Research paper

A meta-analysis of the efficacy of vortioxetine in patients with major depressive disorder (MDD) and high levels of anxiety symptoms

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ABSTRACT

Background: Coexisting anxiety is common in major depressive disorder (MDD) and more difficult to treat than depression without anxiety. This analysis assessed the efficacy, safety, and tolerability of vortioxetine in MDD patients with high levels of anxiety (baseline Hamilton Anxiety Rating Scale [HAM-A] total score ≥ 20).
Methods: Efficacy was assessed using an aggregated, study-level meta-analysis of 10 randomized, placebo-controlled, 6/8-week trials of vortioxetine 5–20 mg/day in adults (18–75 years), with a study in elderly patients (≥ 65 years) analyzed separately. Outcome measures included mean differences from placebo in change from baseline to endpoint (Δ) in the Montgomery-Åsberg Depression Rating Scale (MADRS), HAM-A total, and HAM-A subscales. Safety and tolerability were assessed by treatment-emergent adverse events (TEAEs).
Results: A total of 1497 (48.6%) vortioxetine-treated and 860 (49.1%) placebo-treated patients had baseline HAM-A ≥ 20. There were significant differences from placebo in MADRS (vortioxetine 5 mg/day, $n=415$, $\Delta-2.68$, $P=0.005$; 10 mg/day, $n=373$, $\Delta-3.59$, $P<0.001$; 20 mg/day, $n=207$, $\Delta-4.30$, $P=0.005$) and HAM-A total (5 mg/day, $n=419$, $\Delta-1.64$, $P=0.022$; 10 mg/day, $n=373$, $\Delta-2.04$, $P=0.003$; 20 mg/day, $n=207$, $\Delta-2.19$, $P=0.027$). There were significantly greater improvements versus placebo on the HAM-A psychic subscale for all doses. The most common TEAEs ($\geq 5.0\%$) were nausea, headache, dizziness, dry mouth, diarrhea, nasopharyngitis, constipation, and vomiting. Incidence of serious TEAEs was 1.3% (placebo) and $\leq 1.3\%$ (vortioxetine, across doses).
Limitations: Study heterogeneity limits this analysis. Patients with baseline HAM-A ≥ 20 were not directly compared to baseline HAM-A < 20 or total MDD population.
Conclusions: Vortioxetine was efficacious in reducing depressive and anxiety symptoms in patients with MDD and high levels of anxiety.

1. Introduction

Major depressive disorder (MDD) with prominent, coexisting anxiety symptoms or with comorbid anxiety disorders is common, disabling, and typically more difficult to treat than MDD without prominent anxiety. In population-based samples, 45–75% of MDD patients are reported to have comorbid anxiety disorders (Kessler et al., 2015; Schuch et al., 2014). Compared with patients who have MDD without anxiety disorders, individuals affected by anxiety and depressive symptoms concurrently have generally shown greater functional disability, higher risk of suicidal ideation and behavior (Hirschfeld, 2001; Sareen et al., 2005; Seo et al., 2011), and increased utilization of health care resources (Hirschfeld, 2001; McLaughlin et al., 2006).

Antidepressants such as the SSRIs and SNRIs have efficacy in

treating anxiety disorders, and may be considered as first-line treatments for patients with comorbid MDD and anxiety disorders (Baldwin et al., 2014a; Saltiel and Silvershein, 2015). Clinical trials have demonstrated that these agents are efficacious in reducing depressive symptoms versus placebo in patients with MDD and high levels of anxiety symptoms (whether or not they meet the criteria for anxiety disorders) without any single agent or class showing a clear superiority (Altamura et al., 2004; Boulenger et al., 2010; Fava et al., 2000; Maity et al., 2014; Rush et al., 2001; Thase et al., 2014). However, considerable evidence suggests that high levels of anxiety symptoms are predictive of poor response to pharmacotherapies (Fava et al., 2008; Ionescu et al., 2014). For example, in the STAR*D population, 53% of patients had 'anxious depression' (defined as a Hamilton Depression Rating Scale [HAM-D] anxiety/somatization score ≥ 7) (Hamilton, 1960) in addition to MDD (Fava et al., 2008). Rates of response and remission were significantly lower in patients with anxious depression versus non-anxious depression after citalopram monotherapy. Outcomes continued to be worse in patients with anxious depression after augmentation with or switching to bupropion, sertraline, or venlafaxine. Patients with anxious depression experience more frequent and more severe AEs compared with patients with non-anxious depression (Fava et al., 2008). Furthermore, MDD patients with anxiety symptoms who respond to treatment experience a less durable response than do those without anxious depression (Ionescu et al., 2014; Wiethoff et al., 2010). Based on this evidence, more effective and long-lasting treatments are needed to reduce the burden of illness in this patient population.

Vortioxetine is an antidepressant agent that is approved in the US for the treatment of adults with MDD, and in the EU for the treatment of MDEs in adults. Its mechanism of action is related to its multimodal activity, which combines two pharmacological properties: direct modulation of receptor activity and inhibition of the 5-HT transporter. In addition to inhibiting the 5-HT transporter (Bang-Andersen et al., 2011), vortioxetine is an antagonist at 5-HT$_3$, 5-HT$_7$, and 5-HT$_{1D}$ receptors, a partial agonist at 5-HT$_{1B}$ receptors, and an agonist at 5-HT$_{1A}$ receptors (Bang-Andersen et al., 2011; Mork et al., 2012; Westrich et al., 2012).

As of July 29, 2015, there have been 23 completed and reported phase 2/3 clinical trials of vortioxetine in MDD, including 11 randomized, double-blind, parallel-group, placebo-controlled studies of 6/8 weeks' duration that also included the Hamilton Anxiety Rating Scale (HAM-A) total score (Hamilton, 1959) as a predefined efficacy outcome measure (Alvarez et al., 2012; Baldwin et al., 2012a; Boulenger et al., 2014; Henigsberg et al., 2012; Jacobsen et al., 2015; Jain et al., 2013; Katona et al., 2012; Mahableshwarkar et al., 2015a, 2013, 2015b; Takeda, 2013). In these MDD studies, treatment with vortioxetine (in doses ranging from 5 to 20 mg/day) was consistently associated with a dose related reduction in anxiety symptoms in the overall MDD population. Clinical trials evaluating the efficacy of vortioxetine in the treatment of patients with generalized anxiety disorder (GAD) with doses up to 10 mg/day have yielded variable results (Baldwin et al., 2012b; Bidzan et al., 2012; Mahableshwarkar et al., 2014a, 2014b; Rothschild et al., 2012); though a recent independent meta-analysis of data from 4 short-term, randomized controlled trials concluded that vortioxetine has a favorable safety and efficacy profile in patients with GAD (Pae et al., 2015).

The objectives of the present analyses were to evaluate the efficacy and safety of approved doses of vortioxetine (5–20 mg/day) in the subgroup of MDD patients with high levels of anxiety symptoms at baseline. High levels of anxiety symptoms were predefined in each individual study protocol as patients with HAM-A total score ≥ 20 at baseline. A HAM-A total score cutoff of 20 has been utilized in a number of clinical studies to distinguish between anxious versus non-anxious MDD patients (Bandelow et al., 2014; Boulenger et al., 2010; Seo et al., 2011; Thase et al., 2012). An additional efficacy meta-analysis was also conducted in the subgroup of MDD patients with more severe levels of anxiety symptoms (HAM-A total score ≥ 25 at baseline) (Konstantakopoulos et al., 2013; Matza et al., 2010).

2. Methods

2.1. Studies

The clinical development programme for vortioxetine in MDD included 11 randomized, double-blind, placebo-controlled, multicentre, short-term (6 or 8 weeks' duration) studies that evaluated vortioxetine (5–20 mg/day) in patients ≥ 18 years old with MDD and that documented baseline HAM-A scores (Supplemental Table 1). Of these, 10 were included in the efficacy meta-analyses reported here. The remaining study—NCT00811252 (Katona et al., 2012)—is analyzed separately because its study population differed by excluding individuals aged < 65 years. For the pooled safety analysis, all 11 trials were included.

All studies were designed and conducted in accordance with the principles of the World Medical Association *Declaration of Helsinki*, the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for *Good Clinical Practice*, and all applicable local or regional regulatory requirements. The studies' sponsors (Takeda Pharmaceutical Company, Ltd. and H. Lundbeck A/S) assumed overall responsibility for the studies, including those where monitoring was delegated to a contract research organization. Protocols, statistical analyses, and statistical reporting for all studies were developed and conducted in compliance with current scientific research approaches and relevant guidelines. The details of the study designs and primary efficacy results for all included trials have been published (Alvarez et al., 2012; Baldwin et al., 2012a; Boulenger et al., 2014; Henigsberg et al., 2012; Jacobsen et al., 2015; Jain et al., 2013; Katona et al., 2012; Mahableshwarkar et al., 2015a, 2013, 2015b; Takeda, 2013). Supplemental Table 1 provides a summary of treatment dosages, number of patients in each dosage arm, treatment duration, and key MDD inclusion criteria for all of the trials considered here.

For each of the 10 trials included in the efficacy meta-analyses, patients had to meet the criteria for an MDE (as described in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision [DSM-IV-TR]) lasting at least 3 months and be between 18 and 75 years of age (except NCT00839423 recruited ages 18–65 years and NCT01255787 recruited ages 20–64 years). Additional inclusion criteria included a Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) total score ≥ 22 (NCT00672620 (Mahableshwarkar et al., 2013)), ≥ 30 (NCT00839423 (Alvarez et al., 2012) and NCT00672958 (Jain et al., 2013)), or ≥ 26 (all other studies). An additional eligibility requirement of a Clinical Global Impressions–Severity of Illness (CGI-S) (Guy, 1976) score ≥ 4 was also required for NCT01140906 (Boulenger et al., 2014), NCT01153009 (Mahableshwarkar et al., 2015b), NCT01163266 (Jacobsen et al., 2015), and NCT01179516 (Mahableshwarkar et al., 2015a). In study NCT00811252 (Katona et al., 2012), patients were required to be aged ≥ 65 years with a MADRS total score ≥ 26, as well as have current MDE duration of ≥ 4 weeks with ≥ 1 MDE occurring before 60 years of age. Patients were excluded from these studies if they had any current psychiatric disorder other than MDD (including anxiety disorders) as defined in the DSM-IV-TR.

2.2. Efficacy

To investigate the efficacy profile of vortioxetine in the

subgroup of adult MDD patients with HAM-A total score ≥ 20 at baseline, a primary, conservative meta-analysis (including all positive/supportive and failed/negative studies) was performed using aggregated study-level data. A "positive" study was defined as one that demonstrates statistically significant superiority on the primary efficacy outcome versus either placebo, the current standard (reference) treatment, or both; whereas a "supportive" study was defined as a study that may not demonstrate statistically significant superiority in the primary efficacy outcome, but demonstrates superiority on secondary efficacy outcomes that are also clinically relevant. Studies were considered as "failed" when both the study drug and the reference treatment fail to demonstrate statistically significant superiority in efficacy over placebo. "Negative" studies are those in which the study drug did not separate from placebo but the reference treatment did.

For 7 of the 10 individual studies [i.e., excluding NCT00672958 (Jain et al., 2013), NCT00672620 (Mahableshwarkar et al., 2013), and NCT00735709 (Henigsberg et al., 2012)], as well as for these meta-analyses, the primary outcome measure was pre-defined as the change from baseline in MADRS total score at the end of the treatment period. The primary endpoint for NCT00672958, NCT00672620, and NCT00735709 was the change from baseline in HAM-D 24-item total score, with change from baseline in MADRS total score as a secondary outcome. In the present analyses, secondary endpoints included change from baseline in HAM-A total score, HAM-A Item 1 (anxious mood), HAM-A somatic anxiety subscale (combined Items 7–13 – somatic [muscular], somatic [sensory], cardiovascular symptoms, respiratory symptoms, gastrointestinal symptoms, genitourinary symptoms, and autonomic symptoms, respectively) (Hamilton, 1959), HAM-A psychic anxiety subscale (combined items 1–6 plus Item 14 – anxious mood, tension, fears, insomnia, intellectual, depressed mood, and behavior at interview, respectively) (Hamilton, 1959), MADRS Item 3 (inner tension), CGI-S score, and Clinical Global Impressions–Improvement (CGI-I) score.

A secondary meta-analysis was performed in the high anxiety subgroup, which included only aggregated study-level data from the 5 trials that did not enroll patients from the US (NCT00839423, NCT00635219, NCT00735709, NCT01140906, and NCT01255787) to evaluate issues of region and heterogeneity. Outcome measures evaluated in this subgroup included the MADRS and HAM-A total scores, HAM-A subscale scores, and CGI scores.

An additional meta-analysis was also conducted for the primary efficacy outcome (MADRS total score) in patients with a HAM-A total score ≥ 25 at baseline to evaluate the depression efficacy of vortioxetine in the subgroup with the most severe anxiety symptoms. Results from the 10 adult trials were included in this additional meta-analysis, with a secondary meta-analysis limited to the 5 non-US trials in adults.

The effects of placebo and vortioxetine 5 mg/day treatments on mean changes in MADRS scores and HAM-A scores were compared for patients in the elderly study who had baseline HAM-A total scores ≥ 20.

2.3. Statistical analysis for efficacy

An aggregated meta-analytic approach based on study-level data was chosen as the statistical methodology as this method is considered to provide the most reliable estimates of treatment effect. Specifically, it efficiently and robustly handles heterogeneity and the complexity arising from not having all dosages in all studies.

All efficacy meta-analyses were performed on the full analysis set (FAS), defined as all randomized patients who took at least 1 dose of the study medication and had at least 1 valid post-baseline measurement of the primary efficacy outcome (HAM-A

total score for these analyses). The statistical methodologies used in the individual studies formed the basis for the meta-analyses - either a mixed-effect model for repeated measures (MMRM) or an analysis of covariance (ANCOVA) using last observation carried forward (LOCF) imputation. The MMRM was the primary efficacy analysis method used in 5 studies (NCT01179516, NCT00735709, NCT01153009, NCT01163266, and NCT01140906) and an ANCOVA (LOCF) was the primary in 5 studies (NCT00839423, NCT00635219, NCT01255787, NCT00672958, and NCT00672620); however, all included studies analyzed data by both MMRM and ANCOVA (LOCF). The MMRM has specific attributes suited to the data structure of acute-phase neuropsychiatric clinical studies and has been compared extensively with the LOCF (Siddiqui et al., 2009). Research indicates that, in many scenarios, analyses based on the MMRM provide less biased estimates of treatment effect because the assumption for the LOCF is often problematic in the real world (Armitage and Colton, 1998; Siddiqui et al., 2009). In the current meta-analysis, LOCF is utilized as a sensitivity analysis to the MMRM. Standard methodology for MMRM and LOCF meta-analyses was applied (Armitage and Colton, 1998). Standardized effect sizes were calculated as the Cohen's d statistic as mean and standard deviation data were available for all studies. Results are reported as the least squares (LS) mean difference from baseline versus placebo (95% confidence interval [CI]). All statistical tests were two-sided with a 0.05 significance level without multiplicity adjustment.

2.4. Safety and tolerability

To determine the safety and tolerability profile of vortioxetine in MDD patients with high levels of anxiety symptoms, treatment-emergent adverse events (TEAEs) were compiled separately for placebo and each individual vortioxetine dose group using pooled data from all 11 trials (includes efficacy population plus the study in elderly patients aged ≥ 65 years (Katona et al., 2012)). The safety set population comprised all randomized patients who received at least 1 dose of the study medication. TEAEs were assessed at each study visit (Weeks 1, 2, 4, 6, and 8) and evaluated based on their frequency and whether they led to discontinuation. In addition, listings of TEAEs were manually reviewed for potential anxiogenic effects related to the initiation of vortioxetine, as emergent anxiety has been reported in several studies of anti-depressants after treatment initiation (Gollan et al., 2012; Grillon et al., 2007; Li et al., 2011).

3. Results

3.1. Patients

In the 10 adult studies included in the efficacy meta-analysis, 1590 MDD patients were treated with placebo and 2856 with therapeutic dosages of vortioxetine (Table 1a). At baseline, patients in the overall MDD population had moderate-to-severe depression, as indicated by mean MADRS total score of ≈ 32 and mean CGI-S score of ≈ 4.7, and had moderate anxiety, as indicated by mean HAM-A total score of ≈ 20 (Busner et al., 2011; Matza et al., 2010). A total of 771 (48.5%) patients in the placebo group and 1394 (48.8%) vortioxetine-treated patients had a baseline HAM-A total score ≥ 20 and were included in the primary subgroup meta-analysis (Table 1b). Patients in this subgroup were slightly more likely to be female, have a higher CGI-S score at baseline, and be part of a non-US trial compared to patients in the overall MDD population. Otherwise, the baseline characteristics in the 2 groups were similar.

Table 1a
Summary of demographics, baseline characteristics, and baseline efficacy parameters for the total MDD population included in the efficacy meta-analysis of 10 short-term, placebo-controlled clinical studies of vortioxetine in patients with MDD (full analysis set).

	Placebo	Vortioxetine			
	(N=1590)	5 mg (n=989)	10 mg (n=835)	15 mg (n=436)	20 mg (n=596)
Age, years, mean (SD)	43.8 (12.49)	44.1 (12.79)	44.8 (12.26)	44.9 (13.61)	44.2 (12.71)
Sex, female, n (%)	1019 (64.1)	644 (65.1)	564 (67.5)	300 (68.8)	398 (66.8)
Race, n (%)					
Caucasian	1268 (79.7)	752 (76.0)	631 (75.6)	360 (82.6)	457 (76.7)
Black	210 (13.2)	122 (12.3)	85 (10.2)	68 (15.6)	82 (13.8)
Asian	107 (6.7)	110 (11.1)	110 (13.2)	6 (1.4)	52 (8.7)
Other[a]	5 (0.3)	5 (0.5)	9 (1.1)	2 (0.5)	5 (0.8)
BMI, kg/m^2					
Mean (SD)	28.64 (7.12)	27.88 (7.34)	27.76 (6.85)	29.16 (7.18)	28.03 (6.94)
Duration of current MDE, n (%)					
< 24 weeks	724 (45.5)	494 (49.9)	436 (52.2)	194 (44.5)	248 (41.6)
≥ 24 weeks	866 (54.5)	495 (50.1)	395 (47.3)	242 (55.5)	348 (58.4)
Number of previous MDEs					
Mean (SD)	2.7 (2.26)	2.8 (3.05)	2.7 (2.22)	2.7 (1.90)	2.7 (2.37)
Region, n (%)					
US	892 (56.1)	445 (45.0)	297 (35.6)	287 (65.8)	295 (49.5)
Non-US	698 (43.9)	544 (55.0)	538 (64.4)	149 (34.2)	301 (50.5)
MADRS total score					
Mean (SD)	32.2 (4.02)	32.4 (4.04)	32.5 (4.07)	32.5 (4.09)	31.9 (3.99)
HAM-A total score					
Mean (SD)	19.7 (6.32)	20.1 (6.23)	20.6 (6.46)	19.4 (6.11)	18.9 (6.12)
≥ 20, n (%)	771 (48.5)	494 (49.9)	442 (52.9)	205 (47.0)	253 (42.4)
CGI-S total score					
Mean (SD)	4.7 (0.68)	4.8 (0.70)	4.7 (0.68)	4.7 (0.61)	4.6 (0.63)

CGI-S, Clinical Global Impressions–Severity of Illness; HAM-A, Hamilton Anxiety Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; MDE, major depressive episode; SD, standard deviation.

[a] Other: including American Indian/Alaska Native, Native Hawaiian (or other Pacific Islander), and missing.

Table 1b
Summary of demographics, baseline characteristics, and baseline efficacy parameters for patients with baseline HAM-A total score ≥ 20 included in the efficacy meta-analysis of 10 short-term, placebo-controlled clinical studies of vortioxetine in patients with MDD (full analysis set).

	Placebo	Vortioxetine			
	(N=771)	5 mg (n=494)	10 mg (n=442)	15 mg (n=205)	20 mg (n=253)
Age, years, mean (SD)	44.7 (11.93)	43.8 (12.65)	44.8 (12.48)	44.2 (13.65)	45.4 (12.78)
Sex, female, n (%)	545 (70.7)	351 (71.1)	308 (69.7)	149 (72.7)	185 (73.1)
Race, n (%)					
Caucasian	641 (83.1)	385 (77.9)	343 (77.6)	177 (86.3)	210 (83.0)
Black	76 (9.9)	50 (10.1)	37 (8.4)	27 (13.3)	29 (11.5)
Asian	50 (6.5)	56 (11.3)	59 (13.3)	1 (0.5)	11 (4.3)
Other[a]	4 (0.5)	3 (0.6)	3 (0.7)	0	2 (1.2)
BMI, kg/m^2					
Mean (SD)	28.65 (7.20)	27.76 (7.40)	27.40 (6.49)	28.51 (6.95)	28.01 (6.94)
Duration of current MDE, n (%)					
< 24 weeks	360 (46.7)	249 (50.4)	233 (52.7)	98 (47.8)	106 (41.9)
≥ 24 weeks	411 (53.3)	245 (49.6)	206 (46.6)	107 (52.2)	147 (58.1)
Number of previous MDEs					
Mean (SD)	2.7 (2.23)	2.6 (2.64)	2.5 (2.02)	2.6 (1.77)	2.8 (2.44)
Region, n (%)					
US	376 (48.8)	204 (41.3)	129 (29.2)	118 (57.6)	114 (45.1)
Non-US	395 (51.2)	290 (58.7)	313 (70.8)	87 (42.4)	139 (54.9)
MADRS total score					
Mean (SD)	33.3 (4.04)	33.3 (4.23)	33.3 (4.15)	33.7 (4.23)	33.1 (4.04)
HAM-A total score					
Mean (SD)	24.9 (4.21)	25.1 (4.27)	25.4 (4.59)	24.6 (4.29)	24.6 (4.25)
≥ 20, n (%)	771 (100.0)	494 (100.0)	442 (100.0)	205 (100.0)	253 (100.0)
CGI-S total score					
Mean (SD)	4.9 (0.66)	4.9 (0.68)	4.9 (0.66)	4.7 (0.60)	4.8 (0.64)

CGI-S, Clinical Global Impressions–Severity of Illness; HAM-A, Hamilton Anxiety Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; MDE, major depressive episode; SD, standard deviation.

[a] Other: including American Indian/Alaska Native, Native Hawaiian (or other Pacific Islander), and missing.

3.2. Efficacy

3.2.1. MADRS total score

The difference from placebo in MADRS total score for the change from baseline to Week 6/8 in patients with baseline HAM-A total score ≥ 20 was statistically significantly in favor of vortioxetine 5 mg/day (P=0.005), 10 mg/day ($P < 0.001$), and 20 mg/day (P=0.005), but not vortioxetine 15 mg/day (P=0.650) (Fig. 1). Inspection of standardized effect size (SES) scores in studies analyzing > 1 vortioxetine dose suggests a dose-related trend in clinical response, with larger effects being experienced at higher doses.

When restricting the meta-analysis to MDD patients with a baseline HAM-A total score ≥ 20 in the 5 studies conducted outside of the US, the results were statistically significantly in favor of vortioxetine 5 mg/day (P=0.025), 10 mg/day ($P < 0.001$), and 15 mg/day ($P < 0.001$), with near-significance for vortioxetine 20 mg/day (P=0.051) (Fig. 1).

In the elderly study (NCT00811252) (Katona et al., 2012),

treatment with vortioxetine 5 mg/day in those who had baseline HAM-A total score ≥ 20 resulted in a statistically significant LS mean difference from placebo in change from baseline in MADRS total score.

In the additional analysis of MDD patients with more severe anxiety symptoms (HAM-A total score ≥ 25) at baseline, vortioxetine 5 mg/day and 10 mg/day demonstrated a significantly greater change from baseline versus placebo in MADRS total score (P=0.049 and $P < 0.001$, respectively), while vortioxetine 15 mg/day and 20 mg/day failed to separate (P=0.535 and P=0.090, respectively) (Supplemental Fig. 1). When limiting to studies conducted outside the US, vortioxetine 5 mg/day and 10 mg/day kept their statistical significance versus placebo (P=0.008 and $P < 0.001$, respectively) and vortioxetine 20 mg/day reached statistical significance (P=0.030), whereas vortioxetine 15 mg/day failed to separate from placebo (P=0.102).
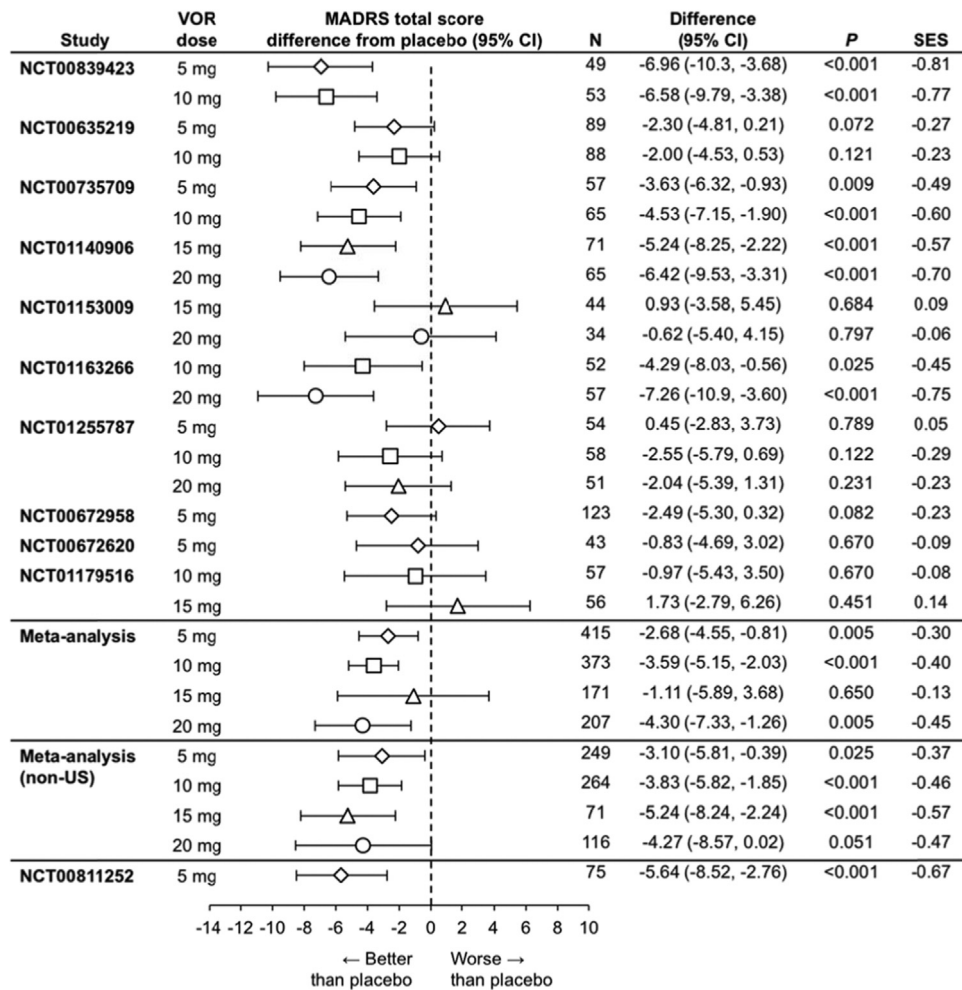
Fig. 1. Difference from placebo in MADRS total score change from baseline at Week 6/8: Baseline HAM-A ≥ 20 population (FAS, MMRM). Studies included in the non-US analysis: NCT00839423, NCT00635219, NCT00735709, NCT01140906, and NCT01255787. CI, confidence interval; SES, standardized effect size; VOR, vortioxetine.

3.2.2. HAM-A total score

In the subgroup of MDD patients with high levels of anxiety symptoms (baseline HAM-A total score ≥ 20), statistically significant differences from placebo in HAM-A total score were demonstrated by vortioxetine 5 mg/day ($P=0.022$), 10 mg/day ($P=0.003$), and 20 mg/day ($P=0.027$) at study endpoint, but not for vortioxetine 15 mg/day ($P=0.886$) (Fig. 2A). In the meta-analysis of studies conducted outside of the US, vortioxetine 5, 10, and 15 mg/day displayed statistically significant mean differences from placebo at study endpoint ($P=0.030$, $P=0.002$, and $P=0.047$, respectively), while vortioxetine 20 mg/day was close to reaching statistical significance ($P=0.053$) (Fig. 2A). In MDD patients with a baseline HAM-A total score ≥ 20 who were treated with vortioxetine 5 mg/day in the dedicated elderly study (NCT00811252), the mean difference from placebo in change from baseline HAM-A total score was statistically significant in favor of vortioxetine ($P=0.001$).

The results from the total MDD population included in this meta-analysis were similar to that of the MDD population with high levels of anxiety symptoms, including the dose-response relationship of vortioxetine 5, 10, and 20 mg/day (Fig. 2B). These results are also similar to the results of the total MDD population enrolled in the non-US studies, including the dose-response relationship.

The LS mean difference from placebo in HAM-A total score change from baseline was additionally assessed by study visit for the MDD population with high levels of anxiety symptoms and the

overall MDD population from the 8-week trials. In the subgroup with high levels of anxiety, the difference from placebo was statistically significant from the second on-treatment study visit (Week 4) for vortioxetine 10 mg/day, and remained significantly different through Week 8 (Fig. 3A). In the overall MDD population, the difference from placebo was statistically significant beginning at Week 2 for vortioxetine 10 mg/day and at Week 4 for vortioxetine 20 mg/day, and remained significant through Week 6 and Week 8, respectively (Fig. 3B).

3.2.3. HAM-A subscale scores

In the evaluation of HAM-A subscales, analysis was based on HAM-A Item 1 (anxious mood), somatic anxiety subscale, and psychic anxiety subscale (Fig. 4). In change from baseline on HAM-A Item 1, the meta-analysis of both the total MDD population and the MDD subgroup with high-level anxiety symptoms yielded statistically significant results versus placebo for vortioxetine 5 mg/day (total, $P=0.009$; high anxiety, $P=0.044$) and 10 mg/day (total, $P < 0.001$; high anxiety, $P=0.003$), but not for vortioxetine 15 mg/day (total, $P=0.331$; high anxiety, $P=0.708$) or 20 mg/day (total, $P=0.162$; high anxiety, $P=0.135$).

On the somatic anxiety subscale, neither population yielded significant results for any of the vortioxetine doses. In contrast, on the psychic anxiety subscale there were statistically significant differences from placebo in change from baseline in both meta-analysis populations for the vortioxetine 5 mg/day (total, $P=0.008$; high anxiety, $P=0.007$), 10 mg/day (total, $P < 0.001$;

A

Study	VOR dose	N	Difference (95% CI)	P	SES
NCT00839423	5 mg	49	-4.86 (-7.27, -2.45)	<0.001	-0.77
	10 mg	53	-4.91 (-7.26, -2.56)	<0.001	-0.78
NCT00635219	5 mg	89	-1.62 (-3.66, 0.43)	0.122	-0.23
	10 mg	88	-1.21 (-3.29, 0.86)	0.251	-0.17
NCT00735709	5 mg	57	-2.36 (-4.55, -0.18)	0.034	-0.39
	10 mg	65	-2.88 (-4.98, -0.78)	0.007	-0.48
NCT01140906	15 mg	71	-2.48 (-4.94, -0.03)	0.048	-0.33
	20 mg	65	-4.21 (-6.74, -1.69)	0.001	-0.56
NCT01153009	15 mg	44	1.52 (-1.51, 4.55)	0.323	0.21
	20 mg	34	0.65 (-2.57, 3.86)	0.691	0.09
NCT01163266	10 mg	52	-1.64 (-4.07, 0.79)	0.184	-0.26
	20 mg	57	-3.19 (-5.57, -0.82)	0.009	-0.51
NCT01255787	5 mg	56	0.21 (-2.20, 2.62)	0.864	0.03
	10 mg	58	-1.48 (-3.84, 0.89)	0.219	-0.23
	20 mg	51	-1.35 (-3.83, 1.13)	0.285	-0.21
NCT00672958	15 mg	125	-1.30 (-3.21, 0.61)	0.182	-0.17
NCT00672620	5 mg	43	0.30 (-2.40, 2.99)	0.830	0.05
NCT01179516	10 mg	57	0.10 (-2.48, 2.68)	0.939	0.01
	15 mg	57	0.72 (-1.90, 3.35)	0.587	0.10
Meta-analysis	5 mg	419	-1.64 (-3.04, -0.23)	0.022	-0.25
	10 mg	373	-2.04 (-3.36, -0.71)	0.003	-0.31
	15 mg	172	-0.18 (-2.64, 2.28)	0.886	-0.02
	20 mg	207	-2.19 (-4.12, -0.25)	0.027	-0.32
Meta-analysis (non-US)	5 mg	251	-2.15 (-4.09, -0.21)	0.030	-0.33
	10 mg	264	-2.59 (-4.20, -0.97)	0.002	-0.40
	15 mg	71	-2.48 (-4.93, -0.04)	0.047	-0.33
	20 mg	116	-2.77 (-5.58, 0.04)	0.053	-0.39
NCT00811252	5 mg	75	-3.77 (-6.08, -1.47)	0.001	-0.56

HAM-A total score difference from placebo (95% CI): −8 −6 −4 −2 0 2 4 6; ← Better than placebo / Worse than placebo →

B

Study	VOR dose	N	Difference (95% CI)	P	SES
NCT00839423	5 mg	93	-3.27 (-4.99, -1.55)	<0.001	-0.56
	10 mg	78	-3.88 (-5.68, -2.09)	<0.001	-0.67
NCT00635219	5 mg	122	-1.87 (-3.50, -0.23)	0.025	-0.29
	10 mg	119	-1.74 (-3.40, -0.08)	0.040	-0.27
NCT00735709	5 mg	129	-2.14 (-3.51, -0.76)	0.002	-0.38
	10 mg	122	-2.88 (-4.28, -1.49)	<0.001	-0.51
NCT01140906	15 mg	118	-2.55 (-4.09, -1.00)	0.001	-0.41
	20 mg	125	-4.09 (-5.62, -2.55)	<0.001	-0.66
NCT01153009	15 mg	113	-0.07 (-1.54, 1.40)	0.928	-0.01
	20 mg	112	-0.63 (-2.09, 0.84)	0.399	-0.11
NCT01163266	10 mg	124	-0.22 (-1.57, 1.14)	0.754	-0.04
	20 mg	122	-1.40 (-2.77, -0.03)	0.045	-0.25
NCT01255787	5 mg	128	-0.05 (-1.33, 1.23)	0.939	-0.01
	10 mg	132	-1.56 (-2.82, -0.30)	0.015	-0.30
	20 mg	131	-0.93 (-2.20, 0.34)	0.149	-0.18
NCT00672958	15 mg	247	-0.41 (-1.53, 0.72)	0.477	-0.06
NCT00672620	5 mg	120	-0.01 (-1.42, 1.39)	0.983	0.00
NCT01179516	10 mg	123	-0.08 (-1.70, 1.53)	0.920	-0.01
	15 mg	114	-0.02 (-1.66, 1.61)	0.978	0.00
Meta-analysis	5 mg	839	-1.21 (-2.21, -0.20)	0.019	-0.21
	10 mg	698	-1.69 (-2.81, -0.57)	0.003	-0.29
	15 mg	345	-0.88 (-2.52, 0.76)	0.291	-0.14
	20 mg	490	-1.73 (-3.19, -0.28)	0.020	-0.30
Meta-analysis (non-US)	5 mg	472	-1.76 (-3.12, -0.41)	0.011	-0.30
	10 mg	451	-2.43 (-3.44, -1.43)	<0.001	-0.42
	15 mg	118	-2.55 (-4.08, -1.01)	0.001	-0.41
	20 mg	256	-2.48 (-5.57, 0.61)	0.116	-0.42
NCT00811252	5 mg	137	-2.69 (-4.12, -1.26)	<0.001	-0.45

HAM-A total score difference from placebo (95% CI): −8 −6 −4 −2 0 2 4 6; ← Better than placebo / Worse than placebo →
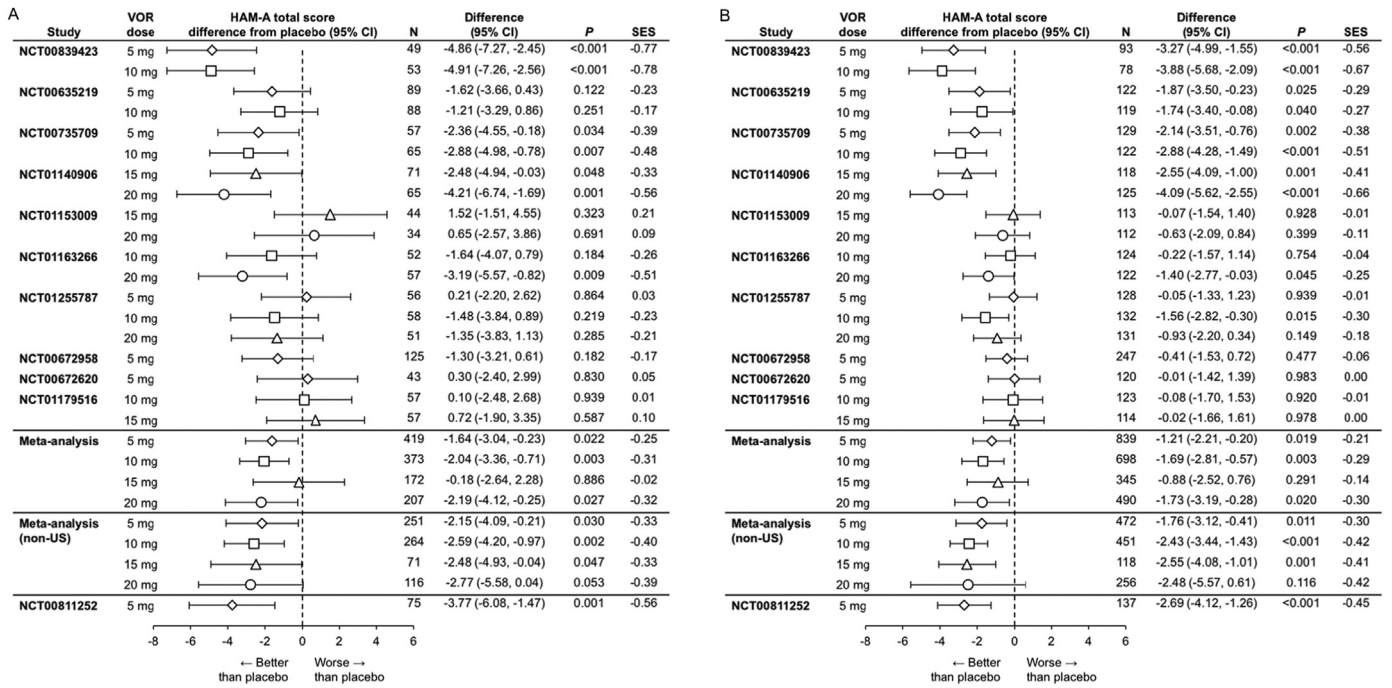
Fig. 2. A. Difference from placebo in HAM-A total score change from baseline at Week 6/8: Baseline HAM-A ≥ 20 population (FAS, MMRM). Studies included in the non-US analysis: NCT00839423, NCT00635219, NCT00735709, NCT01140906, and NCT01255787. CI, confidence interval; SES, standardize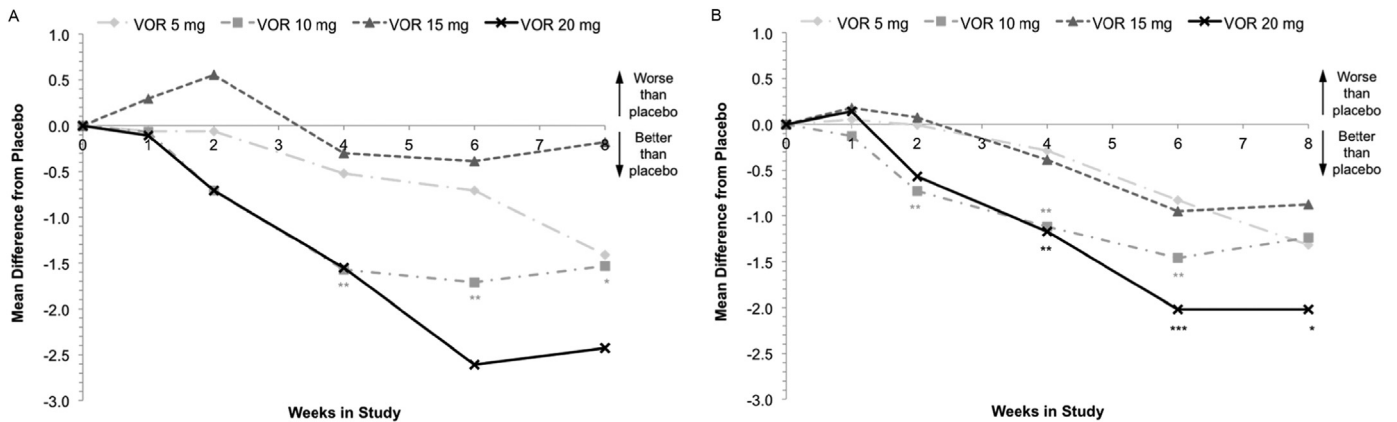d effect size; VOR, vortioxetine. B. Difference from placebo in HAM-A total score change from baseline at Week 6/8: Total MDD population (FAS, MMRM). Studies included in the non-US analysis: NCT00839423, NCT00635219, NCT00735709, NCT01140906, and NCT01255787. CI, confidence interval; SES, standardized effect size; VOR, vortioxetine.

Fig. 3. A. Difference from placebo in HAM-A total score change from baseline by study visit in the 8-week studies: Baseline HAM-A ≥ 20 population (FAS, MMRM). Studies included in the 8-week analysis: NCT00635219, NCT00735709, NCT01140906, NCT01153009, NCT01163266, NCT00672620, and NCT01179516. NCT01255787 was not included because the HAM-A was only assessed at baseline and at Weeks 4 and 8. *$P < 0.05$,**$P < 0.01$ versus placebo. VOR, vortioxetine. B. Difference from placebo in HAM-A total score change from baseline by study visit in the 8-week studies: Total MDD population (FAS, MMRM). Studies included in the 8-week analysis: NCT00635219, NCT00735709, NCT01140906, NCT01153009, NCT01163266, NCT00672620, and NCT01179516. NCT01255787 was not included because the HAM-A was only assessed at baseline and at Weeks 4 and 8. *$P < 0.05$,**$P < 0.01$,***$P < 0.001$ vs placebo. VOR, vortioxetine.

high anxiety, $P < 0.001$), and 20 mg/day doses (total, $P = 0.009$; high anxiety, $P < 0.001$), but not for vortioxetine 15 mg/day (total, $P = 0.108$; high anxiety, $P = 0.329$). The psychic anxiety subscale results provide some evidence for a dose-response relationship (not including vortioxetine 15 mg/day) as seen with the SES (Fig. 4).

In the elderly study, which only assessed vortioxetine 5 mg/day, patients with MDD and high levels of anxiety symptoms demonstrated a statistically significant improvement in both the somatic and psychic anxiety subscales ($P = 0.008$ and $P = 0.001$, respectively). This significance was also attained in the total MDD population for this study in both HAM-A subscales ($P = 0.015$ and $P < 0.001$, respectively) (Fig. 4).

3.2.4. MADRS Item 3 ('Inner Tension') analysis

Analysis of the difference from placebo in the change from baseline to study endpoint in inner tension for patients with baseline HAM-A total score ≥ 20 demonstrated a consistent dose effect in favor of vortioxetine through the range of approved doses (5 mg/day, $n = 415$, $\Delta - 0.28$ [$-0.52, -0.04$], $P = 0.025$; 10 mg/day, $n = 373$, $\Delta - 0.37$ [$-0.53, -0.21$], $P < 0.001$; 15 mg/day, $n = 171$, $\Delta - 0.10$ [$-0.83, 0.63$], $P = 0.783$; 20 mg/day, $n = 207$, $\Delta - 0.39$ [$-0.65, -0.14$], $P = 0.003$).

3.2.5. CGI scores

The meta-analyses of CGI-I and CGI-S scores supported the results of overall analysis of the MADRS and HAM-A total scores. The meta-analysis of difference from placebo in CGI-I score change
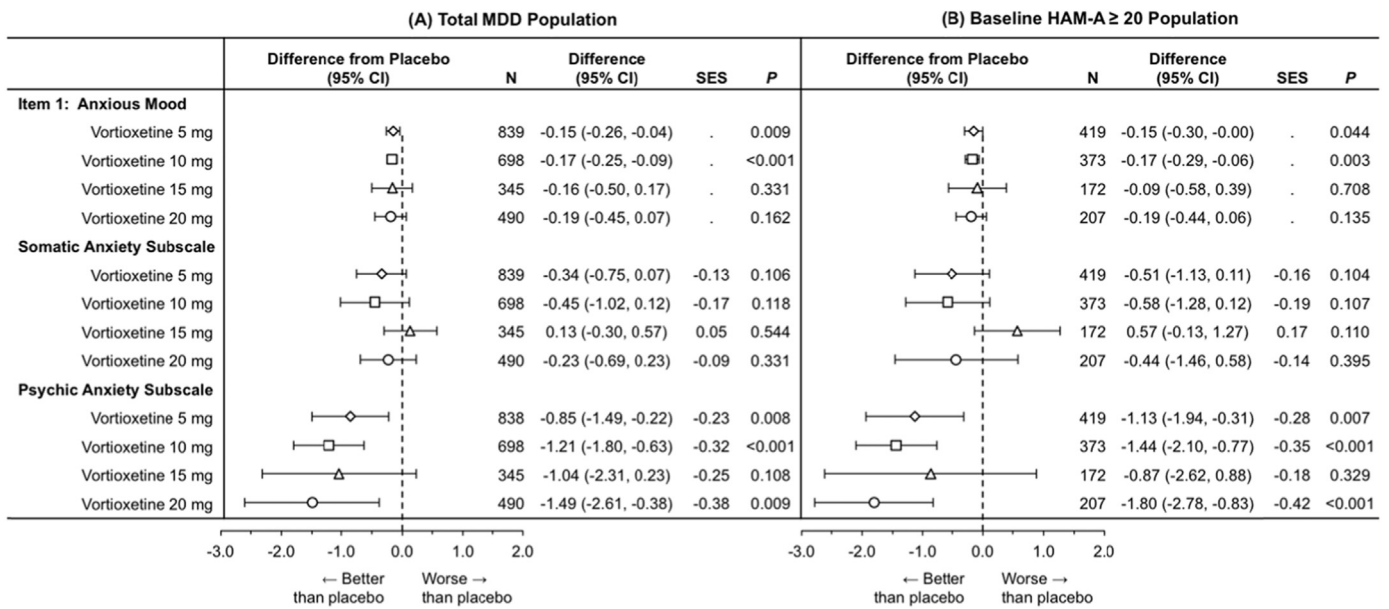
(A) Total MDD Population | (B) Baseline HAM-A ≥ 20 Population

Item 1: Anxious Mood	Difference from Placebo (95% CI)	N	Difference (95% CI)	SES	P	Difference from Placebo (95% CI)	N	Difference (95% CI)	SES	P
Vortioxetine 5 mg		839	-0.15 (-0.26, -0.04)	.	0.009		419	-0.15 (-0.30, -0.00)	.	0.044
Vortioxetine 10 mg		698	-0.17 (-0.25, -0.09)	.	<0.001		373	-0.17 (-0.29, -0.06)	.	0.003
Vortioxetine 15 mg		345	-0.16 (-0.50, 0.17)	.	0.331		172	-0.09 (-0.58, 0.39)	.	0.708
Vortioxetine 20 mg		490	-0.19 (-0.45, 0.07)	.	0.162		207	-0.19 (-0.44, 0.06)	.	0.135
Somatic Anxiety Subscale										
Vortioxetine 5 mg		839	-0.34 (-0.75, 0.07)	-0.13	0.106		419	-0.51 (-1.13, 0.11)	-0.16	0.104
Vortioxetine 10 mg		698	-0.45 (-1.02, 0.12)	-0.17	0.118		373	-0.58 (-1.28, 0.12)	-0.19	0.107
Vortioxetine 15 mg		345	0.13 (-0.30, 0.57)	0.05	0.544		172	0.57 (-0.13, 1.27)	0.17	0.110
Vortioxetine 20 mg		490	-0.23 (-0.69, 0.23)	-0.09	0.331		207	-0.44 (-1.46, 0.58)	-0.14	0.395
Psychic Anxiety Subscale										
Vortioxetine 5 mg		838	-0.85 (-1.49, -0.22)	-0.23	0.008		419	-1.13 (-1.94, -0.31)	-0.28	0.007
Vortioxetine 10 mg		698	-1.21 (-1.80, -0.63)	-0.32	<0.001		373	-1.44 (-2.10, -0.77)	-0.35	<0.001
Vortioxetine 15 mg		345	-1.04 (-2.31, 0.23)	-0.25	0.108		172	-0.87 (-2.62, 0.88)	-0.18	0.329
Vortioxetine 20 mg		490	-1.49 (-2.61, -0.38)	-0.38	0.009		207	-1.80 (-2.78, -0.83)	-0.42	<0.001

```
-3.0  -2.0  -1.0  0.0  1.0  2.0              -3.0  -2.0  -1.0  0.0  1.0  2.0
      ← Better     Worse →                         ← Better     Worse →
      than placebo than placebo                    than placebo than placebo
```

Fig. 4. Difference from placebo in HAM-A subscale scores change from baseline at Week 6/8: (A) total MDD population and (B) baseline HAM-A ≥ 20 population (FAS, MMRM). The psychic anxiety subscale score is the sum of HAM-A items 1, 2, 3, 4, 5, and 6. The somatic anxiety subscale score is the sum of HAM-A Items 7, 8, 9, 10, 11, 12, 13, and 14. CI, confidence interval; SES, standardized effect size.
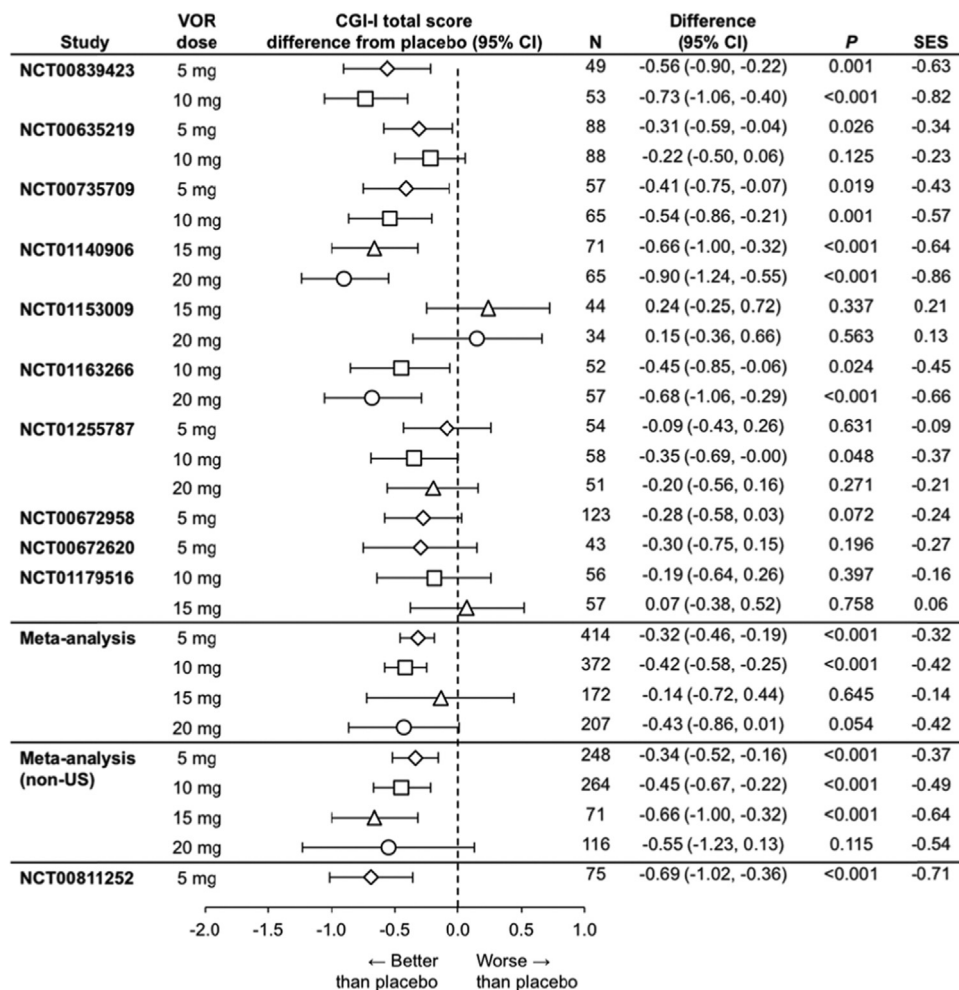
Study	VOR dose	CGI-I total score difference from placebo (95% CI)	N	Difference (95% CI)	P	SES
NCT00839423	5 mg		49	-0.56 (-0.90, -0.22)	0.001	-0.63
	10 mg		53	-0.73 (-1.06, -0.40)	<0.001	-0.82
NCT00635219	5 mg		88	-0.31 (-0.59, -0.04)	0.026	-0.34
	10 mg		88	-0.22 (-0.50, 0.06)	0.125	-0.23
NCT00735709	5 mg		57	-0.41 (-0.75, -0.07)	0.019	-0.43
	10 mg		65	-0.54 (-0.86, -0.21)	0.001	-0.57
NCT01140906	15 mg		71	-0.66 (-1.00, -0.32)	<0.001	-0.64
	20 mg		65	-0.90 (-1.24, -0.55)	<0.001	-0.86
NCT01153009	15 mg		44	0.24 (-0.25, 0.72)	0.337	0.21
	20 mg		34	0.15 (-0.36, 0.66)	0.563	0.13
NCT01163266	10 mg		52	-0.45 (-0.85, -0.06)	0.024	-0.45
	20 mg		57	-0.68 (-1.06, -0.29)	<0.001	-0.66
NCT01255787	5 mg		54	-0.09 (-0.43, 0.26)	0.631	-0.09
	10 mg		58	-0.35 (-0.69, -0.00)	0.048	-0.37
	20 mg		51	-0.20 (-0.56, 0.16)	0.271	-0.21
NCT00672958	5 mg		123	-0.28 (-0.58, 0.03)	0.072	-0.24
NCT00672620	5 mg		43	-0.30 (-0.75, 0.15)	0.196	-0.27
NCT01179516	10 mg		56	-0.19 (-0.64, 0.26)	0.397	-0.16
	15 mg		57	0.07 (-0.38, 0.52)	0.758	0.06
Meta-analysis	5 mg		414	-0.32 (-0.46, -0.19)	<0.001	-0.32
	10 mg		372	-0.42 (-0.58, -0.25)	<0.001	-0.42
	15 mg		172	-0.14 (-0.72, 0.44)	0.645	-0.14
	20 mg		207	-0.43 (-0.86, 0.01)	0.054	-0.42
Meta-analysis (non-US)	5 mg		248	-0.34 (-0.52, -0.16)	<0.001	-0.37
	10 mg		264	-0.45 (-0.67, -0.22)	<0.001	-0.49
	15 mg		71	-0.66 (-1.00, -0.32)	<0.001	-0.64
	20 mg		116	-0.55 (-1.23, 0.13)	0.115	-0.54
NCT00811252	5 mg		75	-0.69 (-1.02, -0.36)	<0.001	-0.71

```
-2.0  -1.5  -1.0  -0.5  0.0  0.5  1.0
          ← Better      Worse →
          than placebo  than placebo
```

Fig. 5. Difference from placebo in CGI-I total score change from baseline at Week 6/8: Baseline HAM-A ≥ 20 population (FAS, MMRM). Studies included in the non-US analysis: NCT00839423, NCT00635219, NCT00735709, NCT01140906, and NCT01255787. CI, confidence interval; SES, standardized effect size; VOR, vortioxetine.

from baseline in the population with baseline HAM-A total score ≥ 20 reached statistical significance for vortioxetine 5 mg/day ($P < 0.001$) and 10 mg/day ($P < 0.001$), with 20 mg/day almost reaching the 0.05 significance level ($P = 0.054$) (Fig. 5). These results also demonstrated the dose-dependent relationship of vortioxetine 5, 10, and 20 mg/day. The meta-analysis of non-US studies demonstrated a possible dose-response trend with vortioxetine 5 mg/day ($P < 0.001$), 10 mg/day ($P < 0.001$), and 15 mg/day ($P < 0.001$), but not for vortioxetine 20 mg/day ($P = 0.115$).

The CGI-S meta-analysis in patients with MDD and high levels of anxiety symptoms yielded very similar results in both the total subgroup and the non-US subgroup. In all patients with baseline HAM-A total score ≥ 20, the difference from placebo was statistically significant for vortioxetine 5 mg/day ($P = 0.003$), 10 mg/day ($P < 0.001$), and 20 mg/day ($P = 0.003$), but not for vortioxetine 15 mg/day ($P = 0.609$). In the non-US subgroup, a statistically significant difference from placebo in change from baseline on CGI-S score was achieved by all vortioxetine doses (5 mg/day, $P = 0.014$; 10 mg/day, $P < 0.001$; 15 mg/day, $P < 0.001$; 20 mg/day, $P = 0.013$) (Supplemental Fig. 2).

3.3. Safety and tolerability

The safety profile of vortioxetine 5–20 mg/day in patients with high levels of anxiety symptoms is shown in Table 2. Rates of the most frequently reported (≥ 5% in any treatment arm) TEAEs (i.e., nausea, headache, dizziness, dry mouth, diarrhea, nasopharyngitis, constipation, and vomiting) were similar to those observed in the overall MDD population, with no difference in the incidence or prevalence of TEAEs, including anxiogenic effects, observed in the first 2 weeks of treatment when compared to the overall safety results (Takeda Pharmaceuticals America Inc., 2016). Nausea was the only TEAE with an overall incidence that was ≥ 2 times higher in the vortioxetine treatment arms than in the placebo arm, which followed a dose-related trend. Discontinuations due to TEAEs were slightly more frequent with vortioxetine and showed a dose-dependent increase. Nausea accounted for the largest percentage of discontinuations due to TEAEs and showed a dose-related pattern; nausea resulted in the discontinuation of 0.3% of the placebo group and 1.5%, 1.6%, 2.4%, and 4.3% of the vortioxetine 5, 10, 15, and 20 mg/day groups, respectively. The rates of serious TEAEs and discontinuations due to serious TEAEs were similar to placebo in all vortioxetine treatment groups. The safety profile of vortioxetine 5–20 mg/day in patients with high levels of anxiety symptoms was similar to the overall MDD population (Takeda Pharmaceuticals America Inc., 2016).

Similar to the safety analysis of vortioxetine in patients with depressive disorders (Baldwin et al., 2016), there was no evidence to suggest that initiation of vortioxetine is associated with anxiogenic effects in this subgroup of MDD patients with high anxiety levels, as assessed by the emergence of anxiety-related adverse events (e.g., irritability, fatigue, jitteriness, malaise, restlessness, tension, anxiety, and insomnia) at any study visit during the duration of the clinical trials (data not shown).

4. Discussion

High levels of anxiety symptoms are seen in approximately half of all individuals with MDD (Kessler et al., 2015; Schuch et al., 2014). The need to identify more effective and better-tolerated therapies for this subgroup of patients is driven by evidence that they are less responsive to and less tolerant of antidepressant therapies than are individuals with non-anxious depression (Fava et al., 2008; Ionescu et al., 2014). Meta-analyses of data from 10 short-term, randomized, placebo-controlled vortioxetine clinical

Table 2

Summary of adverse events at the end of the study period for patients with baseline HAM-A total score ≥ 20 included in the safety meta-analysis of 11 short-term, placebo-controlled clinical studies of vortioxetine in patients with MDD (safety set).

	Placebo	Vortioxetine			
	(N=860)	5 mg (n=583)	10 mg (n=448)	15 mg (n=210)	20 mg (n=256)
Treatment-emergent adverse events (TEAEs), n (%)					
Any TEAE	547 (63.6)	394 (67.6)	295 (65.8)	158 (75.2)	182 (71.1)
TEAEs leading to discontinuation	38 (4.4)	29 (5.0)	31 (6.9)	13 (6.2)	22 (8.6)
Serious TEAEs	11 (1.3)	6 (1.0)	6 (1.3)	1 (0.5)	3 (1.2)
Serious TEAEs leading to discontinuation	4 (0.5)	4 (0.7)	5 (1.1)	0	1 (0.4)
TEAEs with incidence of ≥ 5% in any treatment arm, n (%)					
Nausea	81 (9.4)	131 (22.5)	118 (26.3)	65 (31.0)	72 (28.1)
Headache	137 (15.9)	85 (14.6)	69 (15.4)	35 (16.7)	32 (12.5)
Dizziness	53 (6.2)	36 (6.2)	28 (6.3)	16 (7.6)	25 (9.8)
Dry mouth	59 (6.9)	40 (6.9)	27 (6.0)	16 (7.6)	21 (8.2)
Diarrhea	46 (5.3)	31 (5.3)	30 (6.7)	24 (11.4)	12 (4.7)
Nasopharyngitis	37 (4.3)	26 (4.5)	21 (4.7)	9 (4.3)	14 (5.5)
Constipation	28 (3.3)	23 (3.9)	21 (4.7)	16 (7.6)	15 (5.9)
Vomiting	15 (1.7)	16 (2.7)	23 (5.1)	13 (6.2)	16 (6.3)
TEAEs leading to discontinuation ≥ 2 patients in any treatment arm, n (%)					
Nausea	3 (0.3)	9 (1.5)	7 (1.6)	5 (2.4)	11 (4.3)
Vomiting	3 (0.3)	0	4 (0.9)	2 (1.0)	0
Headache	2 (0.2)	1 (0.2)	1 (0.2)	2 (1.0)	2 (0.8)
Insomnia	1 (0.1)	3 (0.5)	1 (0.2)	1 (0.5)	0
Anxiety	3 (0.3)	1 (0.2)	1 (0.2)	2 (1.0)	0
Depression	5 (0.6)	1 (0.2)	3 (0.7)	0	0
Dizziness	2 (0.2)	1 (0.2)	2 (0.4)	1 (0.5)	0
Abdominal pain upper	3 (0.3)	0	1 (0.2)	1 (0.5)	1 (0.4)
Constipation	0	1 (0.2)	0	0	2 (0.8)
Irritability	2 (0.2)	0	1 (0.2)	0	1 (0.4)
Suicidal ideation	4 (0.5)	0	1 (0.2)	0	1 (0.4)
Suicide attempt	0	1 (0.2)	2 (0.4)	0	1 (0.4)
Agitation	2 (0.2)	1 (0.2)	0	0	0
Dyspepsia	2 (0.2)	0	0	0	0
Crying	2 (0.2)	0	0	0	0

N represents all randomized patients who took at least 1 dose of study drug.
Adverse events occurring on or after the first dose and within 30 days post dosing are included.
Studies included in the safety analysis: NCT00839423, NCT00635219, NCT00735709, NCT01140906, NCT01153009, NCT01163266, NCT01255787, NCT00672958, NCT00672620, NCT01179516, and NCT00811252 (elderly).

trials were conducted to determine whether vortioxetine may be a treatment option for depressed patients with high levels of anxiety. Vortioxetine (5–20 mg/day) demonstrated effective antidepressant activity in patients with MDD and high levels of anxiety symptoms at baseline (HAM-A total score ≥ 20). For vortioxetine 10 mg/day, the recommended starting dose, the LS mean difference from placebo in change from baseline in MADRS total score was −3.59 points (SES −0.40), which exceeds the "clinically meaningful" threshold of a two-point difference from placebo in change from baseline to study endpoint in MADRS total score (Montgomery and Moller, 2009). Among patients with more severe anxiety symptoms (baseline HAM-A total score ≥ 25) enrolled in these trials, patients receiving vortioxetine 10 mg/day had an LS mean difference from placebo in change from baseline in MADRS total score of −3.82, which translated to a standardized effect size of −0.40. However, in this subgroup, the standardized effect sizes were smaller in the 5-, 15-, and 20-mg/day dosing groups. This may be due to insufficient sample sizes, particularly in the vortioxetine 15 mg/day ($n = 70$) and 20 mg/day dose ($n = 85$)

groups. An exploratory analysis of patients with low levels of anxiety symptoms (baseline HAM-A total score < 20) identified a similar dose-dependent effect to that seen in the overall study population, as well as those patients with high anxiety symptoms at baseline (Takeda Pharmaceuticals America Inc., 2016). The standardized effect sizes for change from baseline in MADRS total scores to study end in the population of MDD patients with high-level anxiety symptoms were similar to those observed in the overall MDD population (Baldwin et al., 2014b; Thase et al., 2016), where standard effect sizes were vortioxetine 5 mg; −0.22; 10 mg, −0.32; 15 mg, −0.20; and 20 mg, −0.41. The number needed to treat scores were also similar in the population of patients with high baseline HAM-A scores to the overall MDD population, which were previously reported as vortioxetine 5 mg; 15; 10 mg, 16; 15 mg, 21; and 20 mg, 12. (Thase et al., 2016) Similar rates of response and remission were also identified. (Baldwin et al., 2014b; Thase et al., 2016).

The efficacy of vortioxetine in reducing anxiety symptoms in the overall MDD population and in the MDD subgroup with high levels of anxiety at baseline was investigated. Standardized effect sizes for vortioxetine 10 mg/day were −0.29 in the overall MDD population and −0.31 in the subgroup with high levels of anxiety, suggesting these groups experience similar anxiolytic efficacy. Consistent with studies of other therapies, the effects in the high anxiety subgroup took longer to separate from placebo (Altamura et al., 2004; Davidson et al., 2002; Fava et al., 2008). In the overall MDD group, the vortioxetine 10 and 20 mg/day doses separated from placebo at the first on-treatment study visit, whereas it took until the second on-treatment study visit to see a significant improvement in the patients with high levels of anxiety symptoms. When the effect of vortioxetine was assessed for anxious mood, the symptoms captured by the psychic anxiety subscale and the somatic anxiety subscale, the greatest improvement was observed in the psychic anxiety subscale in these short-term studies. There was improvement in the anxious mood subscale and, to a lesser degree, in the somatic anxiety subscale as well. This result is similar to that seen on MADRS Item 3 (inner tension), where there was a consistent, dose-related effect in favor of vortioxetine. This item refers to feelings of ill-defined discomfort, edginess, inner turmoil, or mental tension mounting to either panic, dread, or anguish (Montgomery and Asberg, 1979) and has been used in other studies of MDD to assess anxiolytic effects of antidepressant treatment (Bandelow et al., 2007; Gorman et al., 2002; Thase et al., 2014).

The CGI-I and CGI-S scores supported the findings that vortioxetine is efficacious in the often difficult-to-treat MDD population with high levels of anxiety symptoms.

With the exception of vortioxetine 15 mg/day, outcomes showed a dose-dependent trend. The inconsistencies in results for vortioxetine 15 mg/day may be attributed, at least in part, to having had the smallest sample size because the dose was only utilized in 3 clinical trials (2 of which were based in the US). As a result, this dose was associated with substantially wider confidence intervals compared with the other doses.

When meta-analyses were performed using data from the 5 non-US studies, efficacy outcomes were more robust and consistent across dosing groups. The reasons for this difference are not completely understood and are discussed elsewhere (Thase et al., 2016). Other studies have reported important differences between the US and other countries with regard to patient characteristics, diagnostic and clinical practices, and the conduct of clinical trials (Chang et al., 2008; Dunlop et al., 2012; Khin et al., 2011; Niklson and Reimitz, 2001; Vieta et al., 2011; Welten et al., 2015).

In the study that included patients aged ≥ 65 years exclusively, vortioxetine 5 mg/day was efficacious in treating late-life depression in both the overall population (Katona et al., 2012), as well as in the subgroup of individuals with high levels of anxiety symptoms at baseline.

Finally, comparison of TEAEs found that the safety profile of vortioxetine was similar in the subgroup of patients with MDD and high levels of anxiety symptoms and in the total population of patients with MDD. Initiation of vortioxetine had no apparent anxiogenic effects in MDD patients with a high level of anxiety symptoms.

5. Limitations

This study conducted meta-analyses of study-level data from 10 randomized, placebo-controlled trials at differing study centres, which are inherently heterogeneous. No direct conclusions can be drawn about the efficacy of vortioxetine in the group with baseline HAM-A total scores ≥ 20 relative to the group with baseline HAM-A total score < 20 or to the overall MDD population. Limited conclusions can also be made regarding the 15 mg/day dose, as only 3 of the 11 total studies included in this meta-analysis included this dose as an active treatment arm.

Characterization of "anxious depression" is confounded by the lack of a consistent definition across trials. Definitions range from MDD with comorbid anxiety disorders to MDD with one of several measures of anxiety symptoms. A commonly used threshold is the HAM-D anxiety/somatization subscale score ≥ 7 (Ionescu et al., 2014; Matza et al., 2010). This analysis used a HAM-A total score cutoff of 20 (as predefined in the individual study protocols) to stratify patients by baseline anxiety symptom severity (high levels versus low levels), which has been used in other studies of MDD (Bandelow et al., 2014; Boulenger et al., 2010; Seo et al., 2011; Seo et al., 2014; Thase et al., 2012). The HAM-A total score cutoff of 20 has also been used as an entry criterion for studies of patients with GAD (Baldwin et al., 2006; Gommoll et al., 2015; Rickels et al., 2005). This cutoff was predefined in the individual study protocols with the idea that using a scale designed to assess anxiety symptoms should be more sensitive than a subscore on a depression scale. This analysis did not relate findings based on HAM-A total score ≥ 20 to those using HAM-D anxiety/somatization score ≥ 7, which limits inferential comparison with other studies. Moreover, because individuals with any current psychiatric disorder other than MDD were excluded from the studies included here, the results of these meta-analyses cannot be generalized to patients with comorbid MDD and anxiety disorders. However, in the STAR*D population, patients with anxious depression (HAM-D anxiety/somatization score ≥ 7) met the criteria for anxiety disorders without having been diagnosed (Fava et al., 2008).

6. Conclusions

This meta-analysis of data from more than 2800 vortioxetine-treated patients in 10 randomized, placebo-controlled, short-term adult MDD studies indicates that in almost 1400 depressed patients with a high level of anxiety (HAM-A total score ≥ 20), vortioxetine (across daily doses of 5–20 mg) is an efficacious treatment choice for depressed patients with anxious symptoms, with increasing efficacy versus placebo with increasing dose. The broad clinical efficacy profile of vortioxetine was demonstrated on multiple analyses of the MADRS total score, HAM-A total score, CGI-I score, and CGI-S score, as well as on various individual item analyses. Vortioxetine was generally safe and well tolerated in patients with MDD and high levels of anxiety symptoms.

Conflict of Interest Statement

Contributors

All authors were involved in the development of the submitted manuscript, from first conception to agreement of the final version: all contributed to the methodology, analysis, and discussion of study strengths and limitations.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2016.07.015.

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