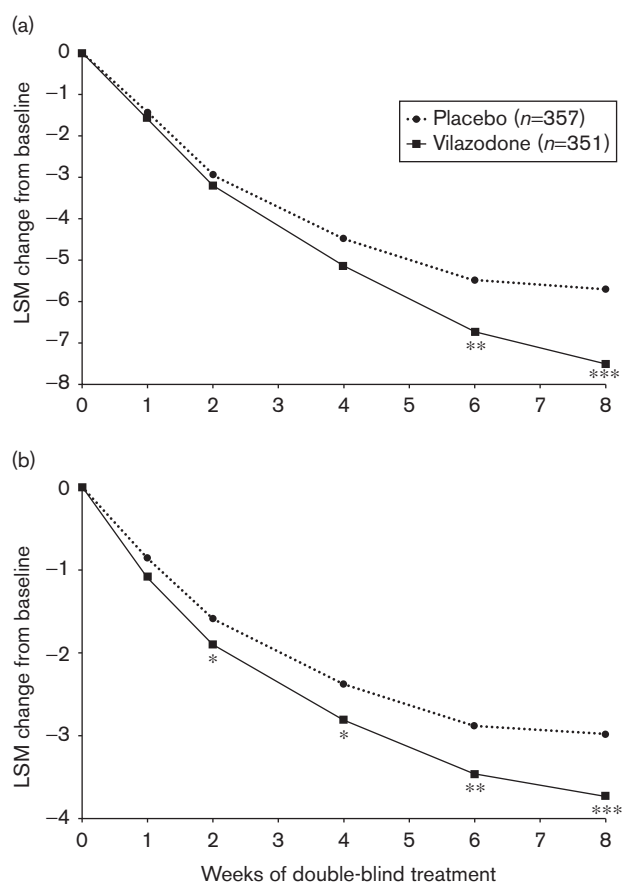
### Discussion

Identifying of effective therapeutic strategies for anxious depression is an important clinical and societal concern; anxiety symptoms in patients with MDD have been associated with increased disease severity, functional disability, treatment resistance, and increased healthcare costs (Rao and Zisook, 2009). We therefore examined the effects of vilazodone in patients with anxious MDD by pooling the samples of two phase III studies. In earlier papers describing the results of the individual studies, vilazodone therapy was reported to have significant effects on the HAMA total score (Rickels *et al.*, 2009; Khan *et al.*, 2011). In the pooled analyses, we could better characterize the types of anxiety symptoms and further evaluate the impact of vilazodone treatment in patients with anxious depression.

We believe that our pooled analysis has yielded several noteworthy findings. Of great relevance to the aims of the current analysis, 82% of the pooled study group met the criteria for anxious depression compared with only about 50% of STAR\*D participants (Fava *et al.*, 2004, 2006, 2008). Although the reasons for this variance cannot be ascertained definitively, it is possible that site investigators in the vilazodone studies preferentially enrolled patients with prominent anxiety. Alternatively, differences in the entry criteria could also be an important factor. Specifically, the studies for this pooled analysis required a much higher HAMD<sub>17</sub> total score for entry ( $\geq 22$ ) than STAR\*D ( $\geq 14$ ). As moderately high correlations between anxiety and depressive symptoms are found in MDD (Fava *et al.*, 2004), it is plausible that the greater severity of patients at the time of entry into the vilazodone studies accounted for the high prevalence of patients with anxious symptoms.

Only 18% of the pooled vilazodone study population had nonanxious depression at baseline. Despite this relatively small number of patients, we analyzed changes in the overall depression measures (i.e. MADRS and HAMD<sub>17</sub> total scores) in this subgroup as well as the anxious subgroup to investigate potential differences in treatment effects. The results suggested larger mean improvements with vilazodone versus placebo in the anxious subgroup relative to the nonanxious subgroup, which was

Fig. 1



Mean changes in (a) HAMA total and (b) HAMD<sub>17</sub> Anxiety/Somatization subscale scores over 8 weeks of treatment in patients with anxious depression. HAMA, Hamilton Anxiety Rating Scale; HAMD<sub>17</sub>, 17-item Hamilton Depression Rating Scale; LSM, least squares mean. \* $P < 0.05$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$  versus placebo.

**Table 2** Mean changes from baseline to 8 weeks in anxiety-related measures in patients with anxious depression (mixed-effects model for repeated measures)

	Placebo ( <i>n</i> = 357)		Vilazodone ( <i>n</i> = 351)		<i>P</i> value	Effect size <sup>a</sup>
	Baseline mean (SD)	LSM change (95% CI)	Baseline mean (SD)	LSM change (95% CI)		
<b>HAMA subscales</b>						
Psychic Anxiety	12.52 (2.73)	−3.83 (−4.32 to −3.35)	12.57 (2.42)	−5.28 (−5.78 to −4.78)	< 0.0001	0.31
Somatic Anxiety	6.18 (3.60)	−1.84 (−2.17 to −1.52)	6.19 (3.47)	−2.24 (−2.58 to −1.91)	0.069	0.13
<b>HAMD<sub>17</sub> items</b>						
Psychic Anxiety	2.33 (0.57)	−0.76 (−0.87 to −0.65)	2.33 (0.58)	−0.98 (−1.09 to −0.87)	0.003	0.21
Somatic Anxiety	2.00 (0.65)	−0.63 (−0.73 to −0.53)	1.99 (0.61)	−0.79 (−0.89 to −0.69)	0.019	0.17
<b>MADRS item</b>						
Inner Tension	3.41 (0.72)	−1.03 (−1.18 to −0.88)	3.47 (0.67)	−1.44 (−1.59 to −1.28)	< 0.001	0.27

CI, confidence interval; HAMA, Hamilton Anxiety Rating Scale; LSM, least squares mean; MADRS, Montgomery–Asberg Depression Rating Scale; HAMD<sub>17</sub>, 17-item Hamilton Depression Rating Scale.

<sup>a</sup>Treatment effect size for vilazodone versus placebo calculated using Cohen's *d* formula.

somewhat unexpected as similar analyses with other antidepressants generally failed to find a difference or found lower efficacy among patients with anxious depression (Fava *et al.*, 2008; Nelson, 2010). Although caution is advised when comparing the anxious and nonanxious groups as the sample size of nonanxious patients was relatively small, resulting in larger deviations (i.e. larger CIs), these results suggest that vilazodone may have additional benefits in treating depression with prominent anxiety symptoms. Given its activity as a 5-HT<sub>1A</sub> receptor partial agonist, vilazodone may have had some preferential effects on anxiety symptoms, which are prevalent symptoms associated with MDD and assessed by both the MADRS and HAMD<sub>17</sub>. Given the statistical limitations of the present analysis, further research may be warranted to evaluate these issues more thoroughly.

At baseline, the mean scores for the HAMA subscales and HAMD<sub>17</sub> items suggest that psychic symptoms (e.g. irritability, tension, worrying) were more pronounced in this patient population than somatic symptoms (e.g. headaches, palpitations, gastrointestinal disturbances, hyperventilation) (Table 2). These results are consistent with other studies that have reported higher baseline scores for psychic anxiety than for somatic anxiety in patients with MDD (Russell *et al.*, 2007; Nelson *et al.*, 2010).

After 8 weeks of treatment, statistically significant improvements in favor of vilazodone versus placebo were observed in the anxious depression subgroup for HAMA total and HAMA Psychic Anxiety subscale scores ( $P < 0.001$  for each measure). Although numerical improvements with vilazodone were also observed on the HAMA Somatic Anxiety subscale, the difference from placebo did not reach statistical significance. This may have been partly because of baseline Somatic Anxiety subscale scores being markedly lower than Psychic Anxiety subscale scores (~6 and 13, respectively), which might have limited the potential to observe statistical improvements for somatic anxiety. It is also possible that as the HAMA was developed primarily as a rating scale for anxiety disorders, it may have relatively low sensitivity to detect somatic anxiety symptoms associated with

depression. As the HAMD<sub>17</sub> was designed to evaluate symptoms in patients with a primary diagnosis of depression, the HAMD<sub>17</sub> Anxiety/Somatization subscale and the Somatic Anxiety item may be more appropriate than the HAMA for evaluating of somatic anxiety in patients with MDD. On both of these anxiety measures, as well as the HAMD<sub>17</sub> Psychic Anxiety subscale and the MADRS Inner Tension item, mean improvements were significantly greater with vilazodone than placebo in patients with anxious depression.

Although treatment effect sizes for anxiety-related measures were generally modest in this analysis ( $d < 0.4$ ), the significant improvements found with vilazodone warrant some consideration. It is not possible to directly compare the vilazodone studies with the STAR\*D study because of considerable differences in patient selection, treatment, and study design. However, the STAR\*D study did show that in patients who did not achieve remission with the SSRI citalopram, the addition of buspirone was a relatively ineffective strategy for patients with anxious depression. Given that patients in the vilazodone studies were immediately randomized to treatment, rather than provided an adjunctive treatment after failing initial antidepressant therapy as in the STAR\*D study, the favorable results found with vilazodone on various anxiety measures suggest that the effective management of anxious depression may require early detection of anxiety symptoms and prompt administration of a medication with potential anxiolytic mechanisms.

The current analyses were limited by the retrospective nature of the evaluations, which were not corrected for multiple comparisons. In addition, although the HAMD<sub>17</sub> definition of anxious depression has been used in other studies, subgrouping patients using another criterion might have resulted in different outcomes for vilazodone versus placebo. Moreover, neither study was designed to specifically recruit or compare patients with anxious versus nonanxious depression, and the observed differences in treatment effects might be related to other differences between these groups in baseline characteristics. Finally, the patients included in the vilazodone

studies are not representative of all patients with MDD and the analyses presented in this report may not be generalizable to a wider population.

### Conclusion

In these post-hoc analyses of pooled data from two pivotal, phase III clinical trials, efficacy across broad measures of anxiety and in a subgroup of patients with anxious depression suggests that vilazodone is an effective treatment option for the large proportion of patients with MDD who have prominent anxiety symptoms. The promising results from these analyses indicate the need for further research evaluating various strategies for the management of patients with anxious depression.

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### Conflicts of interest

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