Journal of Psychiatric Research 64 (2015) 88–98

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Review

Vortioxetine, a multimodal antidepressant for generalized anxiety disorder: A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 19 November 2014
Received in revised form
18 February 2015
Accepted 20 February 2015

Keywords:
Vortioxetine
Meta-analysis
Efficacy
Safety
Tolerability
Generalized anxiety disorder

ABSTRACT

Vortioxetine has a beneficial pharmacological profile for reducing anxiety and depression. Recently, a number of randomized, double-blind, placebo-controlled clinical trials (RCTs) of vortioxetine have been conducted in patients with generalized anxiety disorder (GAD); however, the results from GAD RCTs are inconsistent. With an extensive search of databases and clinical trial registries, four published short-term RCTs were identified and included in the present meta-analysis. The mean change in total scores on the Hamilton Anxiety Rating Scale (HAMA) from baseline was the primary endpoint. The secondary endpoints included the response and remission rates, as defined by a ≥50% reduction in HAMA total scores and a ≤7 change in the HAMA total score at the end of treatment. In addition, the mean change in the HAMA total score from baseline in the subgroup with a HAMA total score ≥25 at baseline was included. Vortioxetine was significantly more effective than was placebo, with a standardized mean difference (SMD) of −0.118 (95% CIs, −0.203 to −0.033, P = 0.007). In particular, those with severe GAD (HAMA total score ≥25 at baseline) had a significantly greater benefit from vortioxetine than those without (SMD = −0.338, 95% CIs = −0.552 to −0.124, p = 0.002). The odds ratios (ORs) for vortioxetine for response and remission were 1.221 (95% CIs, 1.027 to 1.452, P = 0.024) and 1.052 (95% CIs, 0.853 to 1.296, P = 0.637), respectively. Discontinuation due to adverse events (AEs) (OR = 1.560, 1.006 to 2.419, p = 0.047) was marginally higher in vortioxetine than placebo treatment, whereas discontinuation due to any reason (OR = 0.971, 0.794 to 1.187, p = 0.771) and inefficacy (OR = 0.687, 0.380 to 1.243, p = 0.215) were not significantly different among treatment groups. Although our results suggest that vortioxetine may have a potential as an another treatment option for GAD (especially for severe GAD), they should be interpreted and translated into clinical practice with caution, as the meta-analysis was based on a limited number of RCTs.

1. Introduction

Generalized anxiety disorder (GAD) is a common psychiatric illness resulting in deteriorating effects on the patient's functional capacity. In fact, GAD patients may have greater impairment in psychosocial functioning than those with major medical illnesses, including type II diabetes, hypertension, recent myocardial infarction, and congestive heart failure (Weisberg et al., 2010). The impairment in patients with GAD is also comparable to that of major depressive disorder (MDD) (Wittchen et al., 2000). GAD has extensive comorbidity with other psychiatric disorders such as MDD, bipolar disorder, and substance disorders as well (Alegria et al., 2010; Kessler et al., 2012). Furthermore, it may increase the odds of suicidal ideation and attempt two-fold; the unadjusted odds ratio ranged from 3 to 8 in National Comorbidity Survey Replication (NCS-R) and National Epidemiologic Survey on Alcohol

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http://dx.doi.org/10.1016/j.jpsychires.2015.02.017
0022-3956/

and Related Conditions (NESARC) samples (Thibodeau et al., 2013). Somatic anxiety symptoms, including restlessness, irritability, muscle tension, sleep disturbances, and fatigue, are commonly found in patients with GAD. In addition, impaired cognitive functions are problematic in these patients (i.e., difficult concentration and decrease of attention). GAD patients commonly present constant worry that the patient or a relative will shortly become ill or have an accident. Indeed, GAD is one of the most common psychiatric conditions leading to a visit to primary care practitioners and GAD patients have a tendency to seek more help from health professionals. Given the aforementioned findings, proper and effective treatment of GAD is indispensable (Combs and Markman, 2014).

According to the recent treatment guidelines (NIHCE, 2004, Baldwin et al., 2014; Bandelow et al., 2012; Katzman et al., 2014), the first-line pharmacotherapy for GAD includes selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), although there is also good evidence for the efficacy of pregabalin and quetiapine. Buspirone, benzodiazepine, and hydroxyzine may also be useful treatment options (Baldwin et al., 2011). Despite numerous pharmacological agents, response rates to initial treatment with an SSRI or SNRI are still inadequate in the treatment of GAD. According to the results from randomized placebo-controlled trials (RCTs), the difference in the response rate measured by global measures (i.e., Clinical Global Impression [CGI] scale) between antidepressants and placebo ranged from 15 to 20% (Baldwin, 2011). In addition, a substantial portion of GAD patients may suffer adverse events (AEs), relapse or recurrence, a discontinuation of symptoms and functional impairments (Baldwin and Nutt, 2012, Baldwin, 2011). However, the targets of approved psychotropics for treating GAD are mainly antidepressants that are based on neurotransmitter reuptake inhibition, which is partly attributable to the current limited efficacy of pharmacological treatment in the treatment of GAD (Massart et al., 2012). Therefore, there is a considerable unmet need to develop different pharmacological agents with novel mechanisms of action leading to enhanced effectiveness and greater acceptability when compared with existing agents (Baldwin and Nutt, 2012).

Vortioxetine is a multimodal antidepressant approved for the treatment of major depressive disorder (MDD) with proven efficacy and safety in September 2013 by the US FDA. It exerts reuptake inhibition on the serotonin transporter, increasing the level of 5-HT in the neuronal synapse as well as selectively binding to a variety of other serotonin receptors. It selectively binds to and acts as an antagonist of 5-HT3, 5-HT1D, and 5-HT7 receptors; as a partial agonist to 5-HT1B receptors; and as an agonist of 5-HT1A receptors (Bang-Andersen et al., 2011; Dubovsky, 2014; Guilloux et al., 2013; Stenkrona et al., 2013). The net effects of this pharmacological profile may include the modulation of 5-HT, noradrenaline, dopamine, acetylcholine and histamine in crucial brain regions such as nucleus accumbens, dorsal raphe nucleus, ventral hippocampus and medial prefrontal cortex; such effects could be of either the action or the mechanism, but not both (Sanchez et al., 2015).

Currently, 12 RCTs have been available for the treatment of MDD as published or unpublished (Pae et al., in press). The antianxiety effect of vortioxetine has been consistently observed in subgroup analysis in such MDD trials. For instance, the improvement of anxiety symptoms measured by changes in the Hamilton Rating Scale for Anxiety (HAMA) total score (Hamilton, 1959) was significantly different from baseline in the total score from week 2 or week 3 onward compared to placebo treatment (magnitude of difference from placebo: −3.3 with vortioxetine 5 mg, −3.0 with vortioxetine 10 mg, and −2.9 with venlafaxine) in the first MDD RCT (Alvarez et al., 2012). Such a trend toward a favorable efficacy of vortioxetine in the reduction of anxiety was also replicated in subsequent MDD RCTs (Baldwin et al., 2012a; Boulenger et al., 2014; Katona et al., 2012). In this regard, a number of RCTs of GAD have been recently conducted; however, the efficacy of vortioxetine has been inconsistent across the studies.

Systematic reviews and meta-analyses, especially of newly marketed drugs, are important, as they can overcome the limitations of small sample sizes, increase the generalizability of results by including many trials conducted in various populations, increase the statistical power for group comparisons, investigate potential publication biases, and quantify and analyze inconsistencies in results across clinical studies (Cohn and Becker, 2003; Finckh and Tramer, 2008; Han et al., 2014). Therefore, the present work performed a systematic review and meta-analysis of short-term and long-term RCTs of vortioxetine in patients with GAD to summarize currently available RCTs.

2. Methods

2.1. Data search

PubMed, EMBASE, PsycINFO, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, Cochrane Central Register of Controlled Trials Cochrane Library, and ClinicalTrials.gov (www.clinicaltrials.gov) were searched as of 01 August 2014. The search term was “vortioxetine (Lu AA21004).” A final re-search for studies was conducted in the same search engines on 30 October 2014. Reference lists from identified articles and reviews were also used to find additional studies. Abstracts identified by the literature search were independently evaluated by two authors (S.M.W. and C.U.P.); potentially eligible papers were then re-evaluated by two other authors (C.H. and S.J.L.) to determine whether they clearly met the selection criteria. If a disagreement occurred, the article in question was discussed, and a consensus was reached by the second set of review authors.

2.2. Inclusion criteria for the meta-analysis

All RCTs investigating the efficacy and safety of vortioxetine for GAD were the primary inclusion criteria. Patients needed to meet the criteria for GAD used in the individual trials. RCTs' recruitment of patients for the evaluation of other outcomes were considered when they met the aforementioned criteria for GAD and included data for outcomes of GAD. Studies were excluded if the main outcome was the prevention of relapse or if treatment outcomes based on rating scales of GAD were not available. There were no requirements or restrictions regarding the severity of GAD, gender, age, minimum number of subjects, study location, or treatment basis (i.e., inpatient or outpatient). No restrictions regarding the pharmaceutical form or dose regimen (fixed or flexible) were given.

2.3. Data extraction

Data on the characteristics of the subjects, treatment details, study procedures, efficacy measures, dropout rates, and adverse events (AEs) were collected; these included data on, for example, age, gender, severity/treatment outcomes of depression (based on primary and secondary endpoints), type of comparator (active reference drug or placebo), dose, study location, and type of treatment base.

Outcome data related to the characteristics of the individual trial and the reported results were extracted for each trial. For example, the mean changes or reported numbers for the primary and secondary endpoints were extracted from the individual study when appropriate. In addition, the quality of the RCT was also assessed as recommended by the Cochrane Review. Data extraction was

initially performed by C.U.P. and then reassessed independently by C.H.

2.3.1. Efficacy measures

The primary efficacy measure was the mean change from baseline in total scores on the HAMA, as defined by the individual study. The secondary efficacy measures were the response and remission rates, as defined by a ≥50% reduction from baseline in HAMA total scores and a score of ≤7 in the HAMA total scores at the end of treatment, respectively, as indicated by the individual study. Additional analysis included the mean change from baseline in total scores on the HAMA in accordance with HAMA cut-off point at baseline (≥25) to see whether there would be differential efficacy of vortioxetine in severe anxiety.

2.3.2. Safety and tolerability measures

Data on the number of dropouts (for any reason), lack of efficacy, and incidence of adverse events (AEs) were included in the analysis. The meta-analysis also included the relationship of vortioxetine with specific AEs such as nausea, headache, dizziness, and dry mouth, which most commonly occurred across the studies.

2.4. Data synthesis and statistical analysis

In terms of continuous measures, data on the mean change from baseline to the end of treatment, the standard deviation or standard error, and the number of patients were extracted for the primary and secondary efficacy measures. In terms of binary measures, data on the number of patients treated, the number of patients rated as having responded and remitted, and the number of patients leaving the study early were collected for the secondary efficacy measures and safety/tolerability evaluation, respectively.

The effect sizes (ESs) for continuous data related to the primary and secondary efficacy measures used in each study are presented as the standardized mean difference (SMD) using the method developed by Hedges (Hedges g) with 95% confidence intervals (95% CIs). Cohen's classification can be used to evaluate the magnitude of the overall ES, where a SMD of 0.2 is a small ES, a SMD of 0.5 is a medium ES, and a SMD greater than 0.8 is a large ES. The SMD was calculated using the following equation: ([endpoint mean efficacy score]-[baseline efficacy score]/pooled standard deviation (SD) of each treatment group). Odds ratios (ORs) were used to assess binary outcomes such as response and remission rates, including dropout rates.

Separate analyses were performed for each comparison of placebo and vortioxetine. The full analysis set (FAS) was composed of all randomized subjects who received at least one dose of study medication and had at least one valid post-baseline value for the primary efficacy assessment in each study. FAS with a last-observation-carried-forward (LOCF) analysis was used to evaluate efficacy. In cases of missing data, the author of each study was contacted to acquire additional data. The safety set included all randomized subjects who received at least one dose of study medication.

Fixed-effects or random-effects models were applied to the analyses of primary and secondary measures when appropriate. When the I^2 index reflected significant heterogeneity between the study results ($I^2 > 50\%$ and $P < 0.05$), a random-effects model was used to evaluate the primary and secondary endpoints following the hypothesis of heterogeneous study populations. The random-effects model grants more balance than does the fixed-effects model because it allows for sampling variability with and between studies, and smaller studies are weighted more, whereas larger studies are weighted less. In general, a random-effects model is used to combine subgroups and yield an overall effect. All data extracted from the individual studies included in the present meta-analysis were entered into the Comprehensive Meta-analysis version 2.0 software for the final analysis (CMA v2; Englewood, NJ, USA).

2.5. Heterogeneity analysis, sensitivity analysis, and meta-regression

Heterogeneity between studies was assessed using the I^2 statistic. This measure evaluates how much of the variance between studies can be attributed to the actual differences between the studies rather than to chance. A magnitude of considerable heterogeneity is usually $I^2 = 75–100\%$. The heterogeneity threshold was defined as 50% or more in I^2 value and a $P < 0.05$. Sensitivity analyses were conducted to test the robustness of the impact of a single study on the overall results. A meta-regression was also performed to assess the influence of the following moderators on the overall estimate: study location (US only vs. outside the US) and the doses of vortioxetine under investigation; these were included as independent parameters influencing the primary and secondary endpoints.

2.6. Risk of bias

Two authors (C.U.P. and C. H.) independently assessed the risk of bias in individual studies, and any disagreement was resolved by consensus. According to recommendations from the Cochrane Review, the risk of bias associated with sequence generation, allocation concealment, the blinding of participants and investigators, the blinding of outcome assessments, incomplete outcome data, selective outcome reporting, and other sources was evaluated using specific and detailed criteria.

2.7. Publication bias

Visual inspection of funnel plots and the Egger test were used to evaluate publication bias. These methods were adopted because Egger's linear regression method quantifies the bias captured by a funnel plot using the actual values and precision of the ESs, whereas Begg and Mazumdar's test uses ranks.

3. Results

3.1. Description of studies included in the meta-analysis

Of the 359 records identified by the search of the databases, 292 were excluded, as they were irrelevant to our meta-analysis. The remaining 67 studies were retrieved for more detailed evaluation as seen in Fig. 1.

Four short-term RCTs (Bidzan et al., 2012; Mahableshwarkar et al., 2014a, 2014b; Rothschild et al., 2012) met the inclusion criteria, and one long-term trial was a relapse prevention study (Baldwin et al., 2012b). Of the 38 records obtained from ClinicalTrials.gov, all five trials were duplicates of those identified by the aforementioned search (Fig. 1). The long-term study (Baldwin, 2012b) was aimed to evaluate the efficacy of vortioxetine in the prevention of relapse in patients with GAD for 24–56 weeks who had previously responded to an initial 20-week treatment with vortioxetine; the study was separately discussed in a later section. Therefore, four short-term RCTs were finally included in the meta-analysis.

The main characteristics of these four short-term studies are presented in Tables 1 and 2. Studies were multi-centered and internationally conducted throughout the world; three RCTs were conducted in the US exclusively, and one was conducted outside the

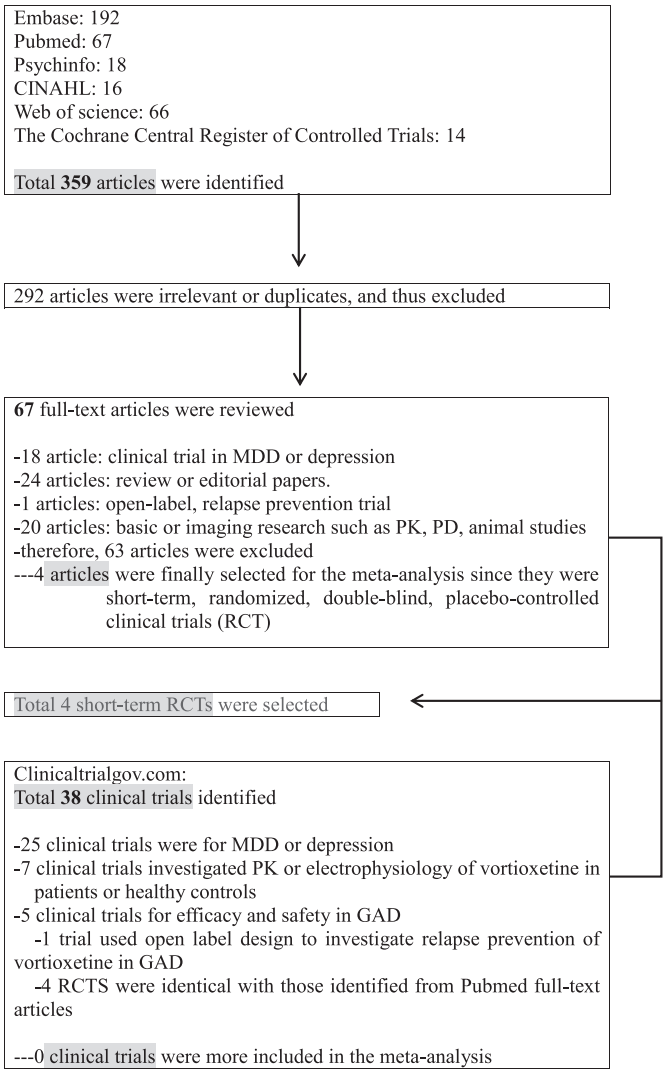

Fig. 1. Schematic presentation of studies selected in the present meta-analysis: RCT, randomized, double-blind, placebo-controlled clinical trial; PD, pharmacodynamics; PK, pharmacokinetic; MDD, major depressive disorder; GAD, generalized anxiety disorder.

US (Table 1). Each study included ≥150 subjects per treatment arm, the entry score of HAMA was ≥20, and the length of follow-up was eight weeks. All subjects were diagnosed with a primary diagnosis of GAD according to Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) criteria. Subjects had an inadequate response to previous treatment with an adequate dose of SSRIs or SNRIs for the current GAD episode. Subjects were excluded if they were comorbid with other psychiatric conditions and/or clinically serious medical conditions.

Among 1831 subjects in the included studies, 1068 patients with GAD were on vortioxetine, 609 were on placebo, and 154 were on active reference drug (duloxetine 60 mg/d). The duloxetine treatment arm was not included in the present meta-analysis. The doses of vortioxetine were 2.5, 5, and 10 mg/d. Of these four RCTs, only one study (Mahableshwarkar, 2014a) included an active control for assay sensitivity (duloxetine 60 mg/d) as well as a placebo arm. The other three RCTs compared vortioxetine with a placebo (Bidzan, 2012; Mahableshwarkar, 2014b; Rothschild, 2012). Two RCTs included different doses of vortioxetine (2.5–10 mg/d) in the treatment arm (Mahableshwarkar, 2014a, 2014b), whereas the other two studies included one fixed dose of vortioxetine (5 mg/d) in the treatment arm (Bidzan, 2012; Rothschild, 2012). All studies included a preponderance of female subjects, with proportions ranging from 61.6% to 72.4%. All subjects included in each treatment arm were considered to carry at least moderate anxiety at baseline on average, presenting mean HAMA total scores ranging from 24.4 to 26.8. All studies were financially supported by the manufacturer. Regarding the primary endpoint analysis, only one study showed a robust efficacy of vortioxetine for treating GAD (Bidzan, 2012), whereas the other three RCTs (Mahableshwarkar, 2014a, 2014b; Rothschild, 2012) failed to separate it from placebo treatment. Such trend was also observed in the analyses of response and remission rates. The additional endpoints included in the four RCTs were various outcomes such as Hospital Anxiety and Depression (HAD), Clinical Global Impression-Improvement of Illness (CGI-I), and Sheehan Disability Scale (SDS). The study by Bidzan et al. (Bidzan, 2012) has shown a superiority of vortioxetine over placebo in all such additional efficacy endpoints, and the others (Mahableshwarkar, 2014a, 2014b; Rothschild, 2012) completely failed to separate it from placebo. Across all of the studies, the most frequently reported AEs were nausea, headache, dizziness, and dry mouth. The early withdrawal rates due to AEs were higher in the vortioxetine group (2–7.1%) than in the placebo group (1.9–4%) across all of the studies; they had an increasing tendency in higher doses versus lower doses of vortioxetine. The early withdrawal rates due to inefficacy were higher in the placebo group (2–4.6%) than in the vortioxetine group (0.6–3.3%).

3.2. Risk of bias

Fig. 2 compares the individual risks of bias of individual studies (See Supplementary Fig. 1 for the overall risk of bias of the studies included). The risk of bias was considered low or unclear in all studies based on evaluations of all domains, and no study scored as presenting a high risk of bias in all domains. Overall, all included studies were of good quality with regard to methodology.

3.3. Efficacy

3.3.1. Primary endpoint

3.3.1.1. Overall efficacy. The result of the meta-analysis regarding the primary endpoint is presented as a forest plot (Fig. 3). The SMD (−0.118) was significantly different between vortioxetine and placebo treatments, favoring vortioxetine over placebo (95% CIs, −0.203 to −0.033, P = 0.007).

3.3.1.2. Sensitivity analysis, heterogeneity, and publication bias. The heterogeneity among studies was not significant according to the SMD (I^2 = 48.451%, P = 0.071). However, a sensitivity analysis by Bidzan et al. strongly affected the primary endpoint result; when excluding Bidzan et al.'s study, there was no statistically significant difference between vortioxetine and placebo (SMD = −0.065, p = 0.166). The Egger test showed no significant difference (P = 0.268), indicating no publication bias.

3.3.1.3. Meta-regression. The study location significantly influenced the primary endpoint result (Z = −3.048, P = 0.0023), favoring outside the US over the US only. When we performed a subanalysis of the studies conducted only in the US, there was no significant difference in the primary endpoint between vortioxetine and placebo treatment (SMD = −0.065, 95% CIs, −0.157 to 0.027, P = 0.166). However, there was no moderating effect of vortioxetine doses on the primary endpoint (Z = 0.434, p = 0.664). The subanalysis by doses across the studies also confirmed the meta-regression result on the SMD (2.5 mg SMD = −0.128, P = 0.352; 5 mg SMD = −0.136, P = 0.223; 10 mg SMD = −0.085, P = 0.534),

Table 1
Summary of currently available short-term randomized, double-blind, placebo-controlled clinical trials of vortioxetine for the treatment of patients with generalized anxiety disorder.[a]

Study	Drugs (mg/d)	N[b]	Mean age years (SD)	Sex (F, n, %)	Duration (weeks)	Baseline HAMA mean (SD)	Entry score[c]	Mean change of HAMA[d]	Baseline CGI-S score	Response (%)[e]	Remission (%)[f]	Study location
Bizdan et al., 2012	PBO	150	45.3 (13.5)	93 (61.6%)	8	26.8 ± 4.0	≥20	10.49 ± 0.7	4.49 ± 0.05	39.9	17.6	Europe/Africa
(NCT00744627)	VTX5	150	45.0 (14.1)	103 (68.7%		26.3 ± 3.9		14.30 ± 0.7	4.49 ± 0.05	61.7	30.2	
Rothchild et al., 2012	PBO	151	41.4 (12.81)	97 (63.8%)	8	24.6 ± 3.6	≥20	13.16 ± 0.66	4.36 ± 0.04	50	22.2	US
(NCT00734071)	VTX5	148	41.0 (14.05)	103 (67.8%)		24.7 ± 3.8		12.57 ± 0.65	4.37 ± 0.04	53.1	25.5	
Mahableshwarkar	PBO	153	39.5 (13.5)	105 (68.6%)	8	25.2 ± 3.9	≥20	9.87 ± 0.58	4.4 ± 0.54	41.9	21.6	US
et al., 2014a	VTX2.5	151	40.8 (13.8)	103 (67.8)		25.0 ± 3.6		10.75 ± 0.60	4.3 ± 0.49	46.5	21.5	
(NCT00731120)	VTX10	152	43.3 (15.0)	96 (63.2)		24.5 ± 3.7		10.68 ± 0.58	4.3 ± 0.47	41.8	19.2	
Mahableshwarkar	PBO	155	36.8 (12.12)	102 (65%)	8	24.4 ± 3.73	≥20	11.27 ± 0.60	4.33 ± 0.04	42.2	22.1	US
et al., 2014b	VTX2.5	156	39.2 (11.90)	109 (69/9%)		25.3 ± 4.25		12.23 ± 0.60	4.40 ± 0.04	44.8	20.1	
(NCT00730691)	VTX5	155	37.7 (11.96)	100 (64.1%)		25.0 ± 3.57		11.57 ± 0.61	4.38 ± 0.04	42.6	19.6	
	VTX10	156	39.8 (12.33)	105 (67.3%)		25.3 ± 3.96		11.66 ± 0.61	4.39 ± 0.04	44.8	20.1	
	DLX60	154	39.5 (12.28)	113 (72.4%)		25.0 ± 3.94		13.87 ± 0.64	4.36 ± 0.04	51.0	28.2	

DLX, Duloxetine; HAMA, Hamilton anxiety rating scale; LOCF, Last observation carried forward; MMRM, Mixed effect model repeat measurement; PBO, Placebo; VTX, Vortioxetine.
[a] Based on randomized set or all-patients-treated set.
[b] Number treated.
[c] By HAMA total score.
[d] Primary end-point measure.
[e] Response defined as 50% reduction in HAMA total score at the endpoint (LOCF).
[f] Remission defined as HAMA ≤7 at the endpoint (LOCF).

Table 2
Safety and tolerability of 4 RCTs of vortioxetine for the treatment of patients with generalized anxiety disorder.

Study	Drugs (mg/d)	N[a]	AE > 5% subjects (%)	Other AE subjects (%)	Total dropout rates	Drop-out due to lack of efficacy	Drop-out due to AE
Rothchild et al., 2012 (NCT00734071)	PBO	151	93 (61.6%)	65 (43%)	38 (25%)	3 (2%)	4 (2.6%)
	VTX5	148	103 (73.6%)	89 (60%)	27 (18%)	1 (0.7%)	3 (2%)
Bizdan et al., 2012 (NCT00744627)	PBO	150	55 (36.7%)	36 (24%)	25 (16.6%)	7 (4.6%)	6 (4%)
	VTX5	150	74 (49.3%)	48 (32%)	22 (14.7%)	3 (2%)	9 (6%)
Mahableshwarkar et al., 2014a	PBO	153	102 (66.7%)	70 (45.8%)	42 (27.4%)	4 (2.6%)	7 (4.6%)
(NCT00731120)	VTX2.5	151	94 (62.3%)	72 (50%)	43 (28.2%)	5 (3.3%)	6 (3.9%)
	VTX10	152	105 (69.1%)	83 (54.6)	36 (23.7%)	4 (2.6%)	8 (5.3%)
Mahableshwarkar et al., 2014b	PBO	155	107 (69%)	85 (55%)	36 (23%)	4 (2.5%)	4 (2.5%)
(NCT00730691)	VTX2.5	156	122 (78.2%)	100 (64%)	36 (23%)	4 (2.6%)	8 (5.2%)
	VTX5	155	119 (76.8%)	104 (67%)	39 (25.1%)	2 (1.3%)	11 (7.1%)
	VTX10	156	123 (78.8%)	111 (71%)	45 (28.8%)	1 (0.6%)	11 (7.1%)
	DLX60	154	126 (81.8%)	116 (75%)	50 (32.5%)	1 (0.6%)	23 (15%)

AE: Adverse events.
[a] Number treated.

indicating no differential efficacy by vortioxetine doses between vortioxetine and placebo treatment.

3.3.2. Secondary endpoint

3.3.2.1. Overall efficacy. The ORs for vortioxetine for response and remission were 1.221 (95% CIs, 1.027 to 1.452, P = 0.024) and 1.052 (95% CIs, 0.853 to 1.296, P = 0.637), respectively (Figs. 4 and 5).

3.3.2.2. Sensitivity analysis, heterogeneity, and publication bias. Heterogeneity was not found in the secondary endpoint analysis for response (I^2 = 41.355%, P = 0.115) and remission (I^2 = 19.119%, P = 0.284) rates. However, sensitivity analysis indicated that Bidzan et al.'s study strongly affected the response rate, but it did not affect the remission rate; when excluding Bidzan et al.'s study, it was no longer significantly different in terms of response (OR = 1.093, 95% Cis, 1.027 to 1.452, P = 0.350) between vortioxetine and placebo. The Egger test showed no significant differences for response and

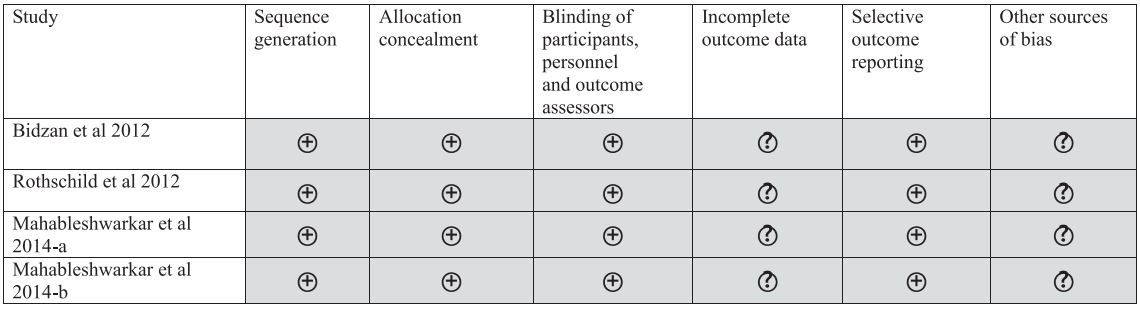

Fig. 2. Risk of bias in individual studies included in the meta-analysis.

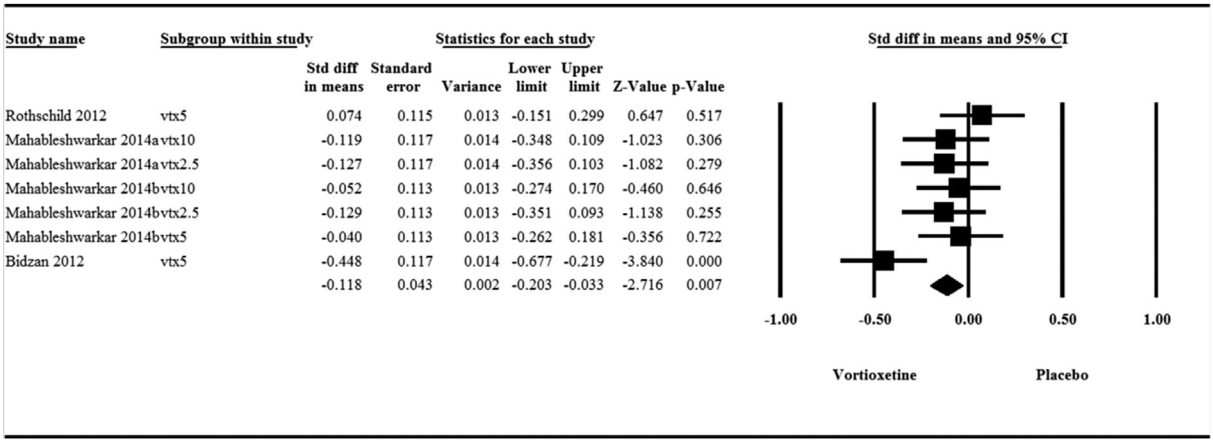

Fig. 3. Meta-analysis of the mean changes of the Hamilton Anxiety Rating Scale total score from baseline between vortioxetine and placebo treatment groups. Abbreviations: std diff, standardized mean difference; 95% CI, 95% confidence interval; vtx, vortioxetine. The numbers coming after vtx represent dosages (mg/day) in individual study.

remission rates (P = 0.249 and P = 0.414, respectively), indicating no publication bias.

3.3.2.3. Meta-regression. In terms of the Ors for the response (Z = 3.125, P = 0.002) and remission (Z = 2.539, P = 0.011) rates, we found a significant moderator effect of study location favoring outside the US over only the US. When we performed a sub-analysis of the studies conducted only in the US, the OR for response (OR = 1.093, 95% Cis, 0.907 to 1.318, P = 0.350) and remission (OR = 0.941, 95% Cis, 0.751 to 1.179, P = 0.596) rates were not significantly different between vortioxetine and placebo treatments. However, there was no moderating effect of vortioxetine doses on the response (Z = −0.674, P = 0.500) and remission (Z = −0.576, P = 0.565) rates. The sub-analysis by doses across the studies also confirmed the meta-regression results on the response (2.5 mg, OR = 1.158, P = 0.539; 5 mg OR = 1.405, P = 0.081; 10 mg OR = 1.053, P = 0.829) and remission (2.5 mg, OR = 0.940, P = 0.777; 5 mg OR = 1.275, P = 0.173; 10 mg OR = 0.875, P = 0.547) rates, indicating no differential efficacy by vortioxetine doses between vortioxetine and placebo.

3.3.3. Additional efficacy analysis by severity of anxiety (≥25 in baseline HAMA total score)

Vortioxetine was significantly more effective in the treatment of more severe anxiety than the placebo, with an SMD of −0.338 (95% Cis, −0.552 to −0.124, P = 0.002) (Fig. 6). The sensitivity analysis showed stability of the overall SMD (ranges of SMDs = −0.392 through −0.243, ranges of 95% Cis, −0.614 through −0.072); indeed, such significant results were retained even if we excluded Bidzan et al.'s study (SMD = −0.243, P = 0.000). The heterogeneity among studies was significant (I^2 = 66.111%, P = 0.007). The Egger test showed no significant difference, indicating no publication bias (P = 0.707). The doses of vortioxetine had a significant moderating effect (Z = −3.284, P = 0.001), and there was no moderating effect of study location (P = 0.678). The sub-analysis by doses also confirmed the meta-regression results on the SMD (2.5 mg, SMD = −0.283, P = 0.232; 5 mg SMD = −0.428, P = 0.027; 10 mg SMD = −0.257, P = 0.283).

3.4. Safety and tolerability

The incidence of treatment emergent (TE) AEs (OR = 1.392, 95% CIs, 1.157 to 1.675, P = 0.000) were significantly higher in vortioxetine group than in placebo group; however, there was no moderating effect of vortioxetine dose in occurrence of TEAE (Z = 0.408, P = 0.683). The incidences of nausea (OR = 2.311, 95% CIs, 1.522 to 3.509, P = 0.000) and dizziness (OR = 1.989, 95% CIs, 1.310 to 3.019, P = 0.001) were significantly higher in the vortioxetine group than in the placebo group; however, the moderating

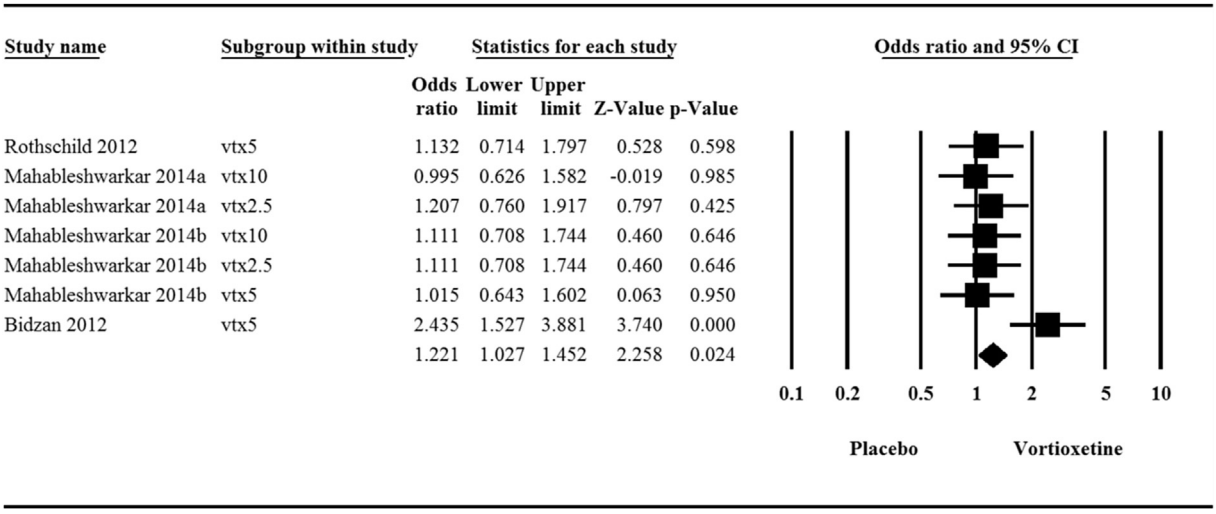

Fig. 4. Meta-analysis of the responder rates between vortioxetine and placebo treatment groups. Abbreviations: 95% CI, 95% confidence interval; vtx, vortioxetine. The numbers coming after vtx represent dosages (mg/day) in individual study.

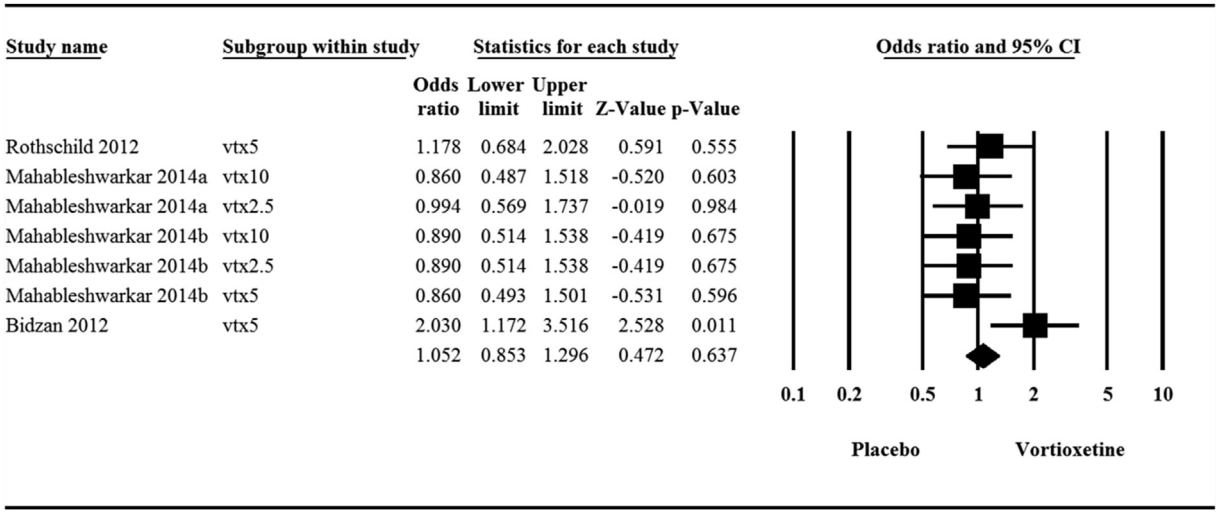

Fig. 5. Meta-analysis of the remission rates between vortioxetine and placebo treatment groups. Abbreviations: 95% CI, 95% confidence interval; vtx, vortioxetine. The numbers coming after vtx represent dosages (mg/day) in individual study.

effect of the vortioxetine dose was only significant in the occurrence of nausea (Z = 2.075, P = 0.038), and it was not in occurrence of dizziness (Z = −0.116, P = 0.908). The incidences of headache (OR = 1.079, 95% CIs, 0.828 to 1.408, P = 0.573) and dry mouth (OR = 1.325, 95% CIs, 0.957 to 1.836, P = 0.09) were not significantly different between the vortioxetine group and placebo group.

No significant difference was observed between the vortioxetine and placebo groups regarding the likelihood of discontinuation for any reason (OR = 0.971, 95% CIs, 0.794 to 1.187, P = 0.771), whereas the discontinuation rate due to AEs was significantly higher in the vortioxetine group than in the placebo group (OR = 1.560, 95% CIs, 1.006 to 2.419, P = 0.047, Supplementary Figs. 2 and 3). The discontinuation rate due to lack of efficacy was not significantly different between the vortioxetine and placebo groups (OR = 0.687, 95% CIs, 0.380 to 1.243, P = 0.215, Supplementary Fig. 4).

3.5. Relapse prevention study

Baldwin et al. investigated the long-term efficacy of vortioxetine in a 24–56-week relapse prevention study (Baldwin, 2012b). Six hundred and eighty-seven (687) patients entered the open-label period. The patients included in the study had moderate to severe anxiety symptoms (HAMA total score = 28.4) along with lower depressive symptoms as measured by the Montgomery–Asberg Depression Rating Scale (MADRS total score = 11.7). Four hundred and fifty-nine (459) patients (66.8%) were randomized to double-blind treatment, where 229 and 230 patients were assigned to either vortioxetine or placebo, respectively. The FAS data comprised 224 and 227 patients in the vortioxetine and placebo groups, respectively.

When entering the double-blind phase (week 20), 79.9% (n = 546) of patients responded based on the HAMA total score (≥50% decrease from baseline) and 60.5% (n = 413) had reached remission (HAM-A total score ≤ 7). The primary endpoint was the time to relapse of GAD using the Cox model in the double-blind period; withdrawals due to reasons other than lack of efficacy (relapse) were considered to be non-relapsed. According to the results, the significant effect of vortioxetine relative to the placebo on the time to relapse of GAD was observed, with a hazard ratio of 2.71 (P < 0.0001), indicating that the risk of relapse for the patients with placebo was almost three times that of patients with vortioxetine. The proportion of patients who relapsed was significantly lower in the vortioxetine group (15%, n = 33) than that in the placebo group (34%, n = 78) (P < 0.0001). The mean change on the

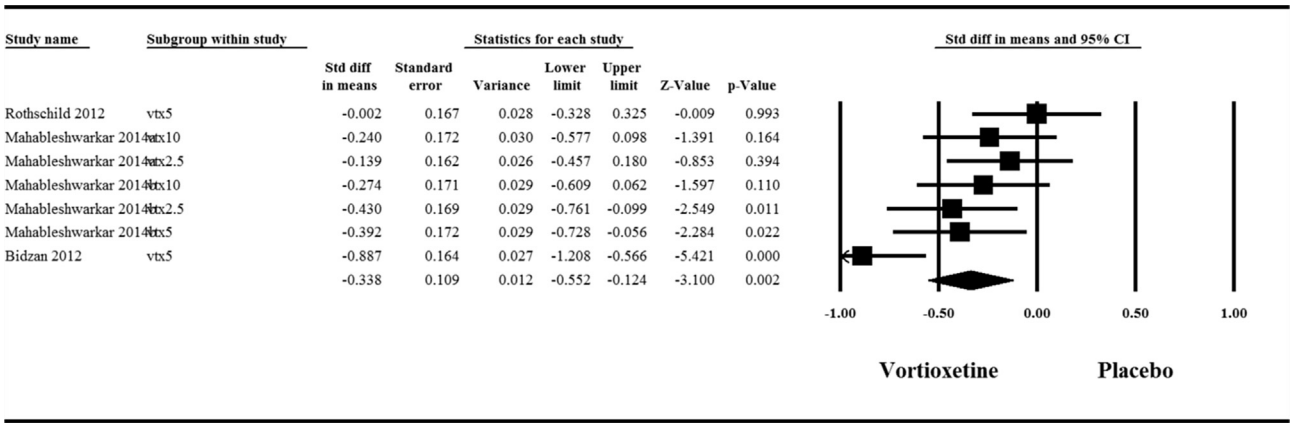

Fig. 6. Meta-analysis of the mean changes of the Hamilton Anxiety Rating Scale (HAMA) total score from baseline between vortioxetine and placebo treatment groups (subgroup analysis of those with ≥25 on the HAMA total score at baseline). Abbreviations: std diff, standardized mean difference; 95% CI, 95% confidence interval; vtx, vortioxetine. The numbers coming after vtx represent dosages (mg/day) in individual study.

HAMA total score after 24 weeks of double-blind phase was significantly higher in placebo treatment (1.2) than in vortioxetine treatment (0.3), with a magnitude of difference (MD) −0.9 (95% CIs, −1.7 to −0.1, P < 0.05); such trends toward significantly favorable efficacy of vortioxetine relative to placebo were consistently observed on the most secondary endpoints such as Clinical Global Impression-Severity (CGI-s, MD = −0.3), Hospital Anxiety and Depression Scale-Anxiety Subscale (HADA, MD = −0.5), MADRS (MD = −1.1), and Sheehan Disability Scale (SDS, MD = −0.4).

Of the 228 (33.2%) patients withdrawn during the open-label phase, 60 (8.7%) withdrew due to AEs. In this period, only nausea and headache had an incidence of at least 10%. In the double-blind treatment phase, the withdrawal rate excluding relapses was 17.0% with vortioxetine treatment, and it was 13.5% with placebo treatment. Due to AEs, 3.5% and 2.6% of patients withdrew in the vortioxetine and placebo treatment groups, respectively. The most common AEs were influenza, headache, and accidental overdose with vortioxetine treatment, and they were headache and insomnia with placebo treatment.

4. Discussion

The present meta-analysis demonstrated the statistically superior efficacy of vortioxetine compared with placebo for the treatment of GAD, but it had small differences in terms of mean changes in HAMA total scores from baseline (SMD = −0.118) and in response rates (OR = 1.221); in fact, the remission rate was not different between the two treatment groups. Intriguingly, the mean change in HAMA total scores from baseline was significantly different between the two treatment groups favoring vortioxetine over placebo (SMD = −0.338), in the treatment of subpopulations with more severe anxiety (≥25 on the HAMA total score in baseline). Regarding acceptability, discontinuation for any reason (OR = 0.971) was not significantly different between the two treatment groups, and discontinuation due to AEs (OR = 1.560) was statistically but marginally higher in vortioxetine group than in the placebo group. The present meta-analysis of short-term vortioxetine RCTs has shown its potential benefit in the treatment of GAD. In addition, one relapse prevention study has proven its efficacy in the prevention of relapse of GAD, retaining its short-term benefits in long-term treatment; it was also tolerable as a maintenance treatment.

Although vortioxetine was superior to placebo in the reduction of anxiety as measured by the mean change in HAMA total score from baseline to the end of treatment, the overall SMD (−0.118) between vortioxetine and placebo was relatively small for its generalizability into clinical significance. These data met the small ES criteria proposed by Cohen. According to previous meta-analysis (Hidalgo et al., 2007), comparing various pharmacotherapies, including antidepressants, versus placebo, the ES was 0.39 (i.e., 0.5 with pregabalin, 0.42 with SNRIs, 0.36 with SSRIs and 0.17 with alprazolam). In other meta-analyses (mainly done with azapirones and benzodiazepines versus placebo) (Mitte et al., 2005), the ES with whole pharmacotherapy (0.33) was similar to that of meta-analysis by Hidalgo et al. (Hidalgo, 2007). According to the pooled results from three RCTs of duloxetine for GAD (n = 1163), the ES was 0.38 (Allgulander et al., 2007). Given the ESs obtained in the present meta-analysis, the ES of vortioxetine was lower than those from other pharmacological treatments. The ORs for vortioxetine for response (1.221) were also weak despite statistical significance, and the OR for remission was not superior to placebo (1.052). Indeed, the proven efficacy of antidepressants in acute treatment of GAD through RCTs is not easy, as evidenced in previous literature (Khan et al., 2002), among 52 RCTs and 93 treatment arms of new or established antidepressants (n = 10,030), only less than half (48%, 45/93) of the antidepressant treatment arms showed superiority to placebo. Similar difficulties in proving efficacy were also noted with anxiolytics trials, in which only 48% (36/75) of anxiolytic treatment arms showed superiority over placebo (Khan, 2002). It should also be noted that GAD had a lower response to treatment in terms of ES in comparison with other anxiety disorders, such as obsessive-compulsive disorder, panic disorder, and social phobia, which ranged from 0.1 to 1.48 (Hidalgo, 2007).

However, one intriguing point was that those with severe GAD (HAMA total score ≥25 at baseline) had a significantly greater benefit from vortioxetine than those without it (SMD = −0.338), indicating a more beneficial effect of vortioxetine in severe GAD. Such potential utility of vortioxetine was also observed in subgroup analysis in a number of previous MDD RCTs (Alvarez, 2012; Baldwin, 2012a; Boulenger, 2014; Katona, 2012). In such RCTs, the antianxiety effect of vortioxetine was early and robust, separating from placebo within two to three weeks of treatment; such a significant effect was maintained throughout the study period. Indeed, the antianxiety effect of vortioxetine was 13.8% higher than venlafaxine treatment in one MDD RCT (Alvarez, 2012).

Meanwhile, according to the recent meta-analysis of vortioxetine for treating MDD (Pae, in press), vortioxetine was significantly more effective than the placebo, with an ES of −0.217 on the mean change of MADRS total score from baseline and ORs for response and remission of 1.652 and 1.399, respectively, versus placebo. Another meta-analysis confirmed the efficacy even of low doses of vortioxetine (5 mg/d) in the treatment of MDD (Fu and Chen, 2015), and subsequent meta-analysis also replicated the efficacy of vortioxetine for MDD (Berhan and Barker, 2014). Interestingly, a statistically more significant reduction in the MADRS total score with patients who used higher doses of vortioxetine was found in Berhan and Barker's meta-analysis (Berhan, 2014), indicating a greater benefit of high doses of vortioxetine for treating MDD. In fact, the doses of SSRIs distinguished from placebo in the treatment of MDD are proposed to occupy 5-HTT occupancy, approximately 80% (Meyer, 2007). According to a recent Positron emission tomography (PET) study (Stenkrona, 2013), the recommended daily doses were 20–30 mg/d to reach a 5-HTT occupancy of approximately 70–80% in further clinical trials. In this PET study, assuming a linear relationship between oral dose and plasma concentration at a steady state, the dose required for 50% occupancy was calculated as 8.5 mg/d. Similarly, 20 mg/d for 70% and 37 mg/d for 80% were required, respectively.

Only 5 RCTs included high-dose vortioxetine treatment of 20 mg/d among 12 MDD RCTs (Pae, in press), indicating insufficient data regarding the high-dose treatment of vortioxetine for MDD. In fact, the recommended doses of vortioxetine for treating MDD ranged from 10 to 20 mg/d by the US FDA. However, vortioxetine of 20 mg/d was not included and only two RCTs used 10 mg/d in currently available RCTs for treating GAD (2.5–10 mg/d only). It should also be noted that recent meta-analysis (Pae, in press) combining all doses of vortioxetine together did not find such a trend in a meta-regression approach, proposing the beneficial effects of high dose of vortioxetine for treating MDD; in addition, the only positive RCT for GAD used vortioxetine of 5 mg/d. Therefore, the relationship between vortioxetine dose and efficacy remains unclear for the treatment of GAD as well as MDD. In fact, the recent meta-analyses of GAD (Hidalgo, 2007) has shown that treatment ESs were independent of fixed vs. flexible dosing regimens.

With regard to comparative efficacy, there has been no direct comparison study between vortioxetine and other antidepressants approved for treating GAD until now. Only one RCT was validated by the duloxetine reference arm (Mahableshwarkar, 2014a). In this study, the difference from placebo in changes from baseline in

HAM-A total score was −2.6, which is similar to those from the three pivotal duloxetine registration trials for the treatment of GAD. However, the differences in such values between vortioxetine and placebo ranged from −0.3 to −0.96. When reflecting that twice as many patients in the duloxetine group withdrew as a result of AEs in the study and more patients with duloxetine had overall AEs rates, we assumed the possibility for functional unblinding for duloxetine because the patients may have assumed that if they were experiencing side effects, they were receiving duloxetine, and so perceived a greater decrease in symptoms; conversely, if they were not experiencing AEs, they may have assumed that they were receiving placebo, thus a possible consideration contributing to a lack of signal detection (Mahableshwarkar, 2014a). Given a lack of availability of comparison studies, it is premature to conclude that vortioxetine may not be equal or inferior to SNRIs. Indeed, a sufficient number of trials that include adequately powered, direct comparisons of vortioxetine at different doses with other antidepressants are required to ultimately address its comparative efficacy.

One intriguing finding of the present meta-analysis is that study location significantly influenced treatment effects, favoring studies outside the US over those in only the US. All of the three RCTs conducted in the US exclusively failed to show the superiority of vortioxetine over placebo, whereas one RCT conducted outside the US showed a robust efficacy of vortioxetine over placebo. Although the study design and methodology were similar across all studies, slight differences between studies conducted outside the US versus those conducted in the US exclusively regarding the baseline parameters and subjects were observed; for instance, the proportion of subjects who were 'lost to follow-up' (6–9%) in the US study was nine times higher than in the studies outside US (1%), which can potentially prevent the detection of significant differences between two treatments. This could also be explained by the different recruitment strategies across centers. Furthermore, baseline GAD symptom severity was lower, and the duration of symptoms was longer in the US RCT. Interestingly, the number of subjects with a previous history of drug treatment was higher in the outside US study (up to 45%) than in the US studies (up to 35%). These differences in efficacy between US exclusive and outside studies were also observed in MDD RCTs of vortioxetine. Among five MDD RCTs conducted in the US exclusively, two failed to show the superiority of vortioxetine over placebo. In detail, the previous meta-analysis (Pae, in press) of vortioxetine trial for MDD found significant differences among the pooled SMDs, as the study location significantly influenced the results ($Z = 2.665$, $P = 0.007$) (favoring outside the US/mixed location over the US exclusive), although the SMD between vortioxetine and placebo treatment also produced a significant difference in favor of vortioxetine in the sub-analysis of US exclusive studies (−0.120, −0.208 to −0.032). Such an effect of study location on the treatment outcome was also present in exploratory analyses of efficacy data from MDD trials (Khin et al., 2011) as well as schizophrenia studies (Khin et al., 2012) submitted to the US FDA. Therefore, international multicenter trials should devote more attention to the design and conduct of RCTs, including the patient population characteristics, diagnostic criteria, patient assessments, and clinical practices used (Mahableshwarkar et al., 2013).

The likelihood of early dropouts due to AEs was marginally but significantly higher in the vortioxetine than in the placebo group. However, there were no prominent differences between each dose of vortioxetine and placebo at the level of individual studies. The most frequently reported AEs were nausea, headache, dizziness, and dry mouth, which were similar with the findings from MDD RCTs of vortioxetine (Pae, in press). Nausea was the single most common AE and its frequency showed a trend toward a dose–response relationship. However, the majority of such AEs were mild to moderate in intensity and not dose-dependent.

4.1. Limitations

There are some limitations in the present review. First, we included only short-term RCTs; indeed, in the meta-analysis, the duration of most of the trials was eight weeks, which is an important issue because GAD patients typically require long-term pharmacological treatment. Only one long-term relapse prevention study showed its beneficial effects on the long-term control of GAD symptoms until now. According to such a relapse-prevention study (Baldwin, 2012b), vortioxetine was effective in preventing the relapse of MDD and was well tolerated; 15% of patients receiving vortioxetine relapsed, whereas 34% of those receiving placebo relapsed. Three out of four of the acute RCTs of vortioxetine for the treatment of GAD failed to separate from placebo in terms of efficacy, whereas the relapse prevention study clearly demonstrated that vortioxetine may have a robust evidence as a maintenance therapy, may also motivate us to consider the undiscovered pharmacological properties of vortioxetine (i.e., delayed-onset 'downstream' effects). Indeed, it is well known that the therapeutic effects of most antidepressant drugs are dependent on long-term cascades of changes in monoamine receptors, neurosignal pathways, and possibly neurogenesis, leading to improved hippocampal and prefrontal cortex activation. It is therefore possible to speculate that the multimodal action of vortioxetine may result in a time-dependent effect, which may differ from traditional SSRIs. According to a recent study (Tedeschini et al., 2011) that analyzed 182 antidepressant-placebo comparisons, the duration of antidepressant clinical trials should be at least four weeks, mainly due to the increased risk of erroneously concluding that an effective treatment is ineffective. Likewise, the proper duration of antidepressant trials in the treatment of GAD has not yet been clearly established till today. Thus, we need more data on long-term effect of vortioxetine for GAD till today.

Second, we did not combine all doses of vortioxetine, and multiple placebo comparisons were done. Third, there is a possibility of clinical heterogeneity (i.e., study location, baseline parameters, etc.), including unidentified variations in study and population characteristics, although we tried to partially control for this bias by performing sensitivity analyses. The presence or absence of AEs that are associated with other currently available antidepressants such as sexual dysfunction, weight change, suicide risk, and cognitive impairment, could not be assessed due to lack of data in the present meta-analysis. Finally, the magnitude of the difference on the primary endpoint between vortioxetine and placebo treatments was relatively small. This weak effect of antidepressants for GAD has been consistently reported in the relevant research (Khan, 2002). Despite the existence of a number of possible reasons for a relatively weak antianxiety effect, such as a high placebo response rate, we should also consider the potential effect of the clinical and biological heterogeneity of GAD. Currently available evidence suggests that GAD may be a complex of neurobiological abnormalities including different neurotransmitters and neuroendocrine systems such as serotonin, dopamine, norepinephrine, histamine, corticotropin-releasing factor (CRF), neurosteroid, gamma-aminobutyric acid (GABA) and hypothalamic–pituitary–adrenal (HPA) axis (Connor and Davidson, 1998; Stein, 2009). Although GAD and MDD may share common biological causes, the two mental illnesses are not same disease. In fact, main alterations at the basis of anxiety disorders are in the reactivity of the amygdala, whereas depression involves hippocampal function, and their heritability estimates differentiate the two, suggesting partially different underlying mechanisms

(Oler et al., 2010). Similarly, antidepressant efficacy may affect different neurodevelopmental areas to induce improvement in the two disorders (Petrik et al., 2012). In fact, many antidepressants are not approved for the treatment of GAD, whereas they were proven to show some potential benefits in the treatment of anxious MDD and are indicated for the treatment of MDD. An anticonvulsant, pregabalin, which possesses a completely different mechanism of action (α2δ binding at presynaptic voltage dependent calcium channels leading to inhibition of excitatory neurotransmission) against antidepressants, has been indicated to treat GAD, but it has not been found to have clinical benefits for MDD (Han & Pae, 2015; Pae et al., 2014). Thus, we may also consider the subtle and hidden differences of neurobiological underpinnings between MDD and GAD.

5. Conclusion

The definite clinical efficacy of vortioxetine for the short-term control of GAD symptoms remains to be further elucidated with subsequent clinical trials to confirm the practical utility of vortioxetine for treating GAD at this point, although vortioxetine seems to be a well-tolerated agent for GAD treatment and may have a clear efficacy for treating severe GAD based on the currently available findings. However, our results should be interpreted and translated into clinical practice with caution due to the limited number of RCTs included in present the meta-analysis. Adequately powered, well-designed, direct-comparison clinical trials should more clearly address the comparative efficacy of vortioxetine relative to different antidepressants.

Role of funding source

This work was supported by a grant from the Ministry of Health and Welfare (HI12C0003); however, the funding source had no further role in preparation, data collection, and writing of the paper.

Contributors

All authors designed the study. C. Pae, S.-M. Wang, C. Han and S.-J. Lee acquired and analyzed the data, which P. Masand and A. Serretti also analyzed. C. Pae, S.-M. Wang, C. Han, S.-J. Lee and A. Patkar wrote the article, which all authors reviewed and approved for publication.

Competing interest

All authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Acknowledgment

This study was supported by a grant of the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (HI12C0003).

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpsychires.2015.02.017.

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