BMJ Open

Vortioxetine Treatment for Generalized Anxiety Disorder: A Meta-Analysis of Anxiety, Quality of Life, and Safety Outcomes

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-033161
Article Type:	Research
Date Submitted by the Author:	23-Jul-2019
Complete List of Authors:	Bin, Qin; Affiliated Liuzhou General Hospital of Guangxi University of Science and Technology Huang, Guangsu; Affiliated Liuzhou General Hospital of Guangxi University of Science and Technology, Department of Neurology Yang, Qian; Affiliated Liuzhou General Hospital of Guangxi University of Science and Technology, Department of Neurology Zhao, Mingjun; The Second Affiliated Hospital of Xinxiang Medical University Chen, Hong; Affiliated Liuzhou General Hospital of Guangxi University of Science and Technology, Department of Neurology Gao, Wen; Affiliated Liuzhou General Hospital of Guangxi University of Science and Technology, Department of Neurology Yang, Mingxiu; Affiliated Liuzhou General Hospital of Guangxi University of Science and Technology, Department of Neurology
Keywords:	Multimodal therapy, Generalized anxiety disorder, Vortioxetine, Meta-analysis

Vortioxetine Treatment for Generalized Anxiety Disorder: A Meta-Analysis of Anxiety, Quality of Life, and Safety Outcomes

Bin Qin,[1] Guangsu Huang,[1] Qian Yang,[1] Mingjun Zhao,[2] Hong Chen,[1] Wen Gao,[1] Mingxiu Yang[1]

Author affiliations

[1]Department of Neurology, Affiliated Liuzhou General Hospital of Guangxi University of Science and Technology (Liuzhou General Hospital), Liuzhou 545006, Guangxi, China,

[2]Department of Pharmacy, The Second Affiliated Hospital of Xinxiang Medical University (Henan Mental Hospital), Xinxiang 453000, China.

Correspondence to Professor Mingxiu Yang; lzrmyyymx@126.com.

Bin Qin, Guangsu Huang and Qian Yang contributed equally to this study

Abstract:

Objectives The aim of this study was to investigate the efficacy, tolerability, safety, and impact on quality of life (QoL) and functional status of vortioxetine treatment for patients with generalized anxiety disorder (GAD) by performing a meta-analysis of randomized controlled trials.

Methods Data mining was conducted in January 2019 across PubMed, EMBASE, PsycINFO, Cochrane Central Register of Controlled Trials Cochrane Library, Web of science, and ClinicalTrials.gov. Four publications, reporting data from a total of four randomized controlled trials, were included. Relevant data was extracted and synthesized narratively. Results were expressed as standardized mean differences (SMDs) or odds ratios (ORs) with 95% confidence intervals (CIs).

Results Our meta-analysis showed that multiple doses (2.5, 5, and 10 mg/day) of vortioxetine did not significantly improve the response rates, compared to placebo (OR = 1.16, 95% CI=0.84–1.60, P=0.38; OR = 1.41, 95% CI=0.82–2.41, P=0.21; and OR = 1.05, 95% CI=0.76–1.46, P=0.75). Moreover, there was no statistically significant difference regarding the remission rates, discontinuation for any reason rates, discontinuation due to adverse events rates, Short Form 36 Health Survey scores, or Sheehan Disability Scale scores between administration of multiple doses (2.5, 5, and 10 mg/day) of vortioxetine and placebo.

Conclusions Although our results suggest that vortioxetine did not improve the generalized anxiety disorder symptoms and QoL and functional status impairment of patients with GAD, it was safe and well tolerated. Clinicians should interpret and translate our data with caution, as the meta-analysis was based on a limited number of randomized controlled trials.

Keywords: Multimodal therapy; Generalized anxiety disorder; Vortioxetine; Meta-analysis

Word count: 3293.

Strengths and limitations of this study

► This systematic review and meta-analysis provides evidence for the efficacy, tolerability, and safety of vortioxetine in patients with generalized anxiety disorder

► Improvement of quality of life and functional status impairment were also evaluated to judge the patients' well-being of vortioxetine.

►Strong and reliable methodological and statistical procedures were applied.

► Due to the short-term follow-up in the evaluated studies, the long-term effect was not studied.

Introduction

Generalized anxiety disorder (GAD) is a common, chronic, costly, and disabling mental disorder that is marked by persistent anxiety and worry, and multiple psychological and physical symptoms.[1,2] It is also characterized by various psychological and somatic complaints, such as autonomic arousal, restlessness, fatigue, problems with concentration, irritability, and sleeplessness.[1] The estimated 1-year prevalence rate of GAD is between 1.2% and 1.9%, and the lifetime prevalence is between 4.3% and 5.9%.[2,3] Since most patients are still affected for 6 to 12 years after diagnosis, GAD is usually considered a chronic disorder and a major burden on the individual, their family, and health care services.[2,4]

Vortioxetine is a multimodal antidepressant that was approved for the treatment of major depressive disorder (MDD), by the US Food and Drug Administration (FDA) in September 2013. Vortioxetine's 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. Several meta-analyses have proved the efficacy of vortioxetine for the treatment of MDD.[5-7] Clinical trials evaluating its efficacy for the treatment of GAD, with doses up to 10 mg/day, have also yielded some interesting findings.[8-11] Moreover, as vortioxetine has been proven to be efficient in the treatment of MDD comorbid with GAD, it is possible that it constitutes an effective treatment for GAD alone, as well.[12] Interestingly, the efficacy of vortioxetine therapy in reducing anxiety symptom severity in GAD is summarized in two previous meta-analyses.[13,14] Both reviews analyzed its efficacy only in terms of symptom severity on the underlying continuous rating scales, and did not assess dichotomous response and remission outcomes. However, a recent meta-analysis examined the efficacy of multiple doses of vortioxetine in terms of dichotomous response outcomes, and the results showed no significant improvement in the outcomes of treating GAD with vortioxetine compared to treating GAD with placebo. [15] The efficacy was only assessed using continuous rating scales or dichotomous response; thus, the authors of these meta-analyses and of a relevant narrative review noted that a comprehensive summary of efficacy data is missing. Further, both these reviews only provided an assessment of efficacy and safety outcomes, and did not include outcomes of importance and patient-focused assessments, such as assessment of functional impairment and quality of life (QoL).

Currently there is growing interest in assessing the QoL and functional status impairment in patients with psychological disorders. In addition, the importance of including such assessments in evaluations of the influence of psychological disorders and their treatment, is widely recognized.[16-19] Our previous network meta-analysis concluded that risperidone and aripiprazole improved the QoL of patients with treatment-resistant depression.[20] Despite the growing interest in the field, studies addressing the impairment of QoL and functional status caused by anxiety disorders have progressed slowly.[21] Moreover, GAD is an important public mental health problem that causes poor QoL and functional status impairment,[16] with substantial impact on work and social roles.[22] Thus, the outcome of post-treatment QoL assessments is recognized as an important measure of treatment efficacy for patients with GAD.[23]

The assessment of antianxiety therapy benefits on QoL and functional status impairment in patients

with GAD is becoming increasingly common in clinical studies, mainly because, both aspects are important for the patients' overall well-being and recovery. Currently, the direct effect of vortioxetine treatment on QoL and functional status impairment in patients with GAD is unclear. Therefore, this meta-analysis was conducted to provide a comprehensive estimate of the efficacy, safety, and improving QoL and functional status impairment profiles of vortioxetine treatment of GAD.

Methods

All steps of this review were performed in strict accordance with the Cochrane Handbook for Systematic Reviews of Interventions.[24] The PRISMA statement guidelines were followed during the meta-analysis and preparation of this review.[25]

Search strategy

As of January 2019, we searched PubMed, EMBASE, PsycINFO, Cochrane Central Register of Controlled Trials (Cochrane Library), Web of science, and ClinicalTrials.gov (www.clinicaltrials.gov). Search terms included "vortioxetine OR Lu AA21004" OR Brintellix'' AND "anxiety OR anxiety disorder OR anxiety disorders OR mood disorder OR mood disorders." No language or time restrictions were applied. Titles and abstracts were screened by two independent reviewers, before full texts of potentially relevant articles were retrieved for further evaluation. The decision to include a study was then made by two independent reviewers, after full-text review. The reference lists of included articles were further hand-searched to identify additional relevant articles.

Eligibility Criteria and Study Selection

We included all clinical trials meeting the following criteria: (a) randomized controlled trials (RCTs) involving patients (≥18 years old) primarily diagnosed with GAD, according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR), and (b) RCTs comparing outcomes in efficacy, QoL, and functional impairment between vortioxetine and placebo. We excluded (a) retrospective and observational studies; (b) non-human studies; (c) theses and conference abstracts; and (d) studies including patients that had any concurrent psychiatric disorders with GAD or any prior history of psychiatric disorders, such as manic or hypomanic episodes, schizophrenia, or substance use disorders. Eligibility screening was performed in two steps, each by two independent reviewers (BQ and WG): (a) title and abstract screening for relevance to the study objective, and (b) full text screening for eligibility for a meta-analysis. Conflicts were resolved by the opinion of a third reviewer (MY).

Outcomes

Efficacy measures

Response was defined across studies as a 50% improvement of the Hamilton Anxiety Rating Scale (HAM-

A) total score from baseline to end point. Remission was defined as a HAM-A total score of ≤7 at the study end point. The continuous measure of efficacy was the mean change from baseline in total scores on the HAM-A, as defined by the individual study.

Safety and tolerability measures

Data on the discontinuation for any reason (tolerability) and the numbers of discontinuation due to adverse events (AEs) (safety) were included in the analysis.

QoL and functioning measures

QoL can be assessed by study-designed questionnaires and disease-specific or generic instruments. These instruments assess an individual's physical, emotional, psychological, and social health.[26, 27] We selected the Short Form 36 Health Survey (SF-36) [28] scores as the outcome indicator for QoL to preserve sufficient homogeneity for meta-analysis, because this instrument is used to measure QoL for the GAD population in many studies. The Sheehan Disability Scale (SDS),[29] a reliable, valid, brief, self-report scale that assesses disability in work, social, and family life, is the only measure of functional impairment employed by the trials included in this meta-analysis.

Data Extraction

Two independent reviewers (BQ and WG) extracted the following data from the included studies: (a) baseline characteristics of enrolled patients, (b) general characteristics of the study design, (c) information on efficacy, safety, tolerability, QoL, and functioning outcome. Data were summarized by one investigator and checked by a second reviewer. Any discrepant data were, again, examined by a third reviewer (MY), to ensure accurate data were obtained.

Risk of Bias Assessment

The risk of bias within each study was assessed by two independent reviewers (BQ and WG) using the Cochrane Risk of Bias assessment tool, as described in the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0.[24] This tool classifies the studies as having low, unclear, or high risk of bias across six domains: sequence generation, allocation concealment, blinding, missing data, selective reporting, and other biases.

Data Analysis

The meta-analysis was conducted using RevMan 5.3 software (Cochrane Collaboration, London, UK) and Stata 13.0 software (StataCorp LP, College Station, TX, USA). Odds ratios (ORs) and 95% CIs were used to assess binary outcomes, such as response and remission rates, as well as discontinuation for any reason rates. In addition, we converted continuous data to standardized mean differences (SMDs) and 95% CIs.

The statistical heterogeneity among trials was measured by Q statistics and the I^2 test. Higher I^2 values indicate greater heterogeneity, with I^2 values of 25, 50, and 75% signifying mild, moderate, and high heterogeneity, respectively. [30, 31] Based on heterogeneity, data were pooled to estimate the overall effect of all the interventions by random-effect or fixed-effect modelling. Sensitivity analyses were performed to test the impact robustness of every single study on the overall results. Publication bias could be assessed by visual inspection of a funnel plot, and the Egger test was used to evaluate publication biases. However, according to Egger and colleagues, assessing publication bias using the funnel plot-based methods is not reliable when fewer than 10 pooled studies are used in the direct comparison.[32]

Results

Search results

We identified 94 references from the electronic literature search. After screening the titles and abstracts, 85 were excluded because they failed to meet the inclusion criteria. By reading the full text of the remaining nine articles, five more were excluded: one study included patients with depression, one study focused on vortioxetine in the prevention of relapse of GAD, another one constituted a conference abstract and did not provide treatment outcomes, and two studies were eliminated because they were review articles. Ultimately, only four studies that fully satisfied the pre-established inclusion criteria of this meta-analysis were included [8-11] (see e-Figure 1).

Study Characteristics

Four included studies were published between 2012 and 2014 (Table 1). [8-11] The collective patient population comprised 1074 individuals in the vortioxetine group and 613 individuals in the placebo group. The administered doses of vortioxetine were 2.5, 5, and 10 mg/day. The mean age of participants ranged from 36.8 to 45.3 years. All studies were characterized by a preponderance of female subjects, with proportions ranging from 60 to 70%. The main characteristics of these studies are presented in Table 1.

Study Quality

The risks of bias in each study is summarized in e-Figure 2. All studies claimed randomization and three articles described the method of random sequence generation (random number table, computer generated). Three trials provided information that allowed us to assess whether an adequate concealment of the allocation procedure was used. All studies reported the blinding of participants. Therefore, all trials were deemed to have a mild-to-moderate risk of bias.

Efficacy

In terms of response, a total of four studies were included in the analysis; the overall ORs observed for groups treated with multiple doses (2.5, 5, and 10 mg/day) of vortioxetine compared to placebo were 1.16 (95% CI=0.84–1.60, Z=0.89, P=0.38), 1.41 (95% CI=0.82–2.41, Z=1.25, P=0.21), and 1.05 (95% CI=0.76–

1.46, Z=0.32, P=0.75), respectively (Figure 1). The results showed that there was no statistically significant difference in the response rates among the vortioxetine- and placebo groups. In addition, there was no statistically significant difference for the remission rates in multiple doses (2.5, 5, and 10 mg/d) of vortioxetine compared to placebo (Figure 2).

Pooled effect sizes for the mean change from baseline in total scores on the HAM-A are provided in Figure 3. The overall SMDs observed for the groups treated with multiple doses (2.5, 5, and 10 mg/d) of vortioxetine compared to the placebo were -0.13 (95% CI=-0.29–0.03, Z=1.56, P=0.12), -0.15 (95% CI=-0.48–0.18, Z=0.87, P=0.38), and -0.08 (95% CI=-0.24–0.08, Z=1.01, P=0.31), respectively. The results also showed that there was no statistically significant difference in the mean change from baseline in total scores on the HAM-A among the vortioxetine and placebo groups.

Tolerability and safety

No significant difference was observed between the vortioxetine and placebo groups in terms of the likelihood of discontinuation for any reason (tolerability). The overall ORs observed for the groups treated with multiple doses (2.5, 5, and 10 mg/day) of vortioxetine compared to the placebo-treated group were 1.03 (95% CI=0.71–1.47, Z=0.14, P=0.89), 0.87 (95% CI=0.63–1.20, Z=0.87, P=0.38), and 1.06 (95% CI=0.74–1.52, Z=0.32, P=0.75), respectively (e-Figure 3). Additionally, there was no statistically significant difference in the discontinuation due to AEs (safety) between the groups treated with multiple doses (2.5, 5, and 10 mg/day) of vortioxetine and the group treated with placebo (e-Figure 4).

Quality of life and functional status results

Three studies in this analysis reported SF-36 scores as the outcome measure of QoL. The overall SMDs of groups treated with multiple doses (2.5, 5, and 10 mg/d) of vortioxetine compared to placebo were 0.12 (95% CI=-0.11-0.35, Z=1.04, P=0.30), 0.22 (95% CI=-0.12-0.56, Z=1.26, P=0.21), and 0.09 (95% CI=-0.14-0.32, Z=0.75, P=0.45), respectively (Figure 4). The results showed that there was no statistically significant difference in SF-36 scores among the different groups. SDS scores were available for all four studies included in this analysis. The overall SMDs for the groups treated with multiple doses (2.5, 5, and 10 mg/d) of vortioxetine compared to placebo were -0.11 (95% CI=-0.30-0.08, Z=1.09, P=0.28), -0.10 (95% CI=-0.27-0.06, Z=1.27, P=0.21), and -0.20 (95% CI=-0.39-0.00, Z=2.00, P=0.05), respectively (Figure 5). The results showed that there was no statistically significant difference in SDS among the different groups.

Publication bias

The Egger test showed no significant difference main outcomes, indicating no publication bias.

Discussion

In this meta-analysis of 4 randomized trials studying vortioxetine as a treatment for GAD, we found that vortioxetine (2.5-, 5- and 10-mg once-daily doses) did not significantly improve GAD symptoms and quality of life/ functional status compared to a placebo treatment. However, vortioxetine might be safe and well tolerated in this patient population. Our findings have some clinical implications for comprehensively understanding the risk–benefit profiles of vortioxetine treatment for GAD.

Our results are not consistent with those of the previous meta-analysis conducted by Pae et al, as that study found that vortioxetine was significantly more effective than the placebo.[13] In their study, they only performed the analysis of mean change from baseline in total scores on the HAM-A, and included all randomized subjects. However, our meta-analysis was separately conducted according to the doses of vortioxetine, and we assessed the efficacy in terms of mean change from baseline in total scores on the HAM-A, response rates, and remission rates. Doses of vortioxetine may be clinically important factors for its efficacy in GAD patients. Thus, the results of our meta-analysis were more reliable and stable. Moreover, a recent meta-analysis showed that there was no statistically significant difference regarding the response rates among groups treated with either multiple doses (2.5, 5, and 10 mg/day) of vortioxetine or a placebo.[33] Furthermore, the results of our meta-analysis demonstrated no statistically significant difference in the mean change from baseline in total scores on the HAM-A, remission rates, quality of life, and functional status among the groups. Thus, the results of our meta-analysis were more comprehensive.

Several reasons for these outcomes may have contributed to the negative results. A previous analysis of the Food and Drug Administration database concluded that negative results are commonly seen in anxiolytic agents administered for the treatment of anxiety disorders, including GAD, where less than one-half (48%) of the treatment arms were statistically superior to the placebo. [34] In this case, all anxiolytic agents included in the study are approved for GAD treatment in the United States, but only three out of seven treatment arms were separated from the placebo. Moreover, the results some studies have found that negative results [9-11] had a higher placebo response rate than those with positive results. [8, 35] Although this correlation has not been established in GAD, it is reasonable to speculate that an elevated placebo response could reduce the treatment effect. Unfortunately, because no positive control was included in our meta-analysis, it is impossible to determine the lack-of-treatment effect. In addition, the racial diversity may have introduced differences in response and remission rates; for example, the studied population of the trial that showed negative results was racially diverse, whereas the population of the trial that showed positive results was almost entirely Caucasian. Hence, the results of the STAR*D study demonstrate that non-Caucasians were significantly less likely to achieve remission. [36] Furthermore, the mean baseline HAM-A total scores in most of the included studies were relatively high (ranging from 24.5 to 27); inflated baseline HAM-A total scores are a possible consequence of less stringent screening practices. However, it is unlikely that any single reason can explain the inconsistent results observed in the vortioxetine for GAD.

Although our meta-analysis did not demonstrate a statistically significant anxiolytic effect of vortioxetine, it did provide information regarding drug tolerability. Our study found that there was no statistically significant difference for the discontinuation for any reason rates and discontinuation due to

AEs rates among groups receiving either multiple doses (2.5, 5, and 10 mg/day) of vortioxetine compared to placebo, which is similar to the findings of a previous meta-analysis. [5,13] Thus, the vortioxetine doses were well tolerated, and were associated with similar discontinuation for any reason rates and discontinuation due to AEs rates when compared to the placebo.

GAD is associated with significant functional impairment in many areas, including social, occupational, and mental consequences; and when combined with physical impairment, together they influence QoL. The effectiveness of GAD treatment for improving QoL and functional outcomes is potentially confounded by the bidirectional relationship of anxiety symptoms and QoL/functional impairment. This is the first meta-analysis to report prospective assessment of QoL/functional status impairment in patients with GAD. Unfortunately, our meta-analysis of randomized controlled trials with GAD patients showed no significant improvement in the aforementioned aspects after vortioxetine treatment compared to after treatment with the placebo. Our results are not consistent with those of a previous meta-analysis of the effect of vortioxetine treatment on overall functioning in patients with MDD. [37] The meta-analysis, conducted by Florea et al, demonstrated that vortioxetine, in doses of 5-20 mg for 6/8 weeks, improved overall functioning in patients with MDD. Relative to placebo, vortioxetine treatment, in doses of 10 and 20 mg, demonstrated significant improvement in SDS total score and functional remission. However, the RCTs that were studied, in accordance with those included in our meta-analysis, used the optimal doses of 2.5-10 mg. Thus, the reason for the lack of congruence between these two meta-analyses may be the difference in the optimal doses. Meanwhile, a recent meta-analysis of vortioxetine in working patients with GAD, [38] showed that vortioxetine benefits adult patients who are working and/or pursuing an education. Thus, future research should be directed to provide more RCTs, specifically targeted to individuals with GAD, in order to assess the efficacy of vortioxetine in a larger sample, as well as to define the best therapeutic dosage.

The results of our meta-analysis should be interpreted in light of the following potential limitations. First, we included only four RCTs, which may have influenced the reliability of the results. Second, the duration of each trial included in our meta-analysis was 8 weeks; this is an important issue because GAD patients typically require long-term pharmacological treatment. We found only one study focusing on long-term relapse prevention, which showed no significant improvement of relapse prevention effect after long-term (maintenance) vortioxetine treatment for GAD compared to placebo. [39] In addition, owing to a limited number of studies included in our meta-analysis, we did not compare the onset time between the groups treated with multiple doses of vortioxetine and placebo. Finally, all the included trials were supported by the Takeda Pharmaceutical Company Ltd. as part of a joint clinical development program with H. Lundbeck A/S, which may have also influenced the results.

Conclusions

In summary, GAD is an illness that is characterized not only by severe anxiety symptoms, but also by diminished functioning and QoL. The challenge for interventions is not only to achieve improvement of

symptoms, but also to enhance patients' functioning ability and QoL. Our comprehensive evaluation of efficacy, safety, and impact on QoL provides a critical insight that may be useful for clinicians attempting to thoroughly understand the risk–benefit profiles of vortioxetine treatment for GAD. Vortioxetine did not significantly improve GAD symptoms and QoL as compared to the placebo; nevertheless, it was safe and well tolerated in this patient population. However, our results should be interpreted and translated into clinical practice with caution, owing to the limited number of RCTs included in the present meta-analysis.

Acknowledgments We thank Editage (www.editage.cn) for editing the English text of a draft of this manuscript.

Contributors BQ, GH, QY and MY were involved in conceptualisation and design of the study and critical review of the manuscript. BQ, GH and MY performed the data extraction. BQ, MZ, HC and WG conceived the study and reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Data sharing statement Additional data can be requested by emailing lzrmyyymx@126.com.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5), Fifth Edition. Washington, DC: American Psychiatric Association; 2013.
2. Tyrer P, Baldwin D. Generalised anxiety disorder. Lancet 2006; 368: 2156-2166.
3. Cuijpers P, Sijbrandij M, Koole S, et al. Psychological treatment of generalized anxiety disorder: a meta-analysis. Clin Psychol Rev 2014; 34: 130-140.
4. Yonkers KA, Dyck IR, Warshaw M, et al. Factors predicting the course of generalised anxiety disorder. Br J Psychiatry 2000; 176: 544-549.
5. Pae CU, Wang SM, Han C, et al. Vortioxetine: a meta-analysis of 12 short-term, randomized, placebo-controlled clinical trials for the treatment of major depressive disorder. J Psychiatry Neurosci 2015; 40: 174-186.
6. Berhan A, Barker A. Vortioxetine in the treatment of adult patients with major depressive disorder: a meta-analysis of randomized double-blind controlled trials. BMC Psychiatry 2014; 14: 276.
7. Fu J, Chen Y. The efficacy and safety of 5 mg/d vortioxetine compared to placebo for major depressive disorder: a meta-analysis. Psychopharmacology (Berl) 2015; 232: 7-16.
8. Bidzan L, Mahableshwarkar AR, Jacobsen P, et al. Vortioxetine (Lu AA21004) in generalized anxiety disorder: results of an 8-week, multinational, randomized, double-blind, placebo-controlled clinical trial. Eur Neuropsychopharmacol 2012; 22: 847-857.
9. Mahableshwarkar AR, Jacobsen PL, Serenko M, et al.A randomized, double-blind, fixed-dose study comparing the efficacy and tolerability of vortioxetine 2.5 and 10mg in acute treatment of adults with generalized anxiety disorder. Hum Psychopharmacol 2014; 29: 64-72.
10. Mahableshwarkar AR, Jacobsen PL, Chen Y, et al. A randomised, double-blind, placebo controlled, duloxetine-referenced study of the efficacy and tolerability of vortioxetine in the acute treatment of adults with generalised anxiety disorder. Int J Clin Pract 2014; 6: 49-59.
11. Rothschild AJ, Mahableshwarkar AR, Jacobsen P, et al. Vortioxetine (Lu AA21004) 5 mg in generalized anxiety disorder: results of an 8-week randomized, double-blind, placebo-controlled clinical trial in the United States. Eur Neuropsychopharmacol 2012; 22: 858-866.

12. Baldwin DS, Florea I, Jacobsen PL, et al. A meta-analysis of the efficacy of vortioxetine in patients with major depressive disorder (MDD) and high levels of anxiety symptoms. J Affect Disord 2016; 206: 140-150.

13. Pae CU, Wang SM, Han C, et al. Vortioxetine, multimodal antidepressant for generalized anxiety disorder: a systematic review and meta-analysis. J Psychiatr Res 2015; 64: 88-98.

14. Yee A, Ng CG, Seng LH. Vortioxetine Treatment for Anxiety Disorder: A Meta-Analysis Study. Curr Drug Targets 2017; 19: 1412-1423.

15. Fu J, Peng L, Li X. The efficacy and safety of multiple doses of vortioxetine for generalized anxiety disorder: a meta-analysis. Neuropsychiatr Dis Treat 2016; 12: 951-959.

16. Bourland SL, Stanley MA, Synder AG, et al. Quality of life in older adults with generalized anxiety disorder. Aging. And Mental Health 2000; 4: 315-323.

17. Frisch MB. Manual and treatment guide for the Quality of Life Inventory. Minneapolis: National Computer Systems Inc; 1994.

18. Katschnig H. How useful is the concept of quality of life in psychiatry? In: Katschnig H, Freeman H, Sartorius N. (Editors), Quality of life in mental disorders. Chichester: Wiley; 1997. p 3-16.

19. Steven EH. Bridging science and service: A report by the National Advisory Mental Health Council's Clinical Treatment and Services Research Workgroup (NIH Publication No. 99–4353). Rockville: Diane Pub Co; 1999.

20. Zhou X, Keitner GI, Qin B, et al. Atypical Antipsychotic Augmentation for Treatment-Resistant Depression: A Systematic Review and Network Meta-Analysis. Int J Neuropsychopharmacol 2015; 18: pyv060.

21. Mogotsi M, Kaminer D, Stein DJ. Quality of life in the anxiety disorders. Harvard Rev Psychiat 2000; 8: 273-282.

22. Henning ER, Turk CL, Mennin DS, et al. Impairment and quality of life in individuals with generalized anxiety disorder. Depress Anxiety 2007; 24: 342-349.

23. Endicott J, Russell JM, Raskin J, et al. Duloxetine treatment for role functioning improvement in generalized anxiety disorder: three independent studies. J Clin Psychiatry 2007; 68: 518-524.

24. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0

updated March 2011. Available at: http://www.cochrane-handbook.org. Accessed November 13, 2018.

25. Moher D, Liberati A, Tetzlaff J, et al. Reprint--preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Phys Ther 2009; 89: 873-880.

26. Testa MA, Simonson DC. Assessment of quality-of-life outcomes. N Engl J Med 1996; 334: 835-840.

27. Urbach DR. Measuring quality of life after surgery. Surg Innov 2005; 12: 161-165.

28. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). Med Care 1992; 30: 473-483.

29. Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. Int Clin Psychopharmacol 1996; 11: 89-95.

30. Higgins J, Thompson S, Deeks J, et al. Statistical heterogeneity in systematic reviews of clinical trials: a critical appraisal of guideline and practice. J Health Serv Res Policy 2002; 7: 51-61.

31. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-660.

32. Egger M, Davey Smith G, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-634.

33. Fu J, Peng L, Li X. The efficacy and safety of multiple doses of vortioxetine for generalized anxiety disorder: a meta-analysis. Neuropsychiatr Dis Treat 2016; 12: 951-959.

34. Khan A, Khan S, Brown WA. Are placebo controlsnecessary to test new antidepressants and anxiolytics? Int J Neuropsychopharmacol 2002; 5: 193–197.

35. Liebowitz MR, Stein MB, Tancer M, et al. A randomized, double-blind, fixed-dose comparison of paroxetine and placebo in the treatment of generalized social anxiety disorder. J Clin Psychiatry. 2002;63(1): 66–74.

36. Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 2006; 163(1): 28-40.

37. Florea I, Loft H, Danchenko N, et al. The effect of vortioxetine on overall patient functioning in

patients with major depressive disorder. Brain Behav 2017; 7: e00622.

38. Christensen MC, Loft H, Florea I, et al. Efficacy of vortioxetine in working patients with generalized anxiety disorder. CNS Spectr 2017. https://doi: 10.1017/S1092852917000761.

39. Baldwin DS, Loft H, Florea I. Lu AA21004, a multimodal psychotropic agent, in the prevention of relapse in adult patients with generalized anxiety disorder. Int Clin Psychopharmacol 2012; 27: 197-207.2

Table 1. Description of included studies.

Study	Patients n	Age (mean, SD)	Sex (Male, n, %)	Interventions	Duration (weeks)	Key inclusion criteria for GAD
Bidzan et al. (2012) [8]	T: 150; C: 151	T: 45.0 (14.1); C: 45.3 (13.5)	T: 47 (31.3); C: 58 (38.4)	T: vtx (5 mg/d); C: placebo	8	DSM-IV-TR, HAM-A ≥20
Mahableshwarkar et al. (2014a) [9]	T: 152, 152; C: 153	T: 40.8 (13.8)' 43.3 (15.0); C: 39.5 (13.5)	T: 49 (32.2), 56 (36.8); C: 48 (31.4)	T: vtx 2.5 mg/d, vtx 10 mg/d; C: placebo	8	DSM-IV-TR, HAM-A ≥20
Mahableshwarkar et al. (2014b) [10]	T: 156, 156, 156; C: 157	T: 39.2 (11.90), 37.7 (11.96), 39.8 (12.33); C: 36.8 (12.12)	T: 47 (30.1), 56 (35.9), 51 (32.7); C: 55 (35)	T: vtx 2.5 mg/d, vtx 5 mg/d, vtx 10 mg/d; C: placebo	8	DSM-IV-TR, HAM-A ≥20
Rothschild et al. (2012) [11]	T: 152; C: 152	T: 41.0 (14.05); C: 41.4 (12.81)	T: 49 (32.2); C: 55 (36.2)	T: vtx 5 mg/d; C: placebo	8	DSM-IV-TR, HAM-A ≥20

Note: T, Treatment group; C, Control group; mg/d, mg/day; GAD, Generalized anxiety disorder; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th edition Text Revision; HAM-A, Hamilton Anxiety Rating; vtx, Vortioxetine.

Figure legends

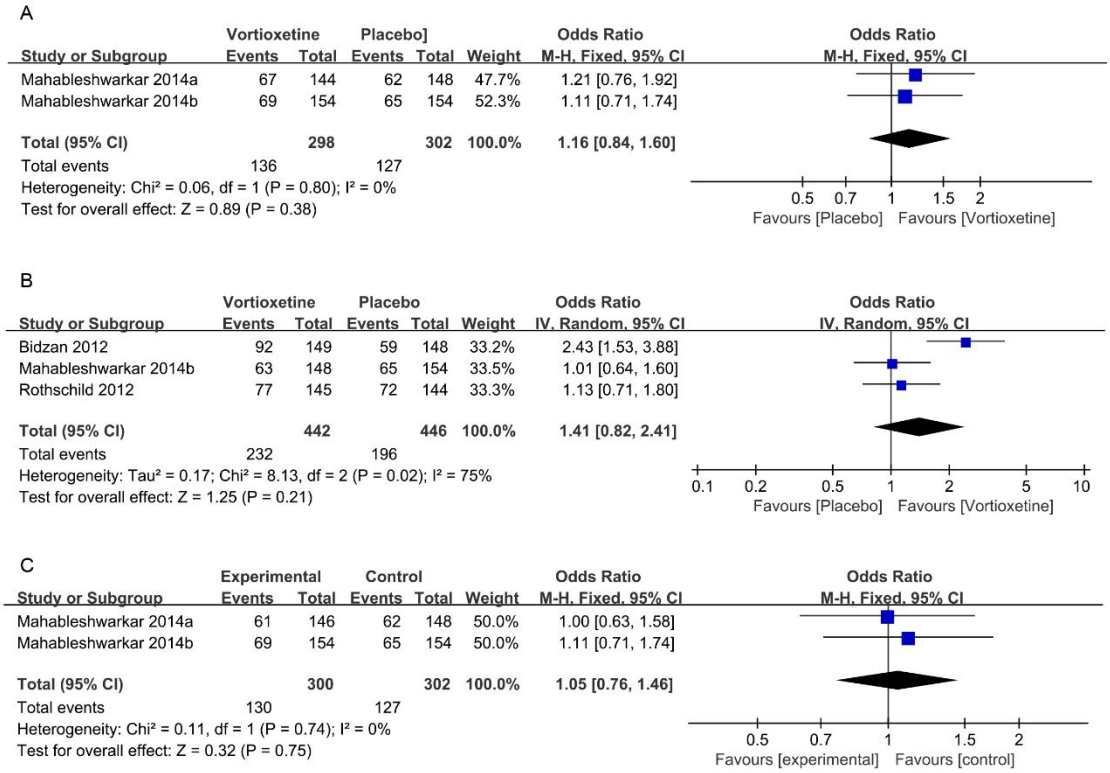


Figure 1: Odds ratios (ORs) and 95% confidence intervals (CIs) of the individual studies and the pooled data, comparing the response rates between the vortioxetine-treated and placebo groups.
Notes: (A) 2.5-mg/day vortioxetine versus placebo, (B) 5-mg/day vortioxetine versus placebo, and (C) 10-mg/day vortioxetine versus placebo.

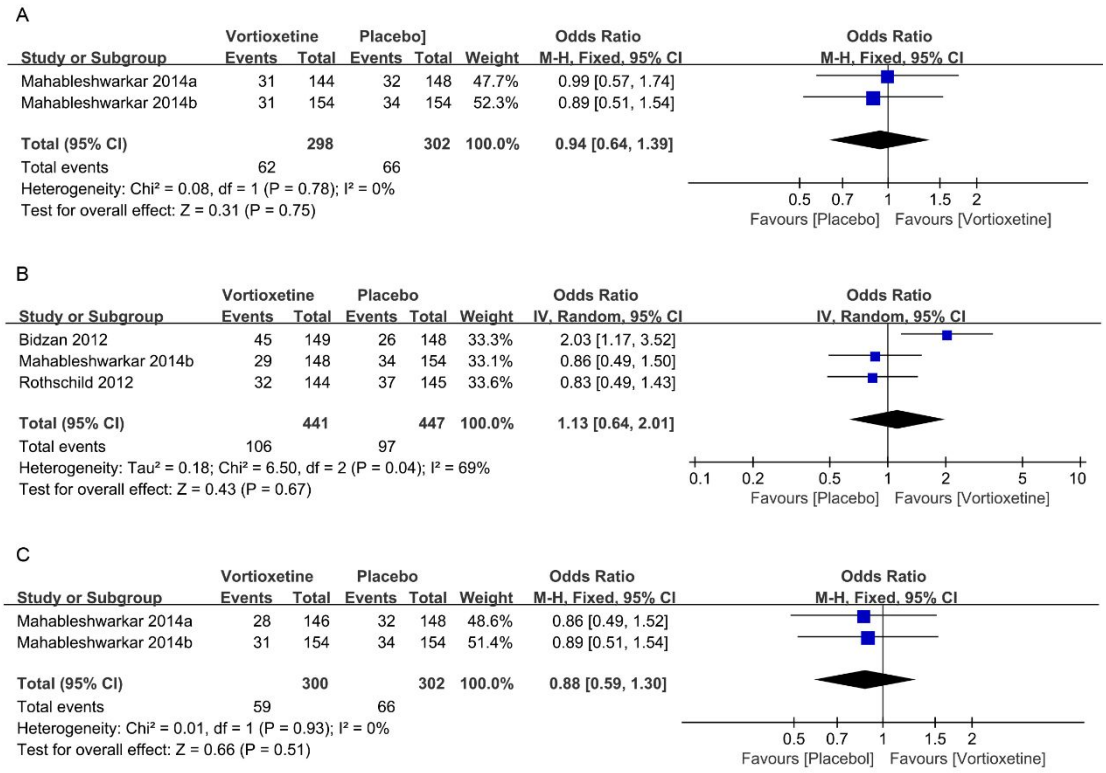


Figure 2: Odds ratios (ORs) and 95% confidence intervals (CIs) of the individual studies and the pooled data, comparing the remission rates between the vortioxetine- and placebo groups.
Notes: (A) 2.5-mg/day vortioxetine versus placebo, (B) 5-mg/day vortioxetine versus placebo, and (C) 10-mg/day vortioxetine versus placebo.

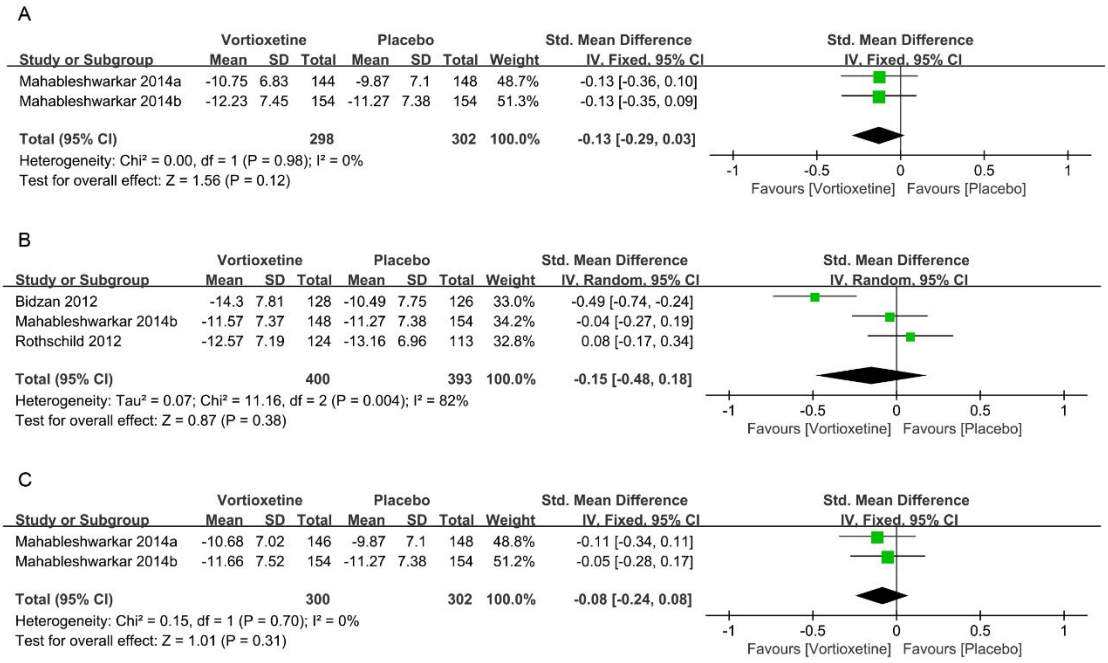


Figure 3: Standardized mean differences (SMDs) and 95% confidence intervals (CIs) of the individual

studies and the pooled data, comparing the mean change from baseline in total scores on the HAM-A, between the vortioxetine- and placebo groups.

Notes: (A) 2.5-mg/day vortioxetine versus placebo, (B) 5-mg/day vortioxetine versus placebo, and (C) 10-mg/day vortioxetine versus placebo.

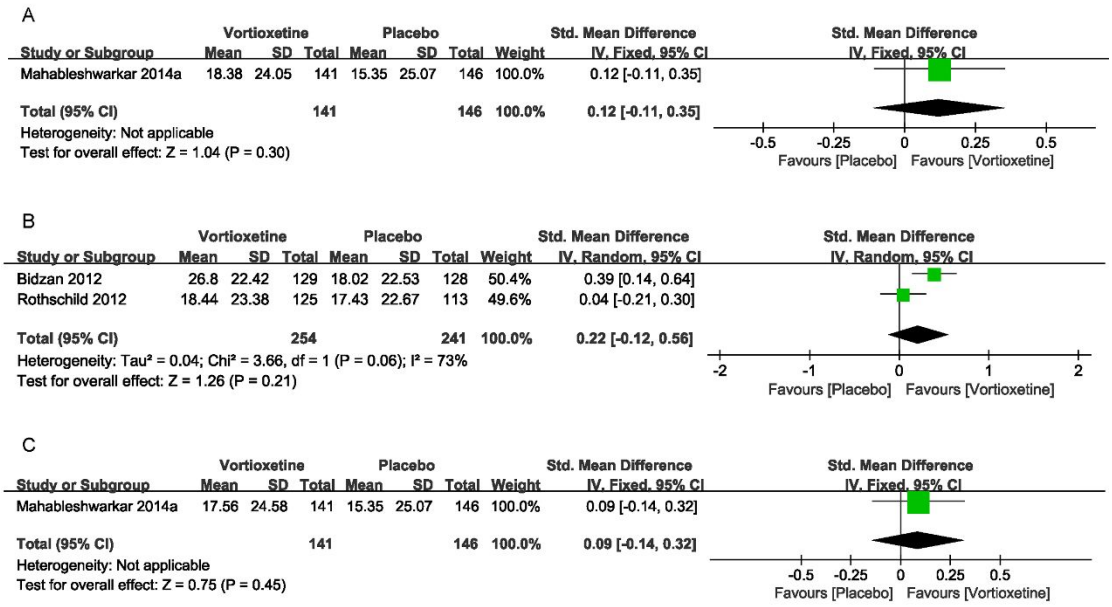


Figure 4: Standardized mean differences (SMDs) and 95% confidence intervals (CIs) of the individual studies and the pooled data, comparing the Short Form 36 Health Survey (SF-36) scores between the vortioxetine- and placebo groups.

Notes: (A) 2.5-mg/day vortioxetine versus placebo, (B) 5-mg/day vortioxetine versus placebo, and (C) 10-mg/day vortioxetine versus placebo.

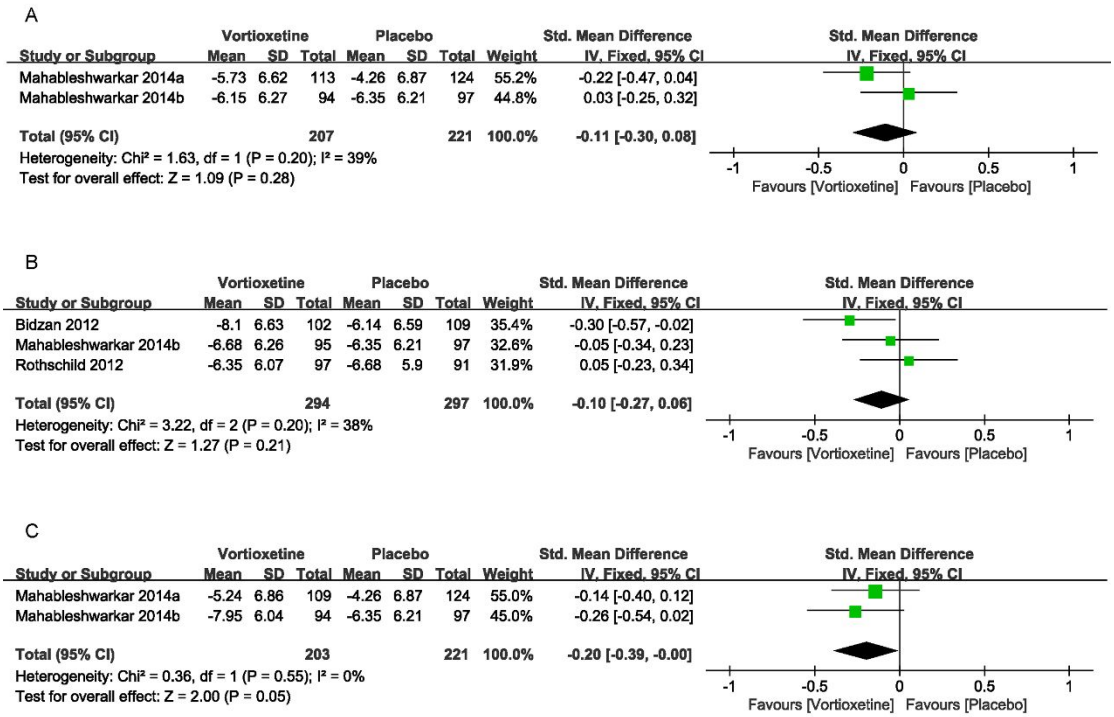
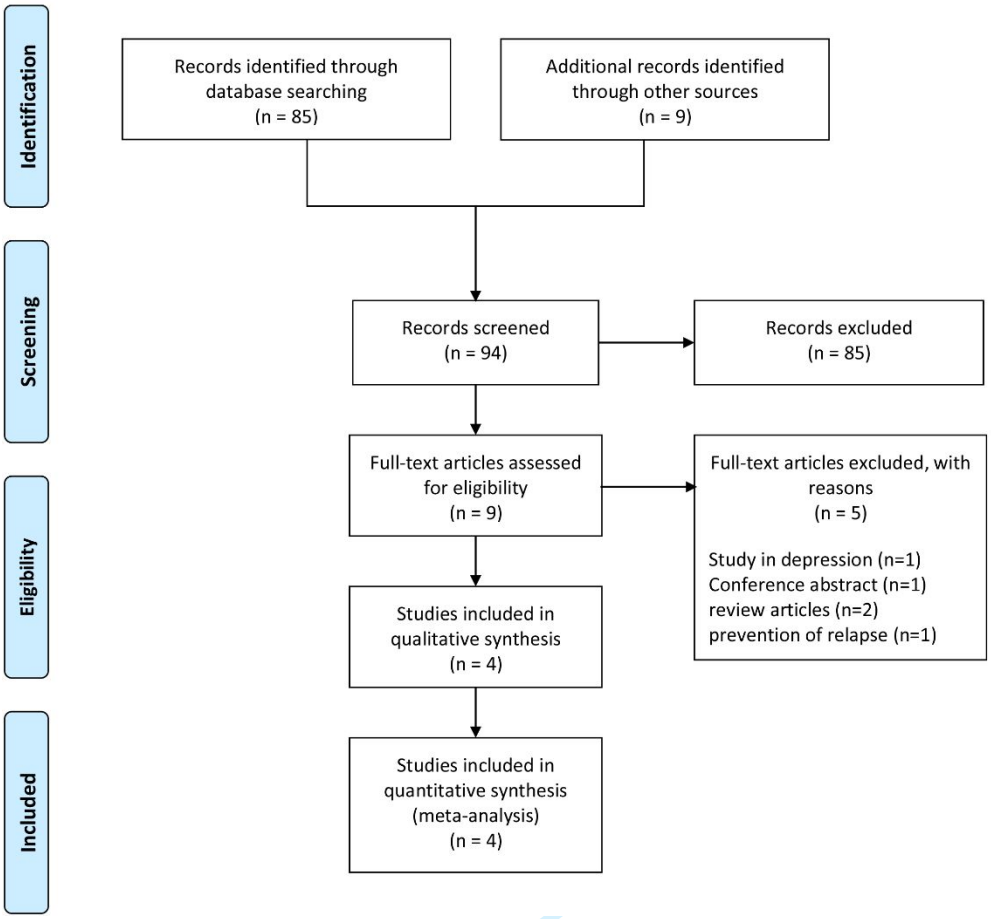
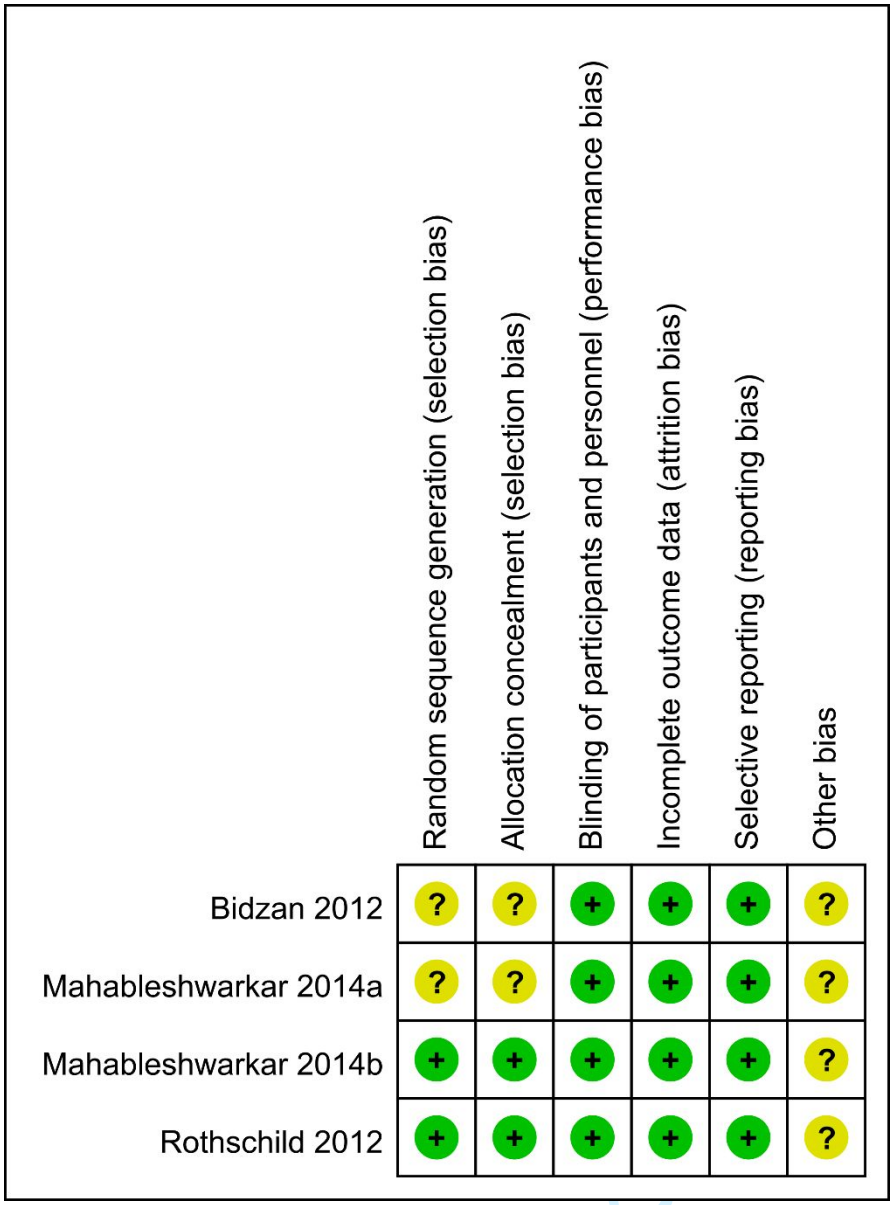


Figure 5: Standardized mean differences (SMDs) and 95% confidence intervals (CIs) of the individual studies and the pooled data, comparing the Sheehan Disability Scale (SDS) scores between the vortioxetine and placebo groups.

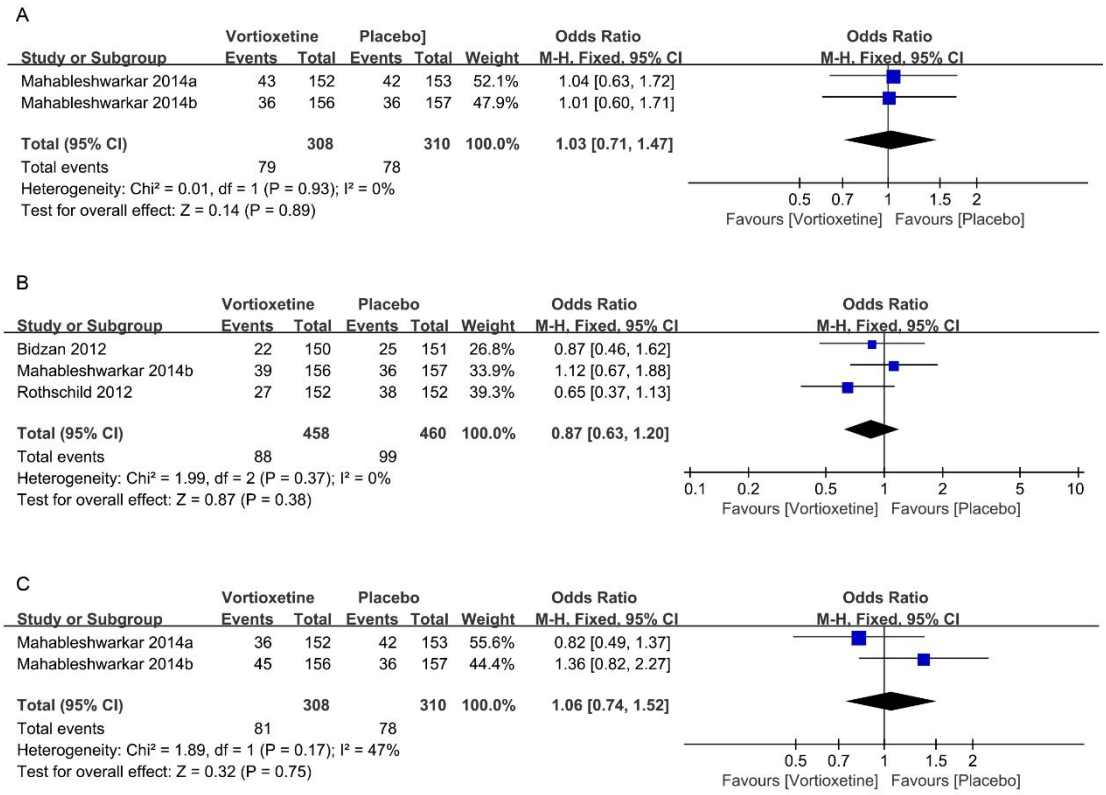
Notes: (A) 2.5-mg/day vortioxetine versus placebo, (B) 5-mg/day vortioxetine versus placebo, and (C) 10-mg/day vortioxetine versus placebo.



e-Figure 1: Search flow for the trial identification and selection process.

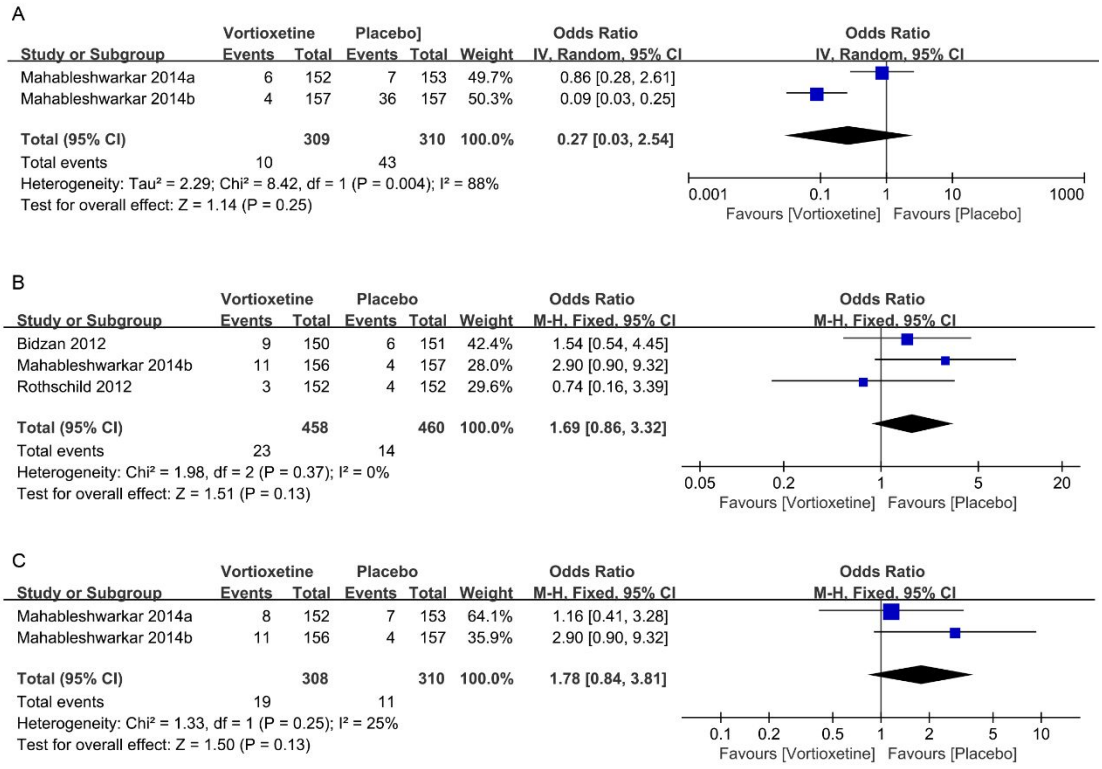


e-Figure 2: Summarized risks of bias for the included studies.



e-Figure 3: Odds ratios (ORs) and 95% confidence intervals (CIs) of the selected studies and the pooled data, comparing the discontinuation rates for any reason, between the vortioxetine and placebo groups.

Notes: (A) 2.5-mg/day vortioxetine versus placebo, (B) 5-mg/day vortioxetine versus placebo, and (C) 10-mg/day vortioxetine versus placebo.



e-Figure 4: Odds ratios (ORs) and 95% confidence intervals (CIs) of the selected studies and the pooled data, comparing the discontinuation rates due to adverse events (AEs), between vortioxetine and placebo groups.

Notes: (A) 2.5-mg/day vortioxetine versus placebo, (B) 5-mg/day vortioxetine versus placebo, and (C) 10-mg/day vortioxetine versus placebo.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3-4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5-6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5-6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5-6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6-7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6-7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	6-7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	7-9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9-10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	10

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

BMJ Open

Vortioxetine Treatment for Generalized Anxiety Disorder: A Meta-Analysis of Anxiety, Quality of Life, and Safety Outcomes

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-033161.R1
Article Type:	Original research
Date Submitted by the Author:	04-Oct-2019
Complete List of Authors:	Bin, Qin; Affiliated Liuzhou General Hospital of Guangxi University of Science and Technology Huang, Guangsu; Affiliated Liuzhou General Hospital of Guangxi University of Science and Technology, Department of Neurology Yang, Qian; Affiliated Liuzhou General Hospital of Guangxi University of Science and Technology, Department of Neurology Zhao, Mingjun; The Second Affiliated Hospital of Xinxiang Medical University Chen, Hong; Affiliated Liuzhou General Hospital of Guangxi University of Science and Technology, Department of Neurology Gao, Wen; Affiliated Liuzhou General Hospital of Guangxi University of Science and Technology, Department of Neurology Yang, Mingxiu; Affiliated Liuzhou General Hospital of Guangxi University of Science and Technology, Department of Neurology
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Pharmacology and therapeutics, Mental health
Keywords:	Multimodal therapy, Generalized anxiety disorder, Vortioxetine, Meta-analysis

Vortioxetine Treatment for Generalized Anxiety Disorder: A Meta-Analysis of Anxiety, Quality of Life, and Safety Outcomes

Bin Qin,[1] Guangsu Huang,[1] Qian Yang,[1] Mingjun Zhao,[2] Hong Chen,[1] Wen Gao,[1] Mingxiu Yang[1]

Author affiliations

[1]Department of Neurology, Affiliated Liuzhou General Hospital of Guangxi University of Science and Technology (Liuzhou General Hospital), Liuzhou 545006, Guangxi, China,

[2]Department of Pharmacy, The Second Affiliated Hospital of Xinxiang Medical University (Henan Mental Hospital), Xinxiang 453000, China.

Correspondence to Professor Mingxiu Yang; lzrmyyymx@126.com.

Bin Qin, Guangsu Huang and Qian Yang contributed equally to this study

Abstract:

Objectives The aim of this study was to investigate the efficacy, tolerability, safety, and impact on quality of life (QoL) and functional status of vortioxetine treatment for patients with generalized anxiety disorder (GAD) by performing a meta-analysis of randomized controlled trials.

Design Systematic review and meta-analysis.

Data sources Data mining was conducted in January 2019 across PubMed, EMBASE, PsycINFO, Cochrane Central Register of Controlled Trials Cochrane Library, Web of science, and ClinicalTrials.gov.

Eligibility criteria for selecting studies All published Randomized controlled trials (RCTs) which assessed the effect of vortioxetine treatment for patients with GAD when compared with a placebo group were included.

Data extraction and synthesis Relevant data was extracted and synthesized narratively. Results were expressed as standardized mean differences (SMDs) or odds ratios (ORs) with 95% confidence intervals (CIs).

Results Our meta-analysis showed that multiple doses (2.5, 5, and 10 mg/day) of vortioxetine did not significantly improve the response rates, compared to placebo (OR = 1.16, 95% CI=0.84–1.60, P=0.38; OR = 1.41, 95% CI=0.82–2.41, P=0.21; and OR = 1.05, 95% CI=0.76–1.46, P=0.75). Moreover, there was no statistically significant difference regarding the remission rates, discontinuation for any reason rates, discontinuation due to adverse events rates, Short Form 36 Health Survey scores, or Sheehan Disability Scale scores between administration of multiple doses (2.5, 5, and 10 mg/day) of vortioxetine and placebo.

Conclusions Although our results suggest that vortioxetine did not improve the generalized anxiety disorder symptoms and QoL and functional status impairment of patients with GAD, it was safe and well tolerated. Clinicians should interpret and translate our data with caution, as the meta-analysis was based on a limited number of randomized controlled trials.

Keywords: Multimodal therapy; Generalized anxiety disorder; Vortioxetine; Meta-analysis

Word count: 3548.

Strengths and limitations of this study

► This systematic review and meta-analysis provides evidence for the efficacy, tolerability, and safety of vortioxetine in patients with generalized anxiety disorder

► Improvement of quality of life and functional status impairment were also evaluated to judge the patients' well-being of vortioxetine.

►Strong and reliable methodological and statistical procedures were applied.

► Due to the short-term follow-up in the evaluated studies, the long-term effect was not studied.

Introduction

Generalized anxiety disorder (GAD) is a common, chronic, costly, and disabling mental disorder that is marked by persistent anxiety and worry, and multiple psychological and physical symptoms.[1,2] It is also characterized by various psychological and somatic complaints, such as autonomic arousal, restlessness, fatigue, problems with concentration, irritability, and sleeplessness.[1] The estimated 1-year prevalence rate of GAD is between 1.2% and 1.9%, and the lifetime prevalence is between 4.3% and 5.9%.[2,3] Since most patients are still affected for 6 to 12 years after diagnosis, GAD is usually considered a chronic disorder and a major burden on the individual, their family, and health care services.[2,4] Anxiety is a common comorbidity of chronic medical diseases including actopic dermatitis, asthma, rheumatoid arthritis, lupus and stroke. Anxiety has a negative impact on the quality of life of patients suffer from chronic diseases.[5,6]

Vortioxetine is a multimodal antidepressant that was approved for the treatment of major depressive disorder (MDD), by the US Food and Drug Administration (FDA) in September 2013. Vortioxetine's 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, and thereby with potential benefits in the treatment of major depressive episode and, probably, GAD and anxiety disorders.[7] In addition, vortioxetine cause significant increase in the hippocampal Brain Derived Neurotrophic Factors levels as compared with selective serotonin reuptake inhibitors.[8] Several meta-analyses have proved the efficacy of vortioxetine for the treatment of MDD.[9-11] A recent scientometric analysis reported the popularity of vortioxetine is on the rising trend.[12] Clinical trials evaluating its efficacy for the treatment of GAD, with doses up to 10 mg/day, have also yielded some interesting findings.[13-16] Moreover, as vortioxetine has been proven to be efficient in the treatment of MDD comorbid with GAD, it is possible that it constitutes an effective treatment for GAD alone, as well.[17]

Interestingly, the efficacy of vortioxetine therapy in reducing anxiety symptom severity in GAD is summarized in two previous meta-analyses.[18,19] Both reviews analyzed its efficacy only in terms of symptom severity on the underlying continuous rating scales, and did not assess dichotomous response and remission outcomes. However, a recent meta-analysis examined the efficacy of multiple doses of vortioxetine in terms of dichotomous response outcomes, and the results showed no significant improvement in the outcomes of treating GAD with vortioxetine compared to treating GAD with placebo.[20] The efficacy was only assessed using continuous rating scales or dichotomous response; thus, the authors of these meta-analyses and of a relevant narrative review noted that a comprehensive summary of efficacy data is missing. Further, both these reviews only provided an assessment of efficacy and safety outcomes, and did not include outcomes of importance and patient-focused assessments, such as assessment of functional impairment and quality of life (QoL). Currently there is growing interest in assessing the QoL and functional status impairment in patients with psychological disorders.[21,22] In addition, the importance of including such assessments in evaluations of the influence of psychological disorders and their treatment, is widely recognized.[23-26] Our previous network meta-analysis concluded that risperidone and aripiprazole improved the QoL of patients with treatment-resistant depression.[27] Despite the growing interest in the

field, studies addressing the impairment of QoL and functional status caused by anxiety disorders have progressed slowly.[28] Moreover, GAD is an important public mental health problem that causes poor QoL and functional status impairment,[23] with substantial impact on work and social roles.[29] Thus, the outcome of post-treatment QoL assessments is recognized as an important measure of treatment efficacy for patients with GAD.[30]

The assessment of antianxiety therapy benefits on QoL and functional status impairment in patients with GAD is becoming increasingly common in clinical studies, mainly because, both aspects are important for the patients' overall well-being and recovery. Currently, the direct effect of vortioxetine treatment on QoL and functional status impairment in patients with GAD is unclear. Therefore, this meta-analysis was conducted to provide a comprehensive estimate of the efficacy, safety, and improving QoL and functional status impairment profiles of vortioxetine treatment of GAD.

Methods

All steps of this review were performed in strict accordance with the Cochrane Handbook for Systematic Reviews of Interventions.[31] The PRISMA statement guidelines were followed during the meta-analysis and preparation of this review.[32]

Search strategy

As of January 2019, we searched PubMed, EMBASE, PsycINFO, Cochrane Central Register of Controlled Trials (Cochrane Library), Web of science, and ClinicalTrials.gov (www.clinicaltrials.gov). Search terms included "vortioxetine OR Lu AA21004" OR Brintellix'' AND "anxiety OR anxiety disorder OR anxiety disorders OR mood disorder OR mood disorders." No language or time restrictions were applied. Titles and abstracts were screened by two independent reviewers, before full texts of potentially relevant articles were retrieved for further evaluation. The decision to include a study was then made by two independent reviewers (BQ and WG), after full-text review. The reference lists of included articles were further hand-searched to identify additional relevant articles.

Eligibility Criteria and Study Selection

We included all clinical trials meeting the following criteria: (a) randomized controlled trials (RCTs) involving patients (≥18 years old) primarily diagnosed with GAD, according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR), and (b) RCTs comparing outcomes in efficacy, QoL, and functional impairment between vortioxetine and placebo. We excluded (a) retrospective and observational studies; (b) non-human studies; (c) theses and conference abstracts; and (d) studies including patients that had any concurrent psychiatric disorders with GAD or any prior history of psychiatric disorders, such as manic or hypomanic episodes, schizophrenia, or substance use disorders. Eligibility screening was performed in two steps, each by two independent reviewers (BQ and WG): (a) title and abstract screening for relevance to the study objective, and (b) full text screening for

eligibility for a meta-analysis. Conflicts were resolved by the opinion of a third reviewer (MY).

Outcomes

Efficacy measures

Response was defined across studies as a 50% improvement of the Hamilton Anxiety Rating Scale (HAM-A) total score from baseline to end point. Remission was defined as a HAM-A total score of ≤7 at the study end point. The continuous measure of efficacy was the mean change from baseline in total scores on the HAM-A, as defined by the individual study.

Safety and tolerability measures

Data on the discontinuation for any reason (tolerability) and the numbers of discontinuation due to adverse events (AEs) (safety) were included in the analysis.

QoL and functioning measures

QoL can be assessed by study-designed questionnaires and disease-specific or generic instruments. These instruments assess an individual's physical, emotional, psychological, and social health.[33,34] We selected the Short Form 36 Health Survey (SF-36) [35] scores as the outcome indicator for QoL to preserve sufficient homogeneity for meta-analysis, because this instrument is used to measure QoL for the GAD population in many studies. And, studies were excluded if the QoL outcome was reported by the other rating scales. The Sheehan Disability Scale (SDS),[36] a reliable, valid, brief, self-report scale that assesses disability in work, social, and family life, is the only measure of functional impairment employed by the trials included in this meta-analysis.

Data Extraction

Two independent reviewers (BQ and WG) extracted the following data from the included studies: (a) baseline characteristics of enrolled patients, (b) general characteristics of the study design, (c) information on efficacy, safety, tolerability, QoL, and functioning outcome. Data were summarized by one investigator and checked by a second reviewer. Any discrepant data were, again, examined by a third reviewer (MY), to ensure accurate data were obtained.

Risk of Bias Assessment

The risk of bias within each study was assessed by two independent reviewers (BQ and WG) using the Cochrane Risk of Bias assessment tool, as described in the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0.[31] This tool classifies the studies as having low, unclear, or high risk of bias across six domains: sequence generation, allocation concealment, blinding, missing data, selective reporting, and other biases.

Data Analysis

The meta-analysis was conducted using RevMan 5.3 software (Cochrane Collaboration, London, UK) and Stata 13.0 software (StataCorp LP, College Station, TX, USA). Odds ratios (ORs) and 95% CIs were used to assess binary outcomes, such as response and remission rates, as well as discontinuation for any reason rates. In addition, we converted continuous data to standardized mean differences (SMDs) and 95% CIs. The statistical heterogeneity among trials was measured by Q statistics and the I^2 test. Higher I^2 values indicate greater heterogeneity, with I^2 values of 25, 50, and 75% signifying mild, moderate, and high heterogeneity, respectively. [37,38] Based on heterogeneity, data were pooled to estimate the overall effect of all the interventions by random-effect or fixed-effect modelling. Fixed-effect models assume that the population effect sizes are the same for all studies. In contrast, random-effects model attempted to generalize findings beyond the included studies by assuming that the selected studies are random samples from a larger population.[39] Sensitivity analyses were performed to test the impact robustness of every single study on the overall results. Publication bias could be assessed by visual inspection of a funnel plot, and the Egger test was used to evaluate publication biases. However, according to Egger and colleagues, assessing publication bias using the funnel plot-based methods is not reliable when fewer than 10 pooled studies are used in the direct comparison.[40]

Patient and public involvement

Patients or the public were not involved in the conceptualisation or carrying out of this research.

Results

Search results

We identified 94 references from the electronic literature search. After screening the titles and abstracts, 85 were excluded because they failed to meet the inclusion criteria. By reading the full text of the remaining nine articles, five more were excluded: one study included patients with depression, one study focused on vortioxetine in the prevention of relapse of GAD, another one constituted a conference abstract and did not provide treatment outcomes, and two studies were eliminated because they were review articles. Ultimately, only four studies that fully satisfied the pre-established inclusion criteria of this meta-analysis were included (see e-Figure 1).[13-16]

Study Characteristics

Four included studies were published between 2012 and 2014 (Table 1).[13-16] The collective patient population comprised 1074 individuals in the vortioxetine group and 613 individuals in the placebo group. The administered doses of vortioxetine were 2.5, 5, and 10 mg/day. The mean age of participants ranged from 36.8 to 45.3 years. All studies were characterized by a preponderance of female subjects, with proportions ranging from 60 to 70%. The main characteristics of these studies are presented in Table 1.

Study Quality

The risks of bias in each study is summarized in e-Figure 2. All studies claimed randomization and three articles described the method of random sequence generation (random number table, computer generated). Three trials provided information that allowed us to assess whether an adequate concealment of the allocation procedure was used. All studies reported the blinding of participants. Therefore, all trials were deemed to have a mild-to-moderate risk of bias.

Efficacy

In terms of response, a total of four studies were included in the analysis; the overall ORs observed for groups treated with multiple doses (2.5, 5, and 10 mg/day) of vortioxetine compared to placebo were 1.16 (95% CI=0.84–1.60, Z=0.89, P=0.38), 1.41 (95% CI=0.82–2.41, Z=1.25, P=0.21), and 1.05 (95% CI=0.76–1.46, Z=0.32, P=0.75), respectively (Figure 1). The results showed that there was no statistically significant difference in the response rates among the vortioxetine- and placebo groups. In addition, there was no statistically significant difference for the remission rates in multiple doses (2.5, 5, and 10 mg/d) of vortioxetine compared to placebo (Figure 2).

Pooled effect sizes for the mean change from baseline in total scores on the HAM-A are provided in Figure 3. The overall SMDs observed for the groups treated with multiple doses (2.5, 5, and 10 mg/d) of vortioxetine compared to the placebo were -0.13 (95% CI=-0.29–0.03, Z=1.56, P=0.12), -0.15 (95% CI=-0.48–0.18, Z=0.87, P=0.38), and -0.08 (95% CI=-0.24–0.08, Z=1.01, P=0.31), respectively. The results also showed that there was no statistically significant difference in the mean change from baseline in total scores on the HAM-A among the vortioxetine and placebo groups.

Tolerability and safety

No significant difference was observed between the vortioxetine and placebo groups in terms of the likelihood of discontinuation for any reason (tolerability). The overall ORs observed for the groups treated with multiple doses (2.5, 5, and 10 mg/day) of vortioxetine compared to the placebo-treated group were 1.03 (95% CI=0.71–1.47, Z=0.14, P=0.89), 0.87 (95% CI=0.63–1.20, Z=0.87, P=0.38), and 1.06 (95% CI=0.74–1.52, Z=0.32, P=0.75), respectively (e-Figure 3). Additionally, there was no statistically significant difference in the discontinuation due to AEs (safety) between the groups treated with multiple doses (2.5, 5, and 10 mg/day) of vortioxetine and the group treated with placebo (e-Figure 4).

Quality of life and functional status results

Three studies in this analysis reported SF-36 scores as the outcome measure of QoL. The overall SMDs of groups treated with multiple doses (2.5, 5, and 10 mg/d) of vortioxetine compared to placebo were 0.12 (95% CI=-0.11-0.35, Z=1.04, P=0.30), 0.22 (95% CI=-0.12-0.56, Z=1.26, P=0.21), and 0.09 (95% CI=-

0.14-0.32, Z=0.75, P=0.45), respectively (Figure 4). The results showed that there was no statistically significant difference in SF-36 scores among the different groups. SDS scores were available for all four studies included in this analysis. The overall SMDs for the groups treated with multiple doses (2.5, 5, and 10 mg/d) of vortioxetine compared to placebo were -0.11 (95% CI=-0.30-0.08, Z=1.09, P=0.28), -0.10 (95% CI=-0.27-0.06, Z=1.27, P=0.21), and -0.20 (95% CI=-0.39-0.00, Z=2.00, P=0.05), respectively (Figure 5). The results showed that there was no statistically significant difference in SDS among the different groups.

Publication bias

The Egger test showed no significant difference main outcomes, indicating no publication bias.

Discussion

In this meta-analysis of 4 randomized trials studying vortioxetine as a treatment for GAD, we found that vortioxetine (2.5-, 5- and 10-mg once-daily doses) did not significantly improve GAD symptoms and quality of life/ functional status compared to a placebo treatment. However, vortioxetine might be safe and well tolerated in this patient population. Our findings have some clinical implications for comprehensively understanding the risk–benefit profiles of vortioxetine treatment for GAD.

Our results are not consistent with those of the previous meta-analysis conducted by Pae et al, as that study found that vortioxetine was significantly more effective than the placebo.[18] In their study, they only performed the analysis of mean change from baseline in total scores on the HAM-A, and included all randomized subjects. However, our meta-analysis was separately conducted according to the doses of vortioxetine, and we assessed the efficacy in terms of mean change from baseline in total scores on the HAM-A, response rates, and remission rates. Doses of vortioxetine may be clinically important factors for its efficacy in GAD patients. Thus, the results of our meta-analysis were more reliable and stable. Moreover, a recent meta-analysis showed that there was no statistically significant difference regarding the response rates among groups treated with either multiple doses (2.5, 5, and 10 mg/day) of vortioxetine or a placebo.[41] Furthermore, the results of our meta-analysis demonstrated no statistically significant difference in the mean change from baseline in total scores on the HAM-A, remission rates, quality of life, and functional status among the groups. Thus, the results of our meta-analysis were more comprehensive.

Several reasons for these outcomes may have contributed to the negative results. A previous analysis of the Food and Drug Administration database concluded that negative results are commonly seen in anxiolytic agents administered for the treatment of anxiety disorders, including GAD, where less than one-half (48%) of the treatment arms were statistically superior to the placebo.[42] In this case, all anxiolytic agents included in the study are approved for GAD treatment in the United States, but only three out of seven treatment arms were separated from the placebo. Moreover, the results some studies have found that negative results[14-16] had a higher placebo response rate than those with positive results.[13,43] Although this correlation has not been established in GAD, it is reasonable to speculate that an elevated placebo response

could reduce the treatment effect. Unfortunately, because no positive control was included in our meta-analysis, it is impossible to determine the lack-of-treatment effect. In addition, the racial diversity may have introduced differences in response and remission rates; for example, the studied population of the trial that showed negative results was racially diverse, whereas the population of the trial that showed positive results was almost entirely Caucasian. Hence, the results of the STAR*D study demonstrate that non-Caucasians were significantly less likely to achieve remission.[44] Furthermore, the mean baseline HAM-A total scores in most of the included studies were relatively high (ranging from 24.5 to 27); inflated baseline HAM-A total scores are a possible consequence of less stringent screening practices. Relative to placebo, vortioxetine treatment, in doses of 10 and 20 mg, demonstrated significant improvement in depressive symptoms, however, the RCTs that were studied, in accordance with those included in our meta-analysis, used the optimal doses of 2.5-10 mg. Higher dosages, such as 20 mg or even more, would be more beneficial in anxiety disorders, whereas lower dosages may unaffect anxiety symptoms. However, it is unlikely that any single reason can explain the inconsistent results observed in the vortioxetine for GAD.

Although our meta-analysis did not demonstrate a statistically significant anxiolytic effect of vortioxetine, it did provide information regarding drug tolerability. Our study found that there was no statistically significant difference for the discontinuation for any reason rates and discontinuation due to AEs rates among groups receiving either multiple doses (2.5, 5, and 10 mg/day) of vortioxetine compared to placebo, which is similar to the findings of a previous meta-analysis.[9,18] Thus, the vortioxetine doses were well tolerated, and were associated with similar discontinuation for any reason rates and discontinuation due to AEs rates when compared to the placebo.

GAD is associated with significant functional impairment in many areas, including social, occupational, and mental consequences; and when combined with physical impairment, together they influence QoL. The effectiveness of GAD treatment for improving QoL and functional outcomes is potentially confounded by the bidirectional relationship of anxiety symptoms and QoL/functional impairment. This is the first meta-analysis to report prospective assessment of QoL/functional status impairment in patients with GAD. Unfortunately, our meta-analysis of randomized controlled trials with GAD patients showed no significant improvement in the aforementioned aspects after vortioxetine treatment compared to after treatment with the placebo. Our results are not consistent with those of a previous meta-analysis of the effect of vortioxetine treatment on overall functioning in patients with MDD.[45] The meta-analysis, conducted by Florea et al, demonstrated that vortioxetine, in doses of 5-20 mg for 6/8 weeks, improved overall functioning in patients with MDD. Relative to placebo, vortioxetine treatment, in doses of 10 and 20 mg, demonstrated significant improvement in SDS total score and functional remission. However, the RCTs that were studied, in accordance with those included in our meta-analysis, used the optimal doses of 2.5-10 mg. Thus, the reason for the lack of congruence between these two meta-analyses may be the difference in the optimal doses. Meanwhile, a recent meta-analysis of vortioxetine in working patients with GAD,[46] showed that vortioxetine benefits adult patients who are working and/or pursuing an education. Thus, future research should be directed to provide more RCTs, specifically targeted to individuals with GAD, in

order to assess the efficacy of vortioxetine in a larger sample, as well as to define the best therapeutic dosage.

The results of our meta-analysis should be interpreted in light of the following potential limitations. First, we included only four RCTs, which may have influenced the reliability of the results. Second, the duration of each trial included in our meta-analysis was 8 weeks; this is an important issue because GAD patients typically require long-term pharmacological treatment. We found only one study focusing on long-term relapse prevention, which showed no significant improvement of relapse prevention effect after long-term (maintenance) vortioxetine treatment for GAD compared to placebo.[47] Furthermore, the systematic review, conducted by Perna et al, indicated that although some recent data support the long-term efficacy of vortioxetine for GAD and showed a favorable tolerability profile, the conflicting short-term studies and limited clinical experience recommend its use only as second-line therapy.[48] In addition, owing to a limited number of studies included in our meta-analysis, we did not compare the onset time between the groups treated with multiple doses of vortioxetine and placebo. Finally, all the included trials were supported by the Takeda Pharmaceutical Company Ltd. as part of a joint clinical development program with H. Lundbeck A/S, which may have also influenced the results.

Conclusions

In summary, GAD is an illness that is characterized not only by severe anxiety symptoms, but also by diminished functioning and QoL. The challenge for interventions is not only to achieve improvement of symptoms, but also to enhance patients' functioning ability and QoL. Our comprehensive evaluation of efficacy, safety, and impact on QoL provides a critical insight that may be useful for clinicians attempting to thoroughly understand the risk–benefit profiles of vortioxetine treatment for GAD. Vortioxetine did not significantly improve GAD symptoms and QoL as compared to the placebo; nevertheless, it was safe and well tolerated in this patient population. However, our results should be interpreted and translated into clinical practice with caution, owing to the limited number of RCTs included in the present meta-analysis.

Acknowledgments We thank Editage (www.editage.cn) for editing the English text of a draft of this manuscript.

Contributors BQ, GH, QY and MY were involved in conceptualisation and design of the study and critical review of the manuscript. BQ, GH and MY performed the data extraction. BQ, MZ, HC and WG conceived the study and reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Data sharing statement Additional data can be requested by emailing lzrmyyymx@126.com.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5), Fifth Edition. Washington, DC: American Psychiatric Association; 2013.
2. Tyrer P, Baldwin D. Generalised anxiety disorder. Lancet 2006; 368: 2156-2166.
3. Cuijpers P, Sijbrandij M, Koole S, et al. Psychological treatment of generalized anxiety disorder: a meta-analysis. Clin Psychol Rev 2014; 34: 130-140.
4. Yonkers KA, Dyck IR, Warshaw M, et al. Factors predicting the course of generalised anxiety disorder. Br J Psychiatry 2000; 176: 544-549.
5. Ngo CQ, Phan PT, Vu GV, et al. Effects of Different Comorbidities on Health-Related Quality of Life among Respiratory Patients in Vietnam. J Clin Med 2019; 8. pii: E214.
6. Nguyen SH, Nguyen LH, Vu GT, et al. Health-Related Quality of Life Impairment among Patients with Different Skin Diseases in Vietnam: A Cross-Sectional Study. Int J Environ Res Public Health 2019; 16. pii: E305.
7. De Berardis D, Olivieri L, Nappi F, et al. Vortioxetine and Aripiprazole Combination in Treatment-Resistant Obsessive-Compulsive Disorder: A Case Report. J Clin Psychopharmacol 2017; 37: 732-734.
8. Lu Y, Ho CS, McIntyre RS, et al. Effects of vortioxetine and fluoxetine on the level of Brain Derived Neurotrophic Factors (BDNF) in the hippocampus of chronic unpredictable mild stress-induced depressive rats. Brain Res Bull 2018; 142: 1-7.
9. Pae CU, Wang SM, Han C, et al. Vortioxetine: a meta-analysis of 12 short-term, randomized, placebo-controlled clinical trials for the treatment of major depressive disorder. J Psychiatry Neurosci 2015; 40: 174-186.
10. Berhan A, Barker A. Vortioxetine in the treatment of adult patients with major depressive disorder: a meta-analysis of randomized double-blind controlled trials. BMC Psychiatry 2014; 14: 276.
11. Fu J, Chen Y. The efficacy and safety of 5 mg/d vortioxetine compared to placebo for major depressive disorder: a meta-analysis. Psychopharmacology (Berl) 2015; 232: 7-16.
12. Tran BX, Ha GH, Vu GT, et al. Indices of Change, Expectations, and Popularity of Biological

Treatments for Major Depressive Disorder between 1988 and 2017: A Scientometric Analysis. Int J Environ Res Public Health 2019; 16. pii: E2255.

13. Bidzan L, Mahableshwarkar AR, Jacobsen P, et al. Vortioxetine (Lu AA21004) in generalized anxiety disorder: results of an 8-week, multinational, randomized, double-blind, placebo-controlled clinical trial. Eur Neuropsychopharmacol 2012; 22: 847-857.

14. Mahableshwarkar AR, Jacobsen PL, Serenko M, et al.A randomized, double-blind, fixed-dose study comparing the efficacy and tolerability of vortioxetine 2.5 and 10mg in acute treatment of adults with generalized anxiety disorder. Hum Psychopharmacol 2014; 29: 64-72.

15. Mahableshwarkar AR, Jacobsen PL, Chen Y, et al. A randomised, double-blind, placebo controlled, duloxetine-referenced study of the efficacy and tolerability of vortioxetine in the acute treatment of adults with generalised anxiety disorder. Int J Clin Pract 2014; 6: 49-59.

16. Rothschild AJ, Mahableshwarkar AR, Jacobsen P, et al. Vortioxetine (Lu AA21004) 5 mg in generalized anxiety disorder: results of an 8-week randomized, double-blind, placebo-controlled clinical trial in the United States. Eur Neuropsychopharmacol 2012; 22: 858-866.

17. Baldwin DS, Florea I, Jacobsen PL, et al. A meta-analysis of the efficacy of vortioxetine in patients with major depressive disorder (MDD) and high levels of anxiety symptoms. J Affect Disord 2016; 206: 140-150.

18. Pae CU, Wang SM, Han C, et al. Vortioxetine, multimodal antidepressant for generalized anxiety disorder: a systematic review and meta-analysis. J Psychiatr Res 2015; 64: 88-98.

19. Yee A, Ng CG, Seng LH. Vortioxetine Treatment for Anxiety Disorder: A Meta-Analysis Study. Curr Drug Targets 2017; 19: 1412-1423.

20. Fu J, Peng L, Li X. The efficacy and safety of multiple doses of vortioxetine for generalized anxiety disorder: a meta-analysis. Neuropsychiatr Dis Treat 2016; 12: 951-959.

21. Choo CC, Chew PKH, Ho CS, et al. Quality of Life in Patients With a Major Mental Disorder in Singapore. Front Psychiatry 2019; 9: 727.

22. Lee Y, Rosenblat JD, Lee J, et al. Efficacy of antidepressants on measures of workplace functioning in major depressive disorder: A systematic review. J Affect Disord 2018; 227: 406-415.

23. Bourland SL, Stanley MA, Synder AG, et al. Quality of life in older adults with generalized anxiety

disorder. Aging. And Mental Health 2000; 4: 315-323.

24. Frisch MB. Manual and treatment guide for the Quality of Life Inventory. Minneapolis: National Computer Systems Inc; 1994.

25. Katschnig H. How useful is the concept of quality of life in psychiatry? In: Katschnig H, Freeman H, Sartorius N. (Editors), Quality of life in mental disorders. Chichester: Wiley; 1997. p 3-16.

26. Steven EH. Bridging science and service: A report by the National Advisory Mental Health Council's Clinical Treatment and Services Research Workgroup (NIH Publication No. 99–4353). Rockville: Diane Pub Co; 1999.

27. Zhou X, Keitner GI, Qin B, et al. Atypical Antipsychotic Augmentation for Treatment-Resistant Depression: A Systematic Review and Network Meta-Analysis. Int J Neuropsychopharmacol 2015; 18: pyv060.

28. Mogotsi M, Kaminer D, Stein DJ. Quality of life in the anxiety disorders. Harvard Rev Psychiat 2000; 8: 273-282.

29. Henning ER, Turk CL, Mennin DS, et al. Impairment and quality of life in individuals with generalized anxiety disorder. Depress Anxiety 2007; 24: 342-349.

30. Endicott J, Russell JM, Raskin J, et al. Duloxetine treatment for role functioning improvement in generalized anxiety disorder: three independent studies. J Clin Psychiatry 2007; 68: 518-524.

31. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 updated March 2011. Available at: http://www.cochrane-handbook.org. Accessed November 13, 2018.

32. Moher D, Liberati A, Tetzlaff J, et al. Reprint--preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Phys Ther 2009; 89: 873-880.

33. Testa MA, Simonson DC. Assessment of quality-of-life outcomes. N Engl J Med 1996; 334: 835-840.

34. Urbach DR. Measuring quality of life after surgery. Surg Innov 2005; 12: 161-165.

35. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). Med Care 1992; 30: 473-483.

36. Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. Int Clin

Psychopharmacol 1996; 11: 89-95.

37. Higgins J, Thompson S, Deeks J, et al. Statistical heterogeneity in systematic reviews of clinical trials: a critical appraisal of guideline and practice. J Health Serv Res Policy 2002; 7: 51-61.

38. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-660.

39. Ho RC, Ong HS, Kudva KG, et al. How to critically appraise and apply meta-analyses in clinical practice. Int J Rheum Dis 2010; 13: 294-299.

40. Egger M, Davey Smith G, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-634.

41. Fu J, Peng L, Li X. The efficacy and safety of multiple doses of vortioxetine for generalized anxiety disorder: a meta-analysis. Neuropsychiatr Dis Treat 2016; 12: 951-959.

42. Khan A, Khan S, Brown WA. Are placebo controlsnecessary to test new antidepressants and anxiolytics? Int J Neuropsychopharmacol 2002; 5: 193–197.

43. Liebowitz MR, Stein MB, Tancer M, et al. A randomized, double-blind, fixed-dose comparison of paroxetine and placebo in the treatment of generalized social anxiety disorder. J Clin Psychiatry. 2002;63(1): 66–74.

44. Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 2006; 163(1): 28-40.

45. Florea I, Loft H, Danchenko N, et al. The effect of vortioxetine on overall patient functioning in patients with major depressive disorder. Brain Behav 2017; 7: e00622.

46. Christensen MC, Loft H, Florea I, et al. Efficacy of vortioxetine in working patients with generalized anxiety disorder. CNS Spectr 2017. https://doi: 10.1017/S1092852917000761.

47. Baldwin DS, Loft H, Florea I. Lu AA21004, a multimodal psychotropic agent, in the prevention of relapse in adult patients with generalized anxiety disorder. Int Clin Psychopharmacol 2012; 27: 197-207.2

48. Perna G, Alciati A, Riva A, et al. Long-Term Pharmacological Treatments of Anxiety Disorders: An Updated Systematic Review. Curr Psychiatry Rep 2016; 18: 23.

Table 1. Description of included studies.

Study	Patients n	Age (mean, SD)	Sex (Male, n, %)	Interventions	Duration (weeks)	Key inclusion criteria for GAD
Bidzan et al. (2012) [13]	T: 150; C: 151	T: 45.0 (14.1); C: 45.3 (13.5)	T: 47 (31.3); C: 58 (38.4)	T: vtx (5 mg/d); C: placebo	8	DSM-IV-TR, HAM-A ≥20
Mahableshwarkar et al. (2014a) [14]	T: 152, 152; C: 153	T: 40.8 (13.8)' 43.3 (15.0); C: 39.5 (13.5)	T: 49 (32.2), 56 (36.8); C: 48 (31.4)	T: vtx 2.5 mg/d, vtx 10 mg/d; C: placebo	8	DSM-IV-TR, HAM-A ≥20
Mahableshwarkar et al. (2014b) [15]	T: 156, 156, 156; C: 157	T: 39.2 (11.90), 37.7 (11.96), 39.8 (12.33); C: 36.8 (12.12)	T: 47 (30.1), 56 (35.9), 51 (32.7); C: 55 (35)	T: vtx 2.5 mg/d, vtx 5 mg/d, vtx 10 mg/d; C: placebo	8	DSM-IV-TR, HAM-A ≥20
Rothschild et al. (2012) [16]	T: 152; C: 152	T: 41.0 (14.05); C: 41.4 (12.81)	T: 49 (32.2); C: 55 (36.2)	T: vtx 5 mg/d; C: placebo	8	DSM-IV-TR, HAM-A ≥20

Note: T, Treatment group; C, Control group; mg/d, mg/day; GAD, Generalized anxiety disorder; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th edition Text Revision; HAM-A, Hamilton Anxiety Rating; vtx, Vortioxetine.

Figure legends

Figure 1: Odds ratios (ORs) and 95% confidence intervals (CIs) of the individual studies and the pooled data, comparing the response rates between the vortioxetine-treated and placebo groups.
Notes: (A) 2.5-mg/day vortioxetine versus placebo, (B) 5-mg/day vortioxetine versus placebo, and (C) 10-mg/day vortioxetine versus placebo.

Figure 2: Odds ratios (ORs) and 95% confidence intervals (CIs) of the individual studies and the pooled data, comparing the remission rates between the vortioxetine- and placebo groups.
Notes: (A) 2.5-mg/day vortioxetine versus placebo, (B) 5-mg/day vortioxetine versus placebo, and (C) 10-mg/day vortioxetine versus placebo.

Figure 3: Standardized mean differences (SMDs) and 95% confidence intervals (CIs) of the individual studies and the pooled data, comparing the mean change from baseline in total scores on the HAM-A, between the vortioxetine- and placebo groups.
Notes: (A) 2.5-mg/day vortioxetine versus placebo, (B) 5-mg/day vortioxetine versus placebo, and (C) 10-mg/day vortioxetine versus placebo.

Figure 4: Standardized mean differences (SMDs) and 95% confidence intervals (CIs) of the individual studies and the pooled data, comparing the Short Form 36 Health Survey (SF-36) scores between the vortioxetine- and placebo groups.
Notes: (A) 2.5-mg/day vortioxetine versus placebo, (B) 5-mg/day vortioxetine versus placebo, and (C) 10-mg/day vortioxetine versus placebo.

Figure 5: Standardized mean differences (SMDs) and 95% confidence intervals (CIs) of the individual studies and the pooled data, comparing the Sheehan Disability Scale (SDS) scores between the vortioxetine and placebo groups.
Notes: (A) 2.5-mg/day vortioxetine versus placebo, (B) 5-mg/day vortioxetine versus placebo, and (C) 10-mg/day vortioxetine versus placebo.

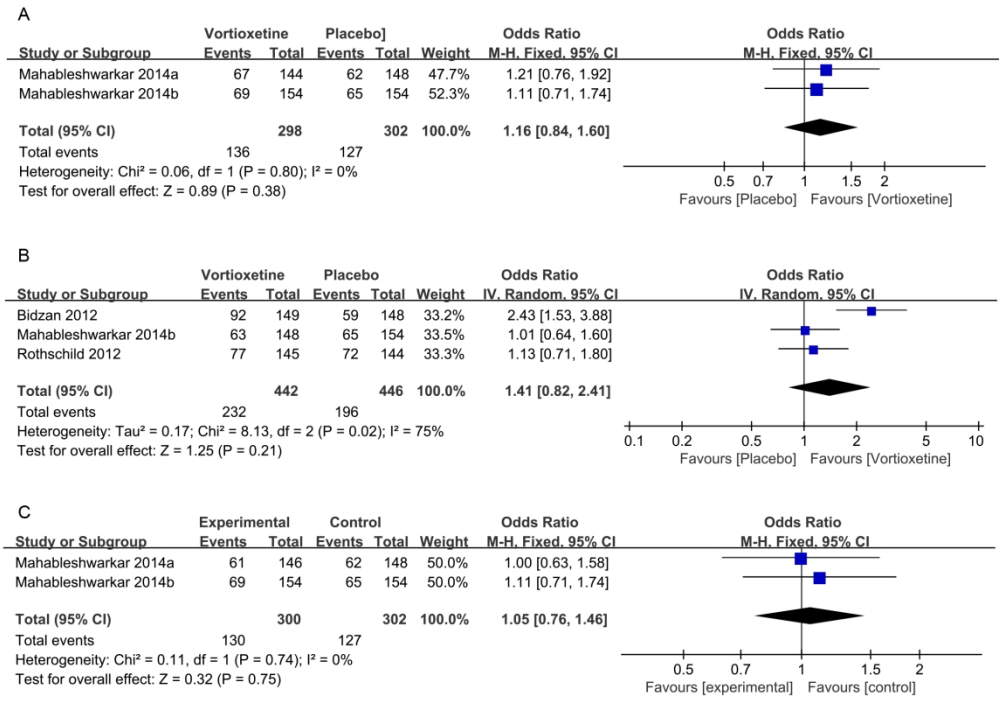

A
Vortioxetine Placebo] Odds Ratio Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% CI
Mahableshwarkar 2014a 67 144 62 148 47.7% 1.21 [0.76, 1.92]
Mahableshwarkar 2014b 69 154 65 154 52.3% 1.11 [0.71, 1.74]
Total (95% CI) 298 302 100.0% 1.16 [0.84, 1.60]
Total events 136 127
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.80); I² = 0%
Test for overall effect: Z = 0.89 (P = 0.38)
0.5 0.7 1 1.5 2
Favours [Placebo] Favours [Vortioxetine]
B
Vortioxetine Placebo Odds Ratio Odds Ratio
Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI IV, Random, 95% CI
Bidzan 2012 92 149 59 148 33.2% 2.43 [1.53, 3.88]
Mahableshwarkar 2014b 63 148 65 154 33.5% 1.01 [0.64, 1.60]
Rothschild 2012 77 145 72 144 33.3% 1.13 [0.71, 1.80]
Total (95% CI) 442 446 100.0% 1.41 [0.82, 2.41]
Total events 232 196
Heterogeneity: Tau² = 0.17; Chi² = 8.13, df = 2 (P = 0.02); I² = 75%
Test for overall effect: Z = 1.25 (P = 0.21)
0.1 0.2 0.5 1 2 5 10
Favours [Placebo] Favours [Vortioxetine]
C
Experimental Control Odds Ratio Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% CI
Mahableshwarkar 2014a 61 146 62 148 50.0% 1.00 [0.63, 1.58]
Mahableshwarkar 2014b 69 154 65 154 50.0% 1.11 [0.71, 1.74]
Total (95% CI) 300 302 100.0% 1.05 [0.76, 1.46]
Total events 130 127
Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² = 0%
Test for overall effect: Z = 0.32 (P = 0.75)
0.5 0.7 1 1.5 2
Favours [experimental] Favours [control]

Figure 1

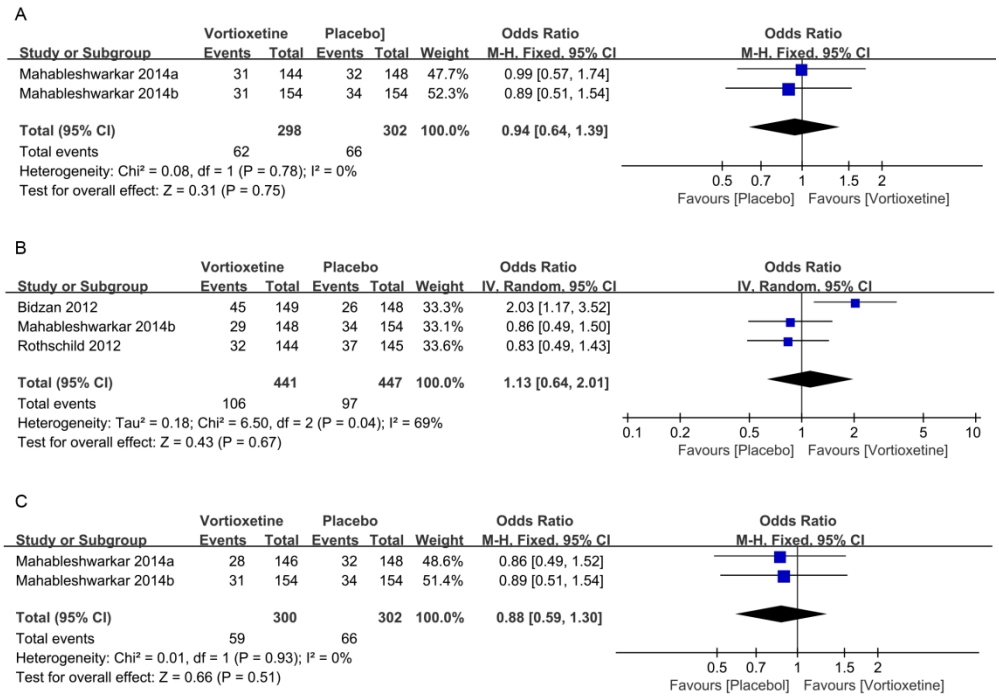

A
Vortioxetine
Placebo]
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Mahableshwarkar 2014a 31 144 32 148 47.7% 0.99 [0.57, 1.74]
Mahableshwarkar 2014b 31 154 34 154 52.3% 0.89 [0.51, 1.54]
Total (95% CI) 298 302 100.0% 0.94 [0.64, 1.39]
Total events 62 66
Heterogeneity: Chi² = 0.08, df = 1 (P = 0.78); I² = 0%
Test for overall effect: Z = 0.31 (P = 0.75)
0.5 0.7 1 1.5 2
Favours [Placebo] Favours [Vortioxetine]
B
Vortioxetine
Placebo
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Bidzan 2012 45 149 26 148 33.3% 2.03 [1.17, 3.52]
Mahableshwarkar 2014b 29 148 34 154 33.1% 0.86 [0.49, 1.50]
Rothschild 2012 32 144 37 145 33.6% 0.83 [0.49, 1.43]
Total (95% CI) 441 447 100.0% 1.13 [0.64, 2.01]
Total events 106 97
Heterogeneity: Tau² = 0.18; Chi² = 6.50, df = 2 (P = 0.04); I² = 69%
Test for overall effect: Z = 0.43 (P = 0.67)
0.1 0.2 0.5 1 2 5 10
Favours [Placebo] Favours [Vortioxetine]
C
Vortioxetine
Placebo
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Mahableshwarkar 2014a 28 146 32 148 48.6% 0.86 [0.49, 1.52]
Mahableshwarkar 2014b 31 154 34 154 51.4% 0.89 [0.51, 1.54]
Total (95% CI) 300 302 100.0% 0.88 [0.59, 1.30]
Total events 59 66
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.93); I² = 0%
Test for overall effect: Z = 0.66 (P = 0.51)
0.5 0.7 1 1.5 2
Favours [Placebo] Favours [Vortioxetine]

Figure 2

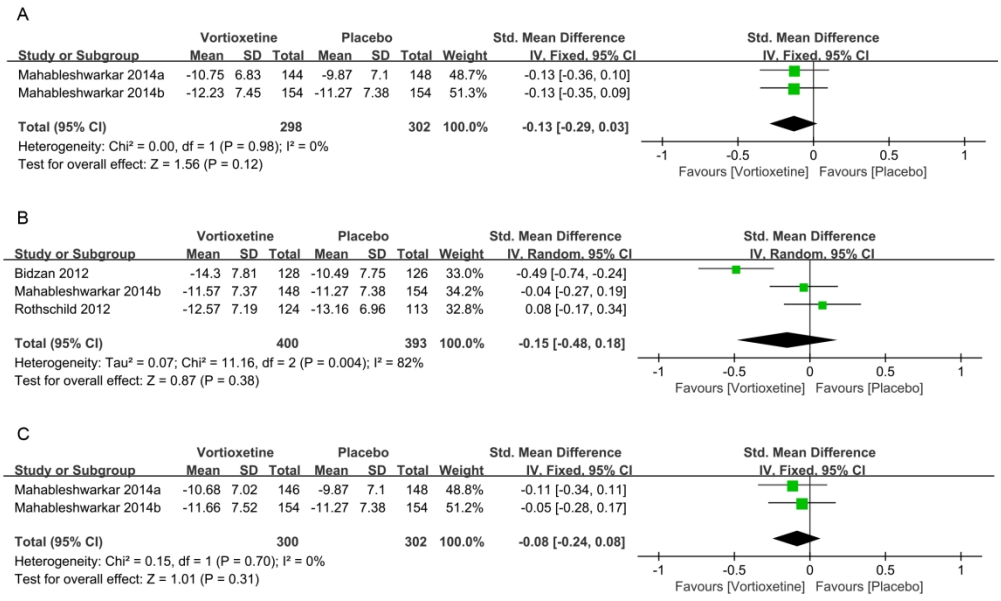

A
Vortioxetine
Placebo
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI
IV, Fixed, 95% CI
Mahableshwarkar 2014a -10.75 6.83 144 -9.87 7.1 148 48.7% -0.13 [-0.36, 0.10]
Mahableshwarkar 2014b -12.23 7.45 154 -11.27 7.38 154 51.3% -0.13 [-0.35, 0.09]
Total (95% CI) 298 302 100.0% -0.13 [-0.29, 0.03]
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.98); I² = 0%
Test for overall effect: Z = 1.56 (P = 0.12)
-1 -0.5 0 0.5 1
Favours [Vortioxetine] Favours [Placebo]
B
Vortioxetine
Placebo
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Bidzan 2012 -14.3 7.81 128 -10.49 7.75 126 33.0% -0.49 [-0.74, -0.24]
Mahableshwarkar 2014b -11.57 7.37 148 -11.27 7.38 154 34.2% -0.04 [-0.27, 0.19]
Rothschild 2012 -12.57 7.19 124 -13.16 6.96 113 32.8% 0.08 [-0.17, 0.34]
Total (95% CI) 400 393 100.0% -0.15 [-0.48, 0.18]
Heterogeneity: Tau² = 0.07; Chi² = 11.16, df = 2 (P = 0.004); I² = 82%
Test for overall effect: Z = 0.87 (P = 0.38)
-1 -0.5 0 0.5 1
Favours [Vortioxetine] Favours [Placebo]
C
Vortioxetine
Placebo
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI
IV, Fixed, 95% CI
Mahableshwarkar 2014a -10.68 7.02 146 -9.87 7.1 148 48.8% -0.11 [-0.34, 0.11]
Mahableshwarkar 2014b -11.66 7.52 154 -11.27 7.38 154 51.2% -0.05 [-0.28, 0.17]
Total (95% CI) 300 302 100.0% -0.08 [-0.24, 0.08]
Heterogeneity: Chi² = 0.15, df = 1 (P = 0.70); I² = 0%
Test for overall effect: Z = 1.01 (P = 0.31)
-1 -0.5 0 0.5 1
Favours [Vortioxetine] Favours [Placebo]

Figure 3

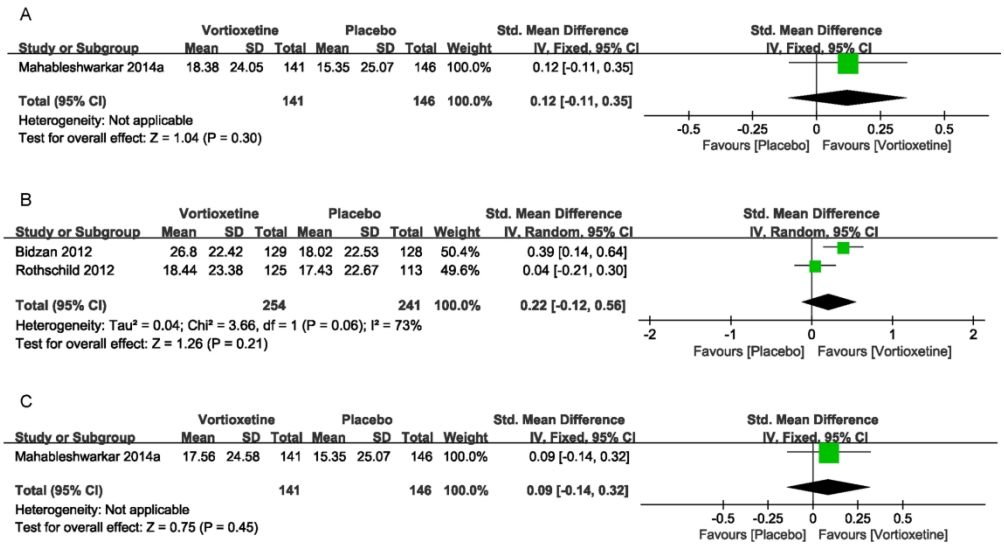


Figure 4

197x108mm (300 x 300 DPI)

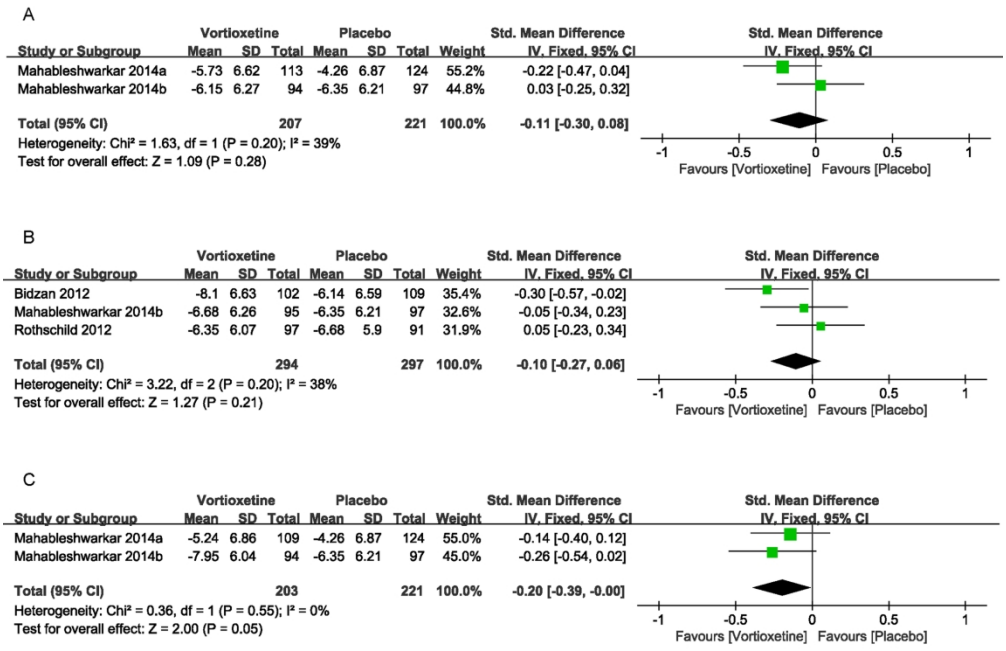
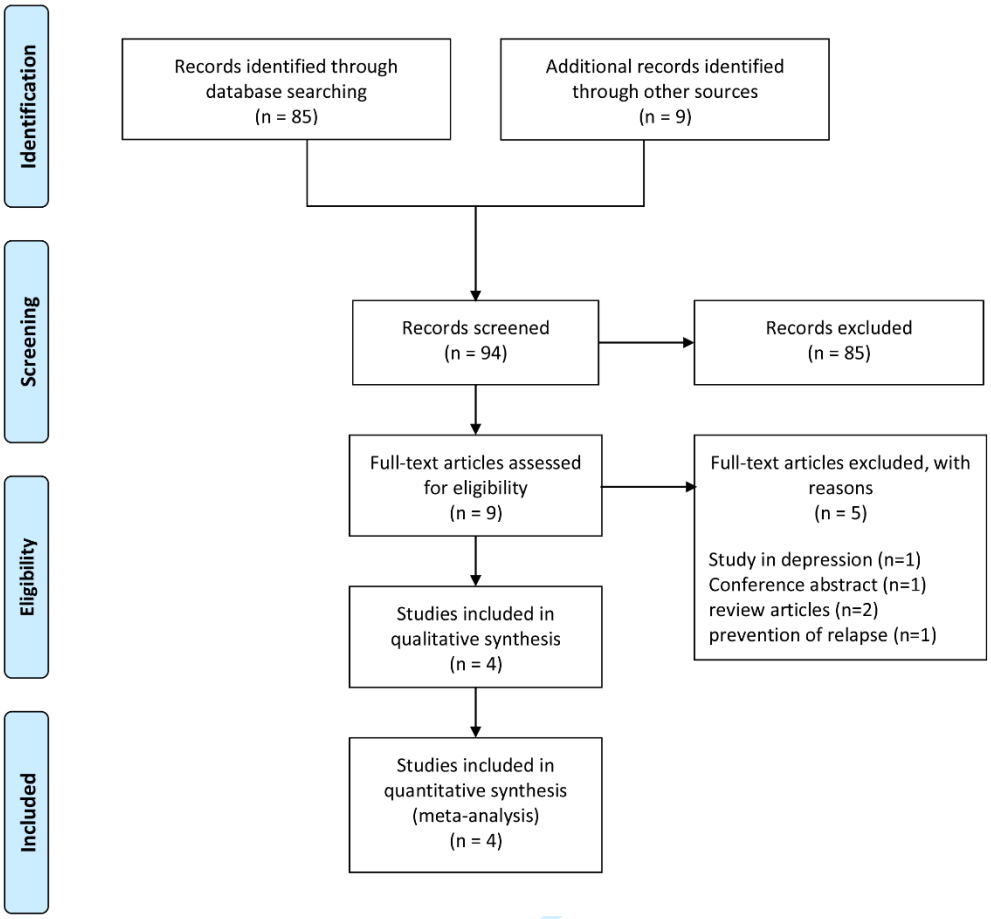
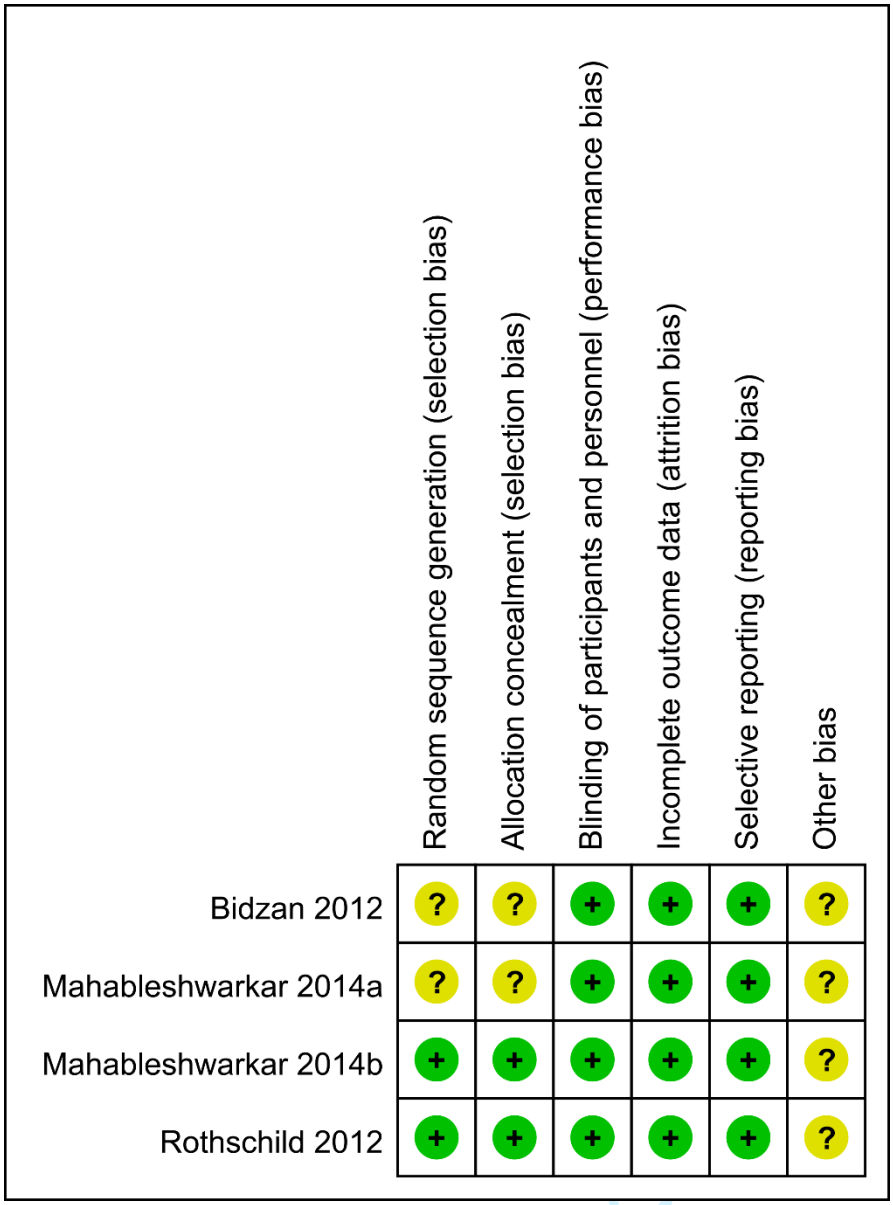


Figure 5

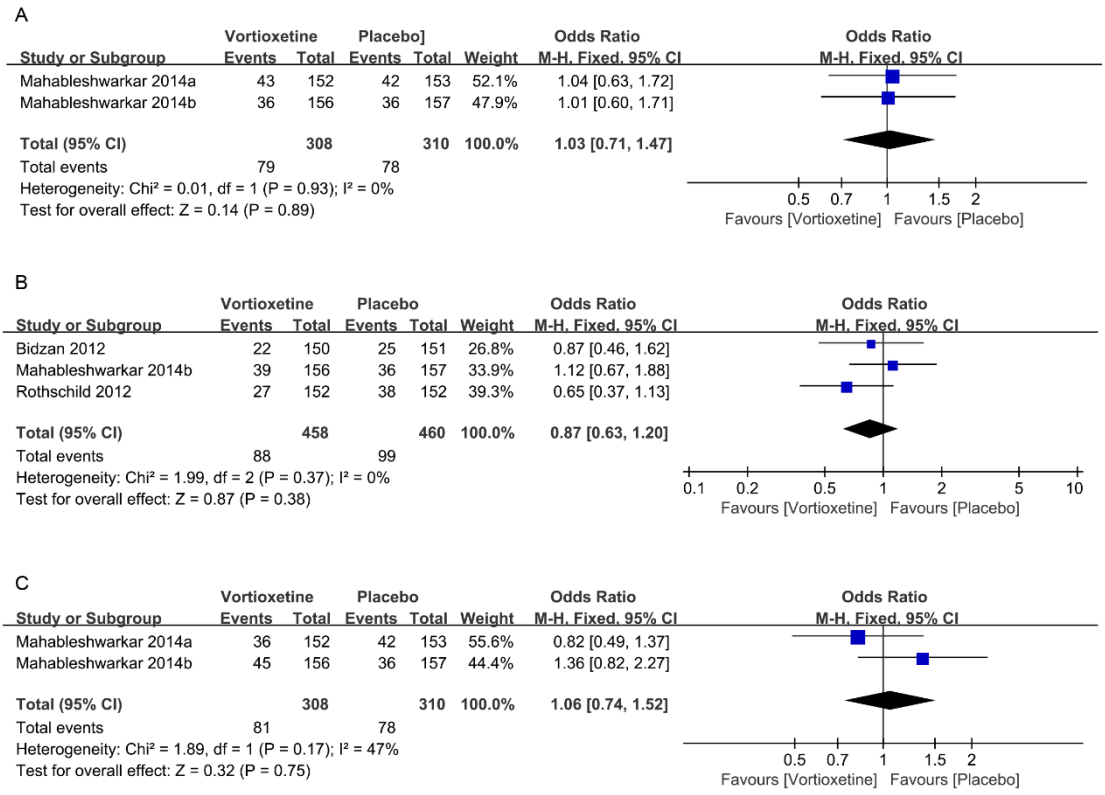
196x128mm (300 x 300 DPI)



e-Figure 1: Search flow for the trial identification and selection process.

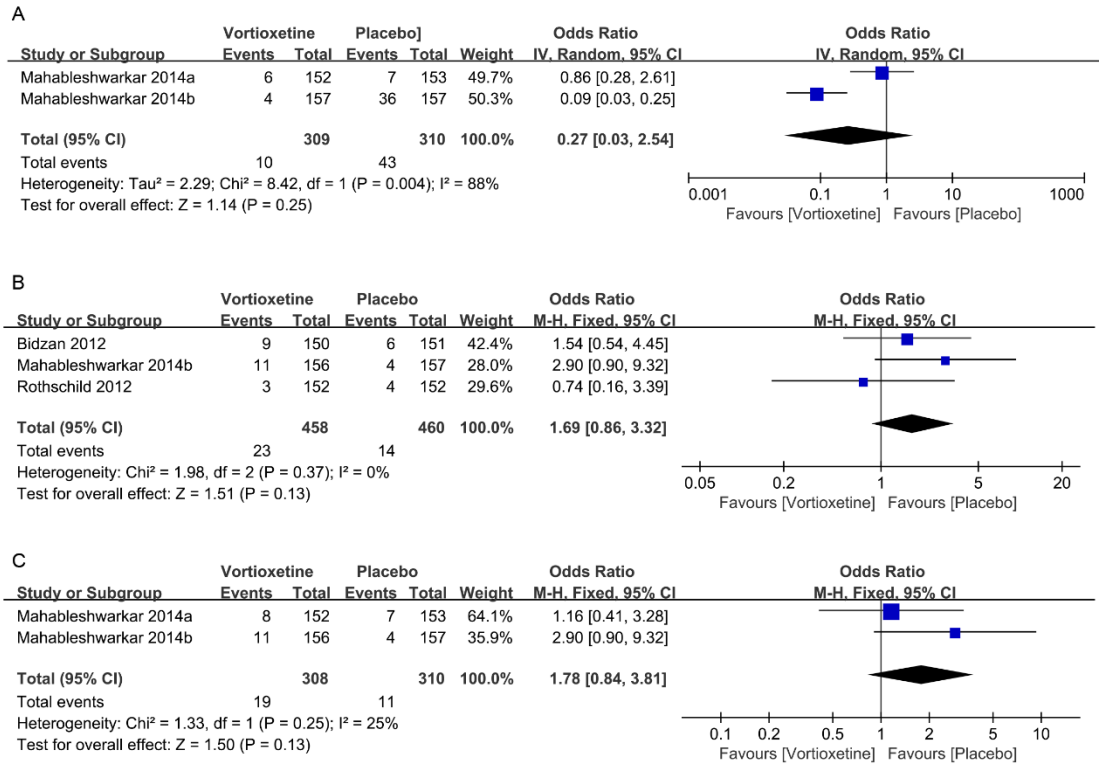


e-Figure 2: Summarized risks of bias for the included studies.



e-Figure 3: Odds ratios (ORs) and 95% confidence intervals (CIs) of the selected studies and the pooled data, comparing the discontinuation rates for any reason, between the vortioxetine and placebo groups.

Notes: (A) 2.5-mg/day vortioxetine versus placebo, (B) 5-mg/day vortioxetine versus placebo, and (C) 10-mg/day vortioxetine versus placebo.



e-Figure 4: Odds ratios (ORs) and 95% confidence intervals (CIs) of the selected studies and the pooled data, comparing the discontinuation rates due to adverse events (AEs), between vortioxetine and placebo groups.

Notes: (A) 2.5-mg/day vortioxetine versus placebo, (B) 5-mg/day vortioxetine versus placebo, and (C) 10-mg/day vortioxetine versus placebo.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3-4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4-5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5-6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5-6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7-8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8-9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	10

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

BMJ Open

Vortioxetine Treatment for Generalized Anxiety Disorder: A Meta-Analysis of Anxiety, Quality of Life, and Safety Outcomes

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-033161.R2
Article Type:	Original research
Date Submitted by the Author:	17-Oct-2019
Complete List of Authors:	Bin, Qin; Affiliated Liuzhou General Hospital of Guangxi University of Science and Technology Huang, Guangsu; Affiliated Liuzhou General Hospital of Guangxi University of Science and Technology, Department of Neurology Yang, Qian; Affiliated Liuzhou General Hospital of Guangxi University of Science and Technology, Department of Neurology Zhao, Mingjun; The Second Affiliated Hospital of Xinxiang Medical University Chen, Hong; Affiliated Liuzhou General Hospital of Guangxi University of Science and Technology, Department of Neurology Gao, Wen; Affiliated Liuzhou General Hospital of Guangxi University of Science and Technology, Department of Neurology Yang, Mingxiu; Affiliated Liuzhou General Hospital of Guangxi University of Science and Technology, Department of Neurology
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Pharmacology and therapeutics, Mental health
Keywords:	Multimodal therapy, Generalized anxiety disorder, Vortioxetine, Meta-analysis

Vortioxetine Treatment for Generalized Anxiety Disorder: A Meta-Analysis of Anxiety, Quality of Life, and Safety Outcomes

Bin Qin,[1] Guangsu Huang,[1] Qian Yang,[1] Mingjun Zhao,[2] Hong Chen,[1] Wen Gao,[1] Mingxiu Yang[1]

Author affiliations

[1]Department of Neurology, Affiliated Liuzhou General Hospital of Guangxi University of Science and Technology (Liuzhou General Hospital), Liuzhou 545006, Guangxi, China,

[2]Department of Pharmacy, The Second Affiliated Hospital of Xinxiang Medical University (Henan Mental Hospital), Xinxiang 453000, China.

Correspondence to Professor Mingxiu Yang; lzrmyyymx@126.com.

Bin Qin, Guangsu Huang and Qian Yang contributed equally to this study

Abstract:

Objectives The aim of this study was to investigate the efficacy, tolerability, safety, and impact on quality of life (QoL) and functional status of vortioxetine treatment for patients with generalized anxiety disorder (GAD) by performing a meta-analysis of randomized controlled trials.

Design Systematic review and meta-analysis.

Data sources Data mining was conducted in January 2019 across PubMed, EMBASE, PsycINFO, Cochrane Central Register of Controlled Trials Cochrane Library, Web of science, and ClinicalTrials.gov.

Eligibility criteria for selecting studies All published Randomized controlled trials (RCTs) which assessed the effect of vortioxetine treatment for patients with GAD when compared with a placebo group were included.

Data extraction and synthesis Relevant data was extracted and synthesized narratively. Results were expressed as standardized mean differences (SMDs) or odds ratios (ORs) with 95% confidence intervals (CIs).

Results Our meta-analysis showed that multiple doses (2.5, 5, and 10 mg/day) of vortioxetine did not significantly improve the response rates, compared to placebo (OR = 1.16, 95% CI=0.84–1.60, P=0.38; OR = 1.41, 95% CI=0.82–2.41, P=0.21; and OR = 1.05, 95% CI=0.76–1.46, P=0.75). Moreover, there was no statistically significant difference regarding the remission rates, discontinuation for any reason rates, discontinuation due to adverse events rates, Short Form 36 Health Survey scores, or Sheehan Disability Scale scores between administration of multiple doses (2.5, 5, and 10 mg/day) of vortioxetine and placebo.

Conclusions Although our results suggest that vortioxetine did not improve the generalized anxiety disorder symptoms, QoL and functional status impairment of patients with GAD, it was safe and well tolerated. Clinicians should interpret and translate our data with caution, as the meta-analysis was based on a limited number of randomized controlled trials.

Keywords: Multimodal therapy; Generalized anxiety disorder; Vortioxetine; Meta-analysis

Word count: 3548.

Strengths and limitations of this study

► This systematic review and meta-analysis provides evidence for the efficacy, tolerability, and safety of vortioxetine in treatment of patients with generalized anxiety disorder

► Improvement of quality of life and functional status impairment were also evaluated to judge the patients' well-being of vortioxetine.

►Strong and reliable methodological and statistical procedures were applied.

► Due to the short-term follow-up in the evaluated studies, the long-term effect was not studied.

Introduction

Generalized anxiety disorder (GAD) is a common, chronic, costly, and disabling mental disorder which is marked by persistent anxiety and worry, and multiple psychological and physical symptoms.[1,2] It is also characterized by various psychological and somatic complaints, such as autonomic arousal, restlessness, fatigue, problems with concentration, irritability, and sleeplessness.[1] The estimated 1-year prevalence rate of GAD is between 1.2% and 1.9%, and the lifetime prevalence is between 4.3% and 5.9%.[2,3] Since most patients are still affected for 6 to 12 years after diagnosis, GAD is usually considered a chronic disorder and a major burden on the individual, their family, and health care services.[2,4] Anxiety is a common comorbidity of chronic medical diseases including actopic dermatitis, asthma, rheumatoid arthritis, lupus and stroke. Anxiety has a negative impact on the quality of life of patients suffer from chronic diseases.[5,6]

Vortioxetine is a multimodal antidepressant that was approved for the treatment of major depressive disorder (MDD), by the US Food and Drug Administration (FDA) in September 2013. Vortioxetine's 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, and thereby with potential benefits in the treatment of major depressive episode and, probably, GAD and anxiety disorders.[7] In addition, vortioxetine cause significant increase in the hippocampal Brain Derived Neurotrophic Factors levels as compared with selective serotonin reuptake inhibitors.[8] Several meta-analyses have proved the efficacy of vortioxetine in treatment of MDD.[9-11] A recent scientometric analysis reported that the popularity of vortioxetine is rising.[12] Clinical trials evaluating its efficacy for the treatment of GAD, with doses up to 10 mg/day, have also yielded some interesting findings.[13-16] Moreover, as vortioxetine has been proven to be efficient in the treatment of MDD comorbid with GAD, it is possible that it constitutes an effective treatment for GAD alone, as well.[17]

Interestingly, the efficacy of vortioxetine therapy in reducing anxiety symptom severity in GAD is summarized in two previous meta-analyses.[18,19] Both reviews analyzed its efficacy only in terms of symptom severity on the underlying continuous rating scales, and did not assess dichotomous outcomes of response and remission rates. However, a recent meta-analysis examined the efficacy of multiple doses of vortioxetine in terms of dichotomous response outcomes, and the results showed no significant improvement in the outcomes of treating GAD with vortioxetine compared to treating GAD with placebo.[20] The efficacy was only assessed using continuous rating scales or dichotomous response; thus, the authors of these meta-analyses and of a relevant narrative review noted that a comprehensive summary of efficacy data is missing. Further, both these reviews only provided an assessment of efficacy and safety outcomes, and did not include important outcomes of patient-focused assessments, such as assessment of functional impairment and quality of life (QoL). Currently there is growing interest in assessing the QoL and functional status impairment in patients with psychological disorders.[21,22] In addition, the importance of including such assessments in evaluations of the influence of psychological disorders and their treatment, is widely recognized.[23-26] Our previous network meta-analysis concluded that risperidone and aripiprazole improved the QoL of patients with treatment-resistant depression.[27] Despite the growing interest in the

field, studies addressing the impairment of QoL and functional status caused by anxiety disorders have progressed slowly.[28] Moreover, GAD is an important public mental health problem that causes poor QoL and functional status impairment,[23] with substantial impact on work and social roles.[29] Thus, the outcome of post-treatment QoL assessments is recognized as an important measure of treatment efficacy for patients with GAD.[30]

The assessment of antianxiety therapy benefits on QoL and functional status impairment in patients with GAD is becoming increasingly common in clinical studies, mainly because, both aspects are important for the patients' overall well-being and recovery. Currently, the direct effect of vortioxetine treatment on QoL and functional status impairment in patients with GAD is unclear. Therefore, this meta-analysis was conducted to provide a comprehensive estimate of the efficacy, safety, and improving QoL and functional status impairment profiles of vortioxetine in treatment of GAD.

Methods

All steps of this review were performed in strict accordance with the Cochrane Handbook for Systematic Reviews of Interventions.[31] The PRISMA statement guidelines were followed during the meta-analysis and preparation of this review.[32]

Search strategy

As of January 2019, we searched PubMed, EMBASE, PsycINFO, Cochrane Central Register of Controlled Trials (Cochrane Library), Web of science, and ClinicalTrials.gov (www.clinicaltrials.gov). Search terms included "vortioxetine OR Lu AA21004" OR Brintellix'' AND "anxiety OR anxiety disorder OR anxiety disorders OR mood disorder OR mood disorders." (Supplementary Table 1) No language or time restrictions were applied. Titles and abstracts were screened by two independent reviewers, before full texts of potentially relevant articles were retrieved for further evaluation. The decision to include a study was then made by two independent reviewers (BQ and WG), after full-text review. The reference lists of included articles were further hand-searched to identify additional relevant articles.

Eligibility Criteria and Study Selection

We included all clinical trials meeting the following criteria: (a) randomized controlled trials (RCTs) involving patients (≥18 years old) primarily diagnosed with GAD, according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR), and (b) RCTs comparing outcomes in efficacy, QoL, and functional impairment between vortioxetine and placebo. We excluded (a) retrospective and observational studies; (b) non-human studies; (c) theses and conference abstracts; and (d) studies including patients that had any concurrent psychiatric disorders with GAD or any prior history of psychiatric disorders, such as manic or hypomanic episodes, schizophrenia, or substance use disorders. Eligibility screening was performed in two steps, each by two independent reviewers (BQ and WG): (a) title and abstract screening for relevance to the study objective, and (b) full text screening for

eligibility for a meta-analysis. Conflicts were resolved by the opinion of a third reviewer (MY).

Outcomes

Efficacy measures

Response was defined across studies as a 50% improvement of the Hamilton Anxiety Rating Scale (HAM-A) total score from baseline to end point. Remission was defined as a HAM-A total score of ≤7 at the study end point. The continuous measure of efficacy was the mean change from baseline in total scores on the HAM-A, as defined by the individual study.

Safety and tolerability measures

Data on the discontinuation for any reason (tolerability) and the numbers of discontinuation due to adverse events (AEs) (safety) were included in the analysis.

QoL and functioning measures

QoL can be assessed by study-designed questionnaires and disease-specific or generic instruments. These instruments assess an individual's physical, emotional, psychological, and social health.[33,34] We selected the Short Form 36 Health Survey (SF-36) [35] scores as the outcome indicator for QoL to preserve sufficient homogeneity for meta-analysis, because this instrument is used to measure QoL for the GAD population in many studies. Studies were excluded if the QoL outcome was reported by the other rating scales. The Sheehan Disability Scale (SDS),[36] a reliable, valid, brief, self-report scale that assesses disability in work, social, and family life, is the only measure of functional impairment employed by the trials included in this meta-analysis.

Data Extraction

Two independent reviewers (BQ and WG) extracted the following data from the included studies: (a) baseline characteristics of enrolled patients, (b) general characteristics of the study design, (c) information on efficacy, safety, tolerability, QoL, and functioning outcome. Data were summarized by one investigator and checked by a second reviewer. Any discrepant data were, again, examined by a third reviewer (MY), to ensure accurate data were obtained.

Risk of Bias Assessment

The risk of bias within each study was assessed by two independent reviewers (BQ and WG) using the Cochrane Risk of Bias assessment tool, as described in the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0.[31] This tool classifies the studies as having low, unclear, or high risk of bias across six domains: sequence generation, allocation concealment, blinding, missing data, selective reporting, and other biases.

Data Analysis

The meta-analysis was conducted using RevMan 5.3 software (Cochrane Collaboration, London, UK) and Stata 13.0 software (StataCorp LP, College Station, TX, USA). Odds ratios (ORs) and 95% CIs were used to assess binary outcomes, such as response, remission rates, as well as discontinuation for any reason rates. In addition, we converted continuous data to standardized mean differences (SMDs) and 95% CIs. The statistical heterogeneity among trials was measured by Q statistics and the I^2 test. Higher I^2 values indicate greater heterogeneity, with I^2 values of 25, 50, and 75% signifying mild, moderate, and high heterogeneity, respectively. [37,38] Based on heterogeneity, data were pooled to estimate the overall effect of all the interventions by random-effect or fixed-effect modelling. Fixed-effect models assume that the population effect sizes are the same for all studies. In contrast, random-effects model attempted to generalize findings beyond the included studies by assuming that the selected studies are random samples from a larger population.[39] Sensitivity analyses were performed to test the impact robustness of every single study on the overall results. Publication bias could be assessed by visual inspection of a funnel plot, and the Egger test was also used to evaluate publication biases. However, according to Egger and colleagues, assessing publication bias using the funnel plot-based methods is not reliable when fewer than 10 pooled studies are used in the direct comparison.[40]

Patient and public involvement

Patients or the public were not involved in the conceptualisation or carrying out of this research.

Results

Search results

We identified 94 references from the electronic literature search. After screening the titles and abstracts, 85 were excluded because they failed to meet the inclusion criteria. By reading the full text of the remaining nine articles, five more were excluded: one study included patients with depression, one study focused on vortioxetine in the prevention of relapse of GAD, another one constituted a conference abstract and did not provide treatment outcomes, and two studies were eliminated because they were review articles. Ultimately, only four studies that fully satisfied the pre-established inclusion criteria of this meta-analysis were included (see Supplementary Figure 1).[13-16]

Study Characteristics

Four included studies were published between 2012 and 2014 (Table 1).[13-16] The collective patient population comprised 1074 individuals in the vortioxetine group and 613 individuals in the placebo group. The administered doses of vortioxetine were 2.5, 5, and 10 mg/day. The mean age of participants ranged from 36.8 to 45.3 years. All studies were characterized by a preponderance of female subjects, with proportions ranging from 60 to 70%. The main characteristics of these studies are presented in Table 1.

Study Quality

The risks of bias in each study is summarized in Supplementary Figure 2. All studies claimed randomization and three articles described the method of random sequence generation (random number table, computer generated). Three trials provided information that allowed us to assess whether an adequate concealment of the allocation procedure was used. All studies reported the blinding of participants. Therefore, all trials were deemed to have a mild-to-moderate risk of bias.

Efficacy

In terms of response, a total of four studies were included in the analysis; the overall ORs observed for groups treated with multiple doses (2.5, 5, and 10 mg/day) of vortioxetine compared to placebo were 1.16 (95% CI=0.84–1.60, Z=0.89, P=0.38), 1.41 (95% CI=0.82–2.41, Z=1.25, P=0.21), and 1.05 (95% CI=0.76–1.46, Z=0.32, P=0.75), respectively (Figure 1). The results showed that there was no statistically significant difference in the response rates among the vortioxetine- and placebo groups. In addition, there was no statistically significant difference for the remission rates in multiple doses (2.5, 5, and 10 mg/d) of vortioxetine compared to placebo (Figure 2).

Pooled effect sizes for the mean change from baseline in total scores on the HAM-A are provided in Figure 3. The overall SMDs observed for the groups treated with multiple doses (2.5, 5, and 10 mg/d) of vortioxetine compared to the placebo were -0.13 (95% CI=-0.29–0.03, Z=1.56, P=0.12), -0.15 (95% CI=-0.48–0.18, Z=0.87, P=0.38), and -0.08 (95% CI=-0.24–0.08, Z=1.01, P=0.31), respectively. The results also showed that there was no statistically significant difference in the mean change from baseline in total scores on the HAM-A among the vortioxetine and placebo groups.

Tolerability and safety

No significant difference was observed between the vortioxetine and placebo groups in terms of the likelihood of discontinuation for any reason (tolerability). The overall ORs observed for the groups treated with multiple doses (2.5, 5, and 10 mg/day) of vortioxetine compared to the placebo-treated group were 1.03 (95% CI=0.71–1.47, Z=0.14, P=0.89), 0.87 (95% CI=0.63–1.20, Z=0.87, P=0.38), and 1.06 (95% CI=0.74–1.52, Z=0.32, P=0.75), respectively (Supplementary Figure 3). Additionally, there was no statistically significant difference in the discontinuation due to AEs (safety) between the groups treated with multiple doses (2.5, 5, and 10 mg/day) of vortioxetine and the group treated with placebo (Supplementary Figure 4).

Quality of life and functional status results

Three studies in this analysis reported SF-36 scores as the outcome measure of QoL. The overall SMDs of groups treated with multiple doses (2.5, 5, and 10 mg/d) of vortioxetine compared to placebo were 0.12

(95% CI=-0.11-0.35, Z=1.04, P=0.30), 0.22 (95% CI=-0.12-0.56, Z=1.26, P=0.21), and 0.09 (95% CI=-0.14-0.32, Z=0.75, P=0.45), respectively (Figure 4). The results showed that there was no statistically significant difference in SF-36 scores among the different groups. SDS scores were available for all four studies included in this analysis. The overall SMDs for the groups treated with multiple doses (2.5, 5, and 10 mg/d) of vortioxetine compared to placebo were -0.11 (95% CI=-0.30-0.08, Z=1.09, P=0.28), -0.10 (95% CI=-0.27-0.06, Z=1.27, P=0.21), and -0.20 (95% CI=-0.39-0.00, Z=2.00, P=0.05), respectively (Figure 5). The results showed that there was no statistically significant difference in SDS among the different groups.

Publication bias

The Egger test showed no significant difference main outcomes, indicating no publication bias.

Discussion

In this meta-analysis of 4 randomized trials studying vortioxetine as a treatment for GAD, we found that vortioxetine (2.5-, 5- and 10-mg once-daily doses) did not significantly improve GAD symptoms, quality of life and functional status compared to a placebo treatment. However, vortioxetine might be safe and well tolerated in this patient population. Our findings have some clinical implications for comprehensively understanding the risk–benefit profiles of vortioxetine treatment for GAD.

Our results are not consistent with those of the previous meta-analysis conducted by Pae et al, as that study found that vortioxetine was significantly more effective than the placebo.[18] In their study, they only performed the analysis of mean change from baseline in total scores on the HAM-A, and included all randomized subjects. However, our meta-analysis was separately conducted according to the doses of vortioxetine, and we assessed the efficacy in terms of mean change from baseline in total scores on the HAM-A, response rates, and remission rates. Doses of vortioxetine may be clinically important factors for its efficacy in GAD patients. Thus, the results of our meta-analysis were more reliable and stable. Moreover, a recent meta-analysis showed that there was no statistically significant difference regarding the response rates among groups treated with either multiple doses (2.5, 5, and 10 mg/day) of vortioxetine or a placebo.[41] Furthermore, the results of our meta-analysis demonstrated no statistically significant difference in the mean change from baseline in total scores on the HAM-A, remission rates, quality of life, and functional status among the groups. Thus, the results of our meta-analysis were more comprehensive.

Several reasons for these outcomes may have contributed to the negative results. A previous analysis of the Food and Drug Administration database concluded that negative results were commonly seen in anxiolytic agents administered for the treatment of anxiety disorders, including GAD, where less than one-half (48%) of the treatment arms were statistically superior to the placebo.[42] In this case, all anxiolytic agents included in the study are approved for GAD treatment in the United States, but only three out of seven treatment arms were separated from the placebo. Moreover, the results some studies have found that negative results[14-16] had a higher placebo response rate than those with positive results.[13,43] Although this

correlation has not been established in GAD, it is reasonable to speculate that an elevated placebo response could reduce the treatment effect. Unfortunately, because no positive control was included in our meta-analysis, it is impossible to determine the lack-of-treatment effect. In addition, the racial diversity may have introduced differences in response and remission rates; for example, the studied population of the trial that showed negative results was racially diverse, whereas the population of the trial that showed positive results was almost entirely Caucasian. Hence, the results of the STAR*D study demonstrate that non-Caucasians were significantly less likely to achieve remission.[44] Furthermore, the mean baseline HAM-A total scores in most of the included studies were relatively high (ranging from 24.5 to 27); inflated baseline HAM-A total scores are a possible consequence of less stringent screening practices. Relative to placebo, vortioxetine treatment, in doses of 10 and 20 mg, demonstrated significant improvement in depressive symptoms, however, the RCTs that were studied, in accordance with those included in our meta-analysis, used the optimal doses of 2.5-10 mg. Higher dosages, such as 20 mg or even more, would be more beneficial in anxiety disorders, whereas lower dosages may unaffect anxiety symptoms. However, it is unlikely that any single reason can explain the inconsistent results observed in the vortioxetine for GAD.

Although our meta-analysis did not demonstrate a statistically significant anxiolytic effect of vortioxetine, it did provide information regarding drug tolerability. Our study found that there was no statistically significant difference for the discontinuation for any reason rates and discontinuation due to AEs rates among groups receiving either multiple doses (2.5, 5, and 10 mg/day) of vortioxetine compared to placebo, which is similar to the findings of a previous meta-analysis.[9,18] Thus, the vortioxetine doses were well tolerated, and were associated with similar discontinuation for any reason rates and discontinuation due to AEs rates when compared to the placebo.

GAD is associated with significant functional impairment in many areas, including social, occupational, and mental consequences; and when combined with physical impairment, together they influence QoL. The effectiveness of GAD treatment for improving QoL and functional outcomes is potentially confounded by the bidirectional relationship of anxiety symptoms and QoL/functional impairment. This is the first meta-analysis to report prospective assessment of QoL/functional status impairment for vortioxetine in treatment of patients with GAD. Unfortunately, our meta-analysis of RCTs with GAD patients showed no significant improvement in the aforementioned aspects after vortioxetine treatment compared to after treatment with the placebo. Our results are not consistent with those of a previous meta-analysis of the effect of vortioxetine treatment on overall functioning in patients with MDD.[45] The meta-analysis, conducted by Florea et al, demonstrated that vortioxetine, in doses of 5-20 mg for 6/8 weeks, improved overall functioning in patients with MDD. Relative to placebo, vortioxetine treatment, in doses of 10 and 20 mg, demonstrated significant improvement in SDS total score and functional remission. However, the RCTs that were studied, in accordance with those included in our meta-analysis, used the optimal doses of 2.5-10 mg. Thus, the reason for the lack of congruence between these two meta-analyses may be the difference in the optimal doses. Meanwhile, a recent meta-analysis of vortioxetine in working patients with GAD,[46] showed that vortioxetine benefits adult patients who are working and/or pursuing an education. Thus,

future research should be directed to provide more RCTs, specifically targeted to individuals with GAD, in order to assess the efficacy of vortioxetine in a larger sample, as well as to define the best therapeutic dosage.

The results of our meta-analysis should be interpreted in light of the following potential limitations. First, we included only four RCTs, which may have influenced the reliability of the results. Second, the duration of each trial included in our meta-analysis was 8 weeks; this is an important issue because GAD patients typically require long-term pharmacological treatment. We found only one study focusing on long-term relapse prevention, which showed no significant improvement of relapse prevention effect after long-term (maintenance) vortioxetine treatment for GAD compared to placebo.[47] Furthermore, the systematic review, conducted by Perna et al, indicated that although some recent data support the long-term efficacy of vortioxetine for GAD and showed a favorable tolerability profile, the conflicting short-term studies and limited clinical experience recommend its use only as second-line therapy.[48] In addition, owing to a limited number of studies included in our meta-analysis, we did not compare the onset time between the groups treated with multiple doses of vortioxetine and placebo. Finally, all the included trials were supported by the Takeda Pharmaceutical Company Ltd. as part of a joint clinical development program with H. Lundbeck A/S, which may have also influenced the results.

Conclusions

In summary, GAD is an illness that is characterized not only by severe anxiety symptoms, but also by diminished functioning and QoL. The challenge for interventions is not only to achieve improvement of symptoms, but also to enhance patients' functioning ability and QoL. Our comprehensive evaluation of efficacy, safety, and impact on QoL provides a critical insight that may be useful for clinicians attempting to thoroughly understand the risk–benefit profiles of vortioxetine treatment for GAD. Vortioxetine did not significantly improve GAD symptoms and QoL as compared to the placebo; nevertheless, it was safe and well tolerated in this patient population. However, our results should be interpreted and translated into clinical practice with caution, owing to the limited number of RCTs included in the present meta-analysis.

Acknowledgments We thank Editage (www.editage.cn) for editing the English text of a draft of this manuscript.

Contributors BQ, GH, QY and MY were involved in conceptualisation and design of the study and critical review of the manuscript. BQ, GH and MY performed the data extraction. BQ, MZ, HC and WG conceived the study and reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Data sharing statement Additional data can be requested by emailing lzrmyyymx@126.com.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5), Fifth Edition. Washington, DC: American Psychiatric Association; 2013.
2. Tyrer P, Baldwin D. Generalised anxiety disorder. Lancet 2006; 368: 2156-2166.
3. Cuijpers P, Sijbrandij M, Koole S, et al. Psychological treatment of generalized anxiety disorder: a meta-analysis. Clin Psychol Rev 2014; 34: 130-140.
4. Yonkers KA, Dyck IR, Warshaw M, et al. Factors predicting the course of generalised anxiety disorder. Br J Psychiatry 2000; 176: 544-549.
5. Ngo CQ, Phan PT, Vu GV, et al. Effects of Different Comorbidities on Health-Related Quality of Life among Respiratory Patients in Vietnam. J Clin Med 2019; 8. pii: E214.
6. Nguyen SH, Nguyen LH, Vu GT, et al. Health-Related Quality of Life Impairment among Patients with Different Skin Diseases in Vietnam: A Cross-Sectional Study. Int J Environ Res Public Health 2019; 16. pii: E305.
7. De Berardis D, Olivieri L, Nappi F, et al. Vortioxetine and Aripiprazole Combination in Treatment-Resistant Obsessive-Compulsive Disorder: A Case Report. J Clin Psychopharmacol 2017; 37: 732-734.
8. Lu Y, Ho CS, McIntyre RS, et al. Effects of vortioxetine and fluoxetine on the level of Brain Derived Neurotrophic Factors (BDNF) in the hippocampus of chronic unpredictable mild stress-induced depressive rats. Brain Res Bull 2018; 142: 1-7.
9. Pae CU, Wang SM, Han C, et al. Vortioxetine: a meta-analysis of 12 short-term, randomized, placebo-controlled clinical trials for the treatment of major depressive disorder. J Psychiatry Neurosci 2015; 40: 174-186.
10. Berhan A, Barker A. Vortioxetine in the treatment of adult patients with major depressive disorder: a meta-analysis of randomized double-blind controlled trials. BMC Psychiatry 2014; 14: 276.
11. Fu J, Chen Y. The efficacy and safety of 5 mg/d vortioxetine compared to placebo for major depressive disorder: a meta-analysis. Psychopharmacology (Berl) 2015; 232: 7-16.
12. Tran BX, Ha GH, Vu GT, et al. Indices of Change, Expectations, and Popularity of Biological

Treatments for Major Depressive Disorder between 1988 and 2017: A Scientometric Analysis. Int J Environ Res Public Health 2019; 16. pii: E2255.

13. Bidzan L, Mahableshwarkar AR, Jacobsen P, et al. Vortioxetine (Lu AA21004) in generalized anxiety disorder: results of an 8-week, multinational, randomized, double-blind, placebo-controlled clinical trial. Eur Neuropsychopharmacol 2012; 22: 847-857.

14. Mahableshwarkar AR, Jacobsen PL, Serenko M, et al.A randomized, double-blind, fixed-dose study comparing the efficacy and tolerability of vortioxetine 2.5 and 10mg in acute treatment of adults with generalized anxiety disorder. Hum Psychopharmacol 2014; 29: 64-72.

15. Mahableshwarkar AR, Jacobsen PL, Chen Y, et al. A randomised, double-blind, placebo controlled, duloxetine-referenced study of the efficacy and tolerability of vortioxetine in the acute treatment of adults with generalised anxiety disorder. Int J Clin Pract 2014; 6: 49-59.

16. Rothschild AJ, Mahableshwarkar AR, Jacobsen P, et al. Vortioxetine (Lu AA21004) 5 mg in generalized anxiety disorder: results of an 8-week randomized, double-blind, placebo-controlled clinical trial in the United States. Eur Neuropsychopharmacol 2012; 22: 858-866.

17. Baldwin DS, Florea I, Jacobsen PL, et al. A meta-analysis of the efficacy of vortioxetine in patients with major depressive disorder (MDD) and high levels of anxiety symptoms. J Affect Disord 2016; 206: 140-150.

18. Pae CU, Wang SM, Han C, et al. Vortioxetine, multimodal antidepressant for generalized anxiety disorder: a systematic review and meta-analysis. J Psychiatr Res 2015; 64: 88-98.

19. Yee A, Ng CG, Seng LH. Vortioxetine Treatment for Anxiety Disorder: A Meta-Analysis Study. Curr Drug Targets 2017; 19: 1412-1423.

20. Fu J, Peng L, Li X. The efficacy and safety of multiple doses of vortioxetine for generalized anxiety disorder: a meta-analysis. Neuropsychiatr Dis Treat 2016; 12: 951-959.

21. Choo CC, Chew PKH, Ho CS, et al. Quality of Life in Patients With a Major Mental Disorder in Singapore. Front Psychiatry 2019; 9: 727.

22. Lee Y, Rosenblat JD, Lee J, et al. Efficacy of antidepressants on measures of workplace functioning in major depressive disorder: A systematic review. J Affect Disord 2018; 227: 406-415.

23. Bourland SL, Stanley MA, Synder AG, et al. Quality of life in older adults with generalized anxiety

disorder. Aging. And Mental Health 2000; 4: 315-323.

24. Frisch MB. Manual and treatment guide for the Quality of Life Inventory. Minneapolis: National Computer Systems Inc; 1994.

25. Katschnig H. How useful is the concept of quality of life in psychiatry? In: Katschnig H, Freeman H, Sartorius N. (Editors), Quality of life in mental disorders. Chichester: Wiley; 1997. p 3-16.

26. Steven EH. Bridging science and service: A report by the National Advisory Mental Health Council's Clinical Treatment and Services Research Workgroup (NIH Publication No. 99–4353). Rockville: Diane Pub Co; 1999.

27. Zhou X, Keitner GI, Qin B, et al. Atypical Antipsychotic Augmentation for Treatment-Resistant Depression: A Systematic Review and Network Meta-Analysis. Int J Neuropsychopharmacol 2015; 18: pyv060.

28. Mogotsi M, Kaminer D, Stein DJ. Quality of life in the anxiety disorders. Harvard Rev Psychiat 2000; 8: 273-282.

29. Henning ER, Turk CL, Mennin DS, et al. Impairment and quality of life in individuals with generalized anxiety disorder. Depress Anxiety 2007; 24: 342-349.

30. Endicott J, Russell JM, Raskin J, et al. Duloxetine treatment for role functioning improvement in generalized anxiety disorder: three independent studies. J Clin Psychiatry 2007; 68: 518-524.

31. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 updated March 2011. Available at: http://www.cochrane-handbook.org. Accessed November 13, 2018.

32. Moher D, Liberati A, Tetzlaff J, et al. Reprint--preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Phys Ther 2009; 89: 873-880.

33. Testa MA, Simonson DC. Assessment of quality-of-life outcomes. N Engl J Med 1996; 334: 835-840.

34. Urbach DR. Measuring quality of life after surgery. Surg Innov 2005; 12: 161-165.

35. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). Med Care 1992; 30: 473-483.

36. Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. Int Clin

Psychopharmacol 1996; 11: 89-95.

37. Higgins J, Thompson S, Deeks J, et al. Statistical heterogeneity in systematic reviews of clinical trials: a critical appraisal of guideline and practice. J Health Serv Res Policy 2002; 7: 51-61.

38. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-660.

39. Ho RC, Ong HS, Kudva KG, et al. How to critically appraise and apply meta-analyses in clinical practice. Int J Rheum Dis 2010; 13: 294-299.

40. Egger M, Davey Smith G, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-634.

41. Fu J, Peng L, Li X. The efficacy and safety of multiple doses of vortioxetine for generalized anxiety disorder: a meta-analysis. Neuropsychiatr Dis Treat 2016; 12: 951-959.

42. Khan A, Khan S, Brown WA. Are placebo controlsnecessary to test new antidepressants and anxiolytics? Int J Neuropsychopharmacol 2002; 5: 193–197.

43. Liebowitz MR, Stein MB, Tancer M, et al. A randomized, double-blind, fixed-dose comparison of paroxetine and placebo in the treatment of generalized social anxiety disorder. J Clin Psychiatry. 2002;63(1): 66–74.

44. Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 2006; 163(1): 28-40.

45. Florea I, Loft H, Danchenko N, et al. The effect of vortioxetine on overall patient functioning in patients with major depressive disorder. Brain Behav 2017; 7: e00622.

46. Christensen MC, Loft H, Florea I, et al. Efficacy of vortioxetine in working patients with generalized anxiety disorder. CNS Spectr 2017. https://doi: 10.1017/S1092852917000761.

47. Baldwin DS, Loft H, Florea I. Lu AA21004, a multimodal psychotropic agent, in the prevention of relapse in adult patients with generalized anxiety disorder. Int Clin Psychopharmacol 2012; 27: 197-207.2

48. Perna G, Alciati A, Riva A, et al. Long-Term Pharmacological Treatments of Anxiety Disorders: An Updated Systematic Review. Curr Psychiatry Rep 2016; 18: 23.

Table 1. Description of included studies.

Study	Patients n	Age (mean, SD)	Sex (Male, n, %)	Interventions	Duration (weeks)	Key inclusion criteria for GAD
Bidzan et al. (2012) [13]	T: 150; C: 151	T: 45.0 (14.1); C: 45.3 (13.5)	T: 47 (31.3); C: 58 (38.4)	T: vtx (5 mg/d); C: placebo	8	DSM-IV-TR, HAM-A ≥20
Mahableshwarkar et al. (2014a) [14]	T: 152, 152; C: 153	T: 40.8 (13.8)' 43.3 (15.0); C: 39.5 (13.5)	T: 49 (32.2), 56 (36.8); C: 48 (31.4)	T: vtx 2.5 mg/d, vtx 10 mg/d; C: placebo	8	DSM-IV-TR, HAM-A ≥20
Mahableshwarkar et al. (2014b) [15]	T: 156, 156, 156; C: 157	T: 39.2 (11.90), 37.7 (11.96), 39.8 (12.33); C: 36.8 (12.12)	T: 47 (30.1), 56 (35.9), 51 (32.7); C: 55 (35)	T: vtx 2.5 mg/d, vtx 5 mg/d, vtx 10 mg/d; C: placebo	8	DSM-IV-TR, HAM-A ≥20
Rothschild et al. (2012) [16]	T: 152; C: 152	T: 41.0 (14.05); C: 41.4 (12.81)	T: 49 (32.2); C: 55 (36.2)	T: vtx 5 mg/d; C: placebo	8	DSM-IV-TR, HAM-A ≥20

Note: T, Treatment group; C, Control group; mg/d, mg/day; GAD, Generalized anxiety disorder; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th edition Text Revision; HAM-A, Hamilton Anxiety Rating; vtx, Vortioxetine.

Figure legends

Figure 1: Odds ratios (ORs) and 95% confidence intervals (CIs) of the individual studies and the pooled data, comparing the response rates between the vortioxetine-treated and placebo groups.
Notes: (A) 2.5-mg/day vortioxetine versus placebo, (B) 5-mg/day vortioxetine versus placebo, and (C) 10-mg/day vortioxetine versus placebo.

Figure 2: Odds ratios (ORs) and 95% confidence intervals (CIs) of the individual studies and the pooled data, comparing the remission rates between the vortioxetine- and placebo groups.
Notes: (A) 2.5-mg/day vortioxetine versus placebo, (B) 5-mg/day vortioxetine versus placebo, and (C) 10-mg/day vortioxetine versus placebo.

Figure 3: Standardized mean differences (SMDs) and 95% confidence intervals (CIs) of the individual studies and the pooled data, comparing the mean change from baseline in total scores on the HAM-A, between the vortioxetine- and placebo groups.
Notes: (A) 2.5-mg/day vortioxetine versus placebo, (B) 5-mg/day vortioxetine versus placebo, and (C) 10-mg/day vortioxetine versus placebo.

Figure 4: Standardized mean differences (SMDs) and 95% confidence intervals (CIs) of the individual studies and the pooled data, comparing the Short Form 36 Health Survey (SF-36) scores between the vortioxetine- and placebo groups.
Notes: (A) 2.5-mg/day vortioxetine versus placebo, (B) 5-mg/day vortioxetine versus placebo, and (C) 10-mg/day vortioxetine versus placebo.

Figure 5: Standardized mean differences (SMDs) and 95% confidence intervals (CIs) of the individual studies and the pooled data, comparing the Sheehan Disability Scale (SDS) scores between the vortioxetine and placebo groups.
Notes: (A) 2.5-mg/day vortioxetine versus placebo, (B) 5-mg/day vortioxetine versus placebo, and (C) 10-mg/day vortioxetine versus placebo.

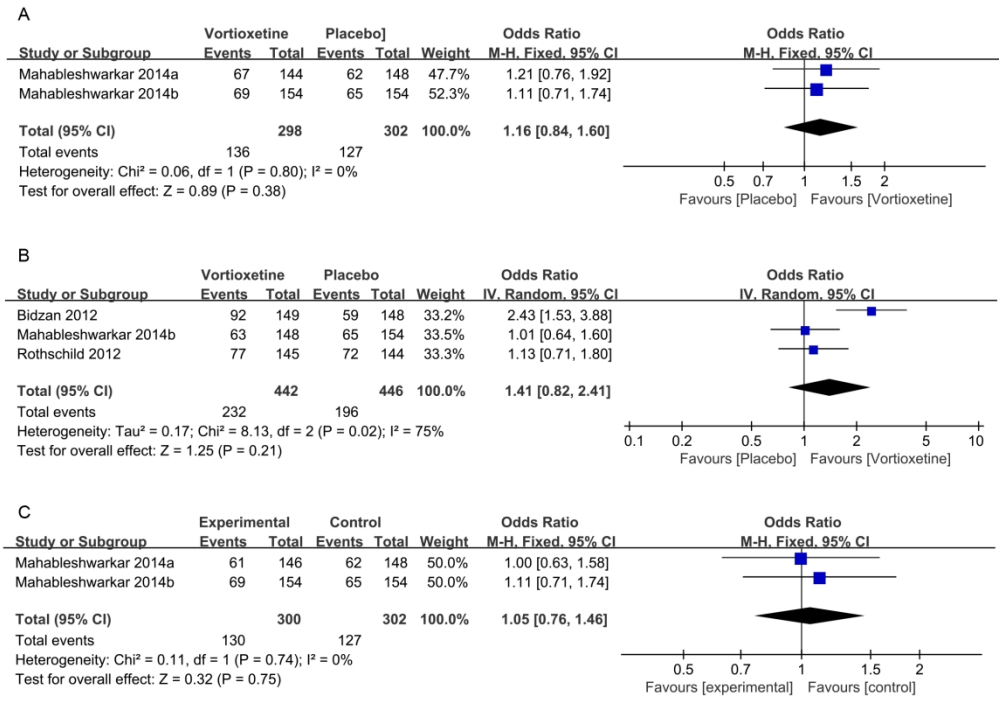

A
Vortioxetine
Placebo]
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Mahableshwarkar 2014a 67 144 62 148 47.7% 1.21 [0.76, 1.92]
Mahableshwarkar 2014b 69 154 65 154 52.3% 1.11 [0.71, 1.74]
Total (95% CI) 298 302 100.0% 1.16 [0.84, 1.60]
Total events 136 127
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.80); I² = 0%
Test for overall effect: Z = 0.89 (P = 0.38)
0.5 0.7 1 1.5 2
Favours [Placebo] Favours [Vortioxetine]
B
Vortioxetine
Placebo
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Bidzan 2012 92 149 59 148 33.2% 2.43 [1.53, 3.88]
Mahableshwarkar 2014b 63 148 65 154 33.5% 1.01 [0.64, 1.60]
Rothschild 2012 77 145 72 144 33.3% 1.13 [0.71, 1.80]
Total (95% CI) 442 446 100.0% 1.41 [0.82, 2.41]
Total events 232 196
Heterogeneity: Tau² = 0.17; Chi² = 8.13, df = 2 (P = 0.02); I² = 75%
Test for overall effect: Z = 1.25 (P = 0.21)
0.1 0.2 0.5 1 2 5 10
Favours [Placebo] Favours [Vortioxetine]
C
Experimental
Control
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Mahableshwarkar 2014a 61 146 62 148 50.0% 1.00 [0.63, 1.58]
Mahableshwarkar 2014b 69 154 65 154 50.0% 1.11 [0.71, 1.74]
Total (95% CI) 300 302 100.0% 1.05 [0.76, 1.46]
Total events 130 127
Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² = 0%
Test for overall effect: Z = 0.32 (P = 0.75)
0.5 0.7 1 1.5 2
Favours [experimental] Favours [control]

Figure 1

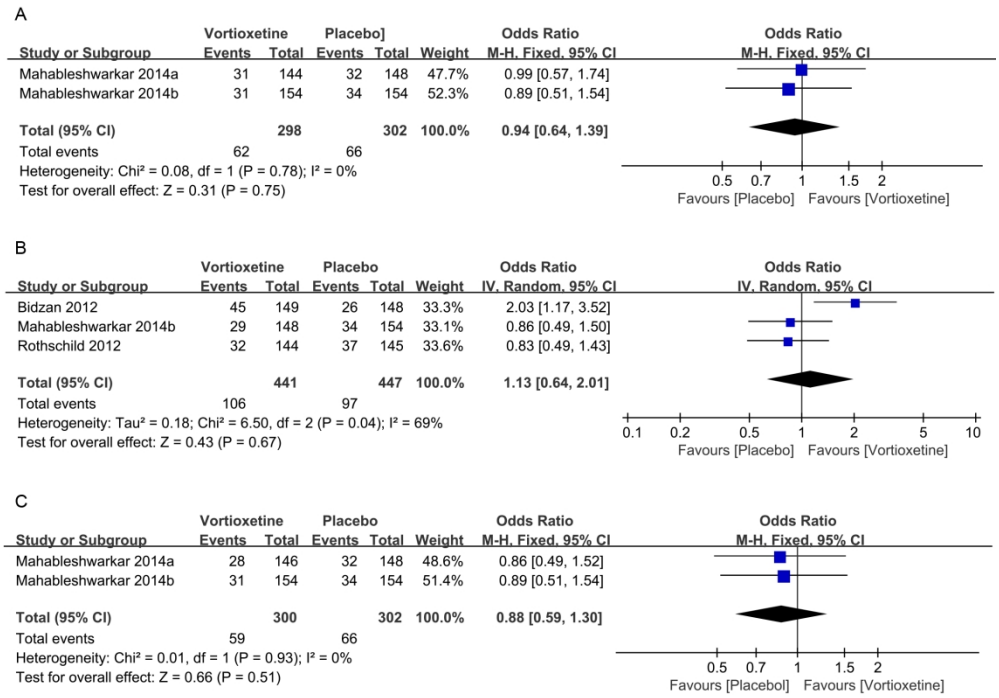

A
Vortioxetine
Placebo]
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Mahableshwarkar 2014a 31 144 32 148 47.7% 0.99 [0.57, 1.74]
Mahableshwarkar 2014b 31 154 34 154 52.3% 0.89 [0.51, 1.54]
Total (95% CI) 298 302 100.0% 0.94 [0.64, 1.39]
Total events 62 66
Heterogeneity: Chi² = 0.08, df = 1 (P = 0.78); I² = 0%
Test for overall effect: Z = 0.31 (P = 0.75)
0.5 0.7 1 1.5 2
Favours [Placebo] Favours [Vortioxetine]
B
Vortioxetine
Placebo
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Bidzan 2012 45 149 26 148 33.3% 2.03 [1.17, 3.52]
Mahableshwarkar 2014b 29 148 34 154 33.1% 0.86 [0.49, 1.50]
Rothschild 2012 32 144 37 145 33.6% 0.83 [0.49, 1.43]
Total (95% CI) 441 447 100.0% 1.13 [0.64, 2.01]
Total events 106 97
Heterogeneity: Tau² = 0.18; Chi² = 6.50, df = 2 (P = 0.04); I² = 69%
Test for overall effect: Z = 0.43 (P = 0.67)
0.1 0.2 0.5 1 2 5 10
Favours [Placebo] Favours [Vortioxetine]
C
Vortioxetine
Placebo
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Mahableshwarkar 2014a 28 146 32 148 48.6% 0.86 [0.49, 1.52]
Mahableshwarkar 2014b 31 154 34 154 51.4% 0.89 [0.51, 1.54]
Total (95% CI) 300 302 100.0% 0.88 [0.59, 1.30]
Total events 59 66
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.93); I² = 0%
Test for overall effect: Z = 0.66 (P = 0.51)
0.5 0.7 1 1.5 2
Favours [Placebo] Favours [Vortioxetine]

Figure 2

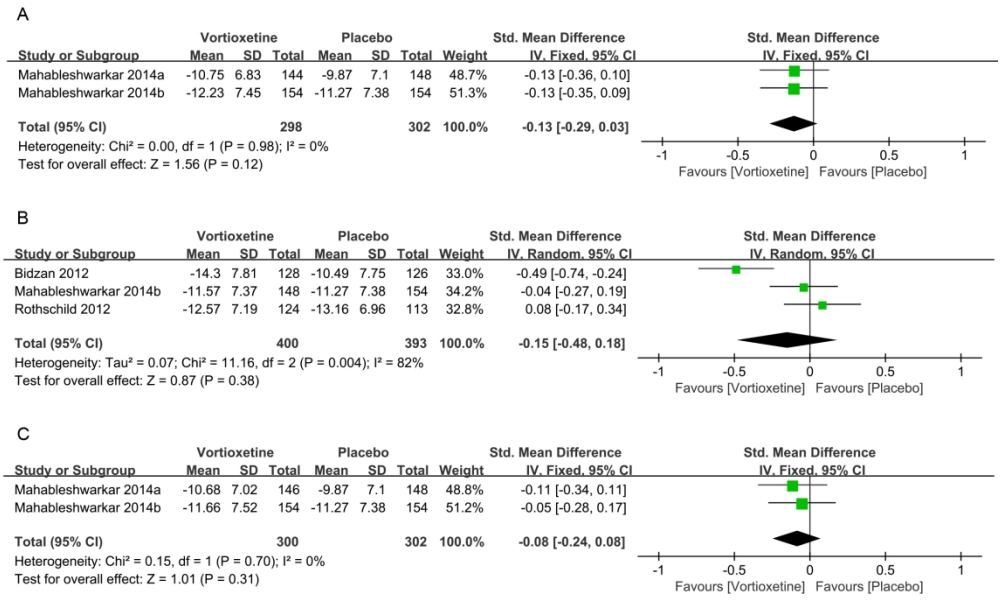

A
Vortioxetine
Placebo
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI
IV, Fixed, 95% CI
Mahableshwarkar 2014a -10.75 6.83 144 -9.87 7.1 148 48.7% -0.13 [-0.36, 0.10]
Mahableshwarkar 2014b -12.23 7.45 154 -11.27 7.38 154 51.3% -0.13 [-0.35, 0.09]
Total (95% CI) 298 302 100.0% -0.13 [-0.29, 0.03]
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.98); I² = 0%
Test for overall effect: Z = 1.56 (P = 0.12)
-1 -0.5 0 0.5 1
Favours [Vortioxetine] Favours [Placebo]
B
Vortioxetine
Placebo
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Bidzan 2012 -14.3 7.81 128 -10.49 7.75 126 33.0% -0.49 [-0.74, -0.24]
Mahableshwarkar 2014b -11.57 7.37 148 -11.27 7.38 154 34.2% -0.04 [-0.27, 0.19]
Rothschild 2012 -12.57 7.19 124 -13.16 6.96 113 32.8% 0.08 [-0.17, 0.34]
Total (95% CI) 400 393 100.0% -0.15 [-0.48, 0.18]
Heterogeneity: Tau² = 0.07; Chi² = 11.16, df = 2 (P = 0.004); I² = 82%
Test for overall effect: Z = 0.87 (P = 0.38)
-1 -0.5 0 0.5 1
Favours [Vortioxetine] Favours [Placebo]
C
Vortioxetine
Placebo
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI
IV, Fixed, 95% CI
Mahableshwarkar 2014a -10.68 7.02 146 -9.87 7.1 148 48.8% -0.11 [-0.34, 0.11]
Mahableshwarkar 2014b -11.66 7.52 154 -11.27 7.38 154 51.2% -0.05 [-0.28, 0.17]
Total (95% CI) 300 302 100.0% -0.08 [-0.24, 0.08]
Heterogeneity: Chi² = 0.15, df = 1 (P = 0.70); I² = 0%
Test for overall effect: Z = 1.01 (P = 0.31)
-1 -0.5 0 0.5 1
Favours [Vortioxetine] Favours [Placebo]

Figure 3

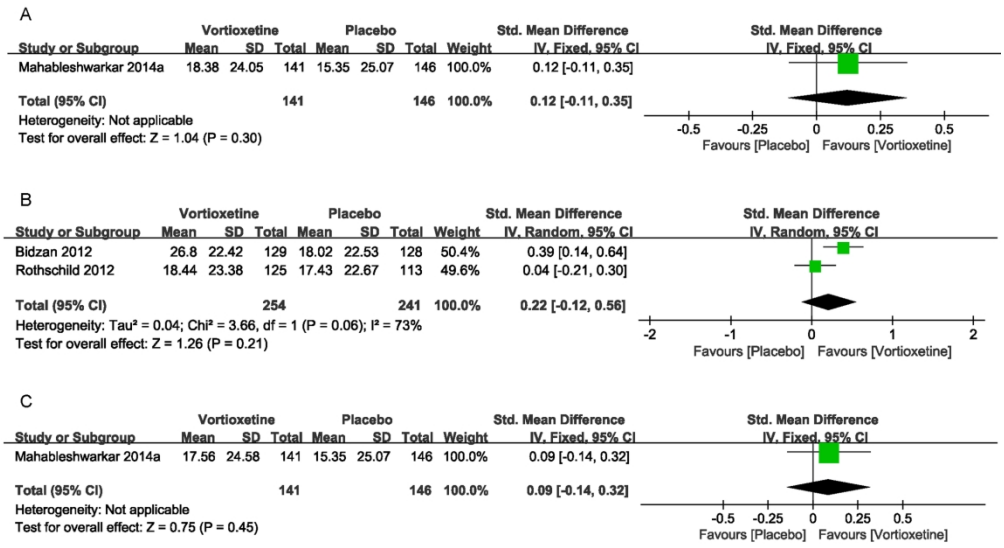


Figure 4

197x108mm (300 x 300 DPI)

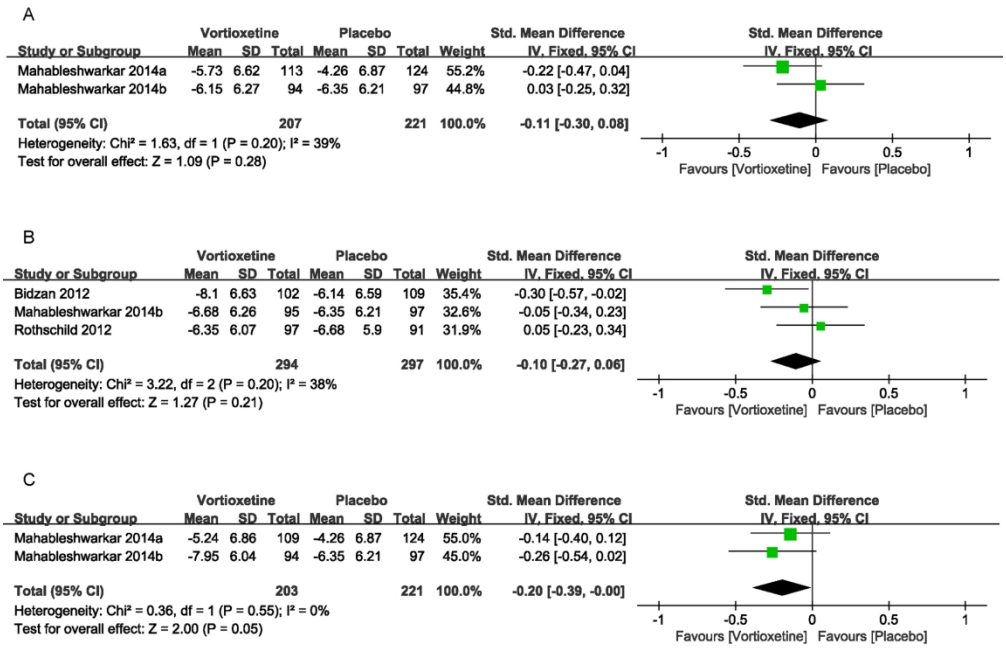
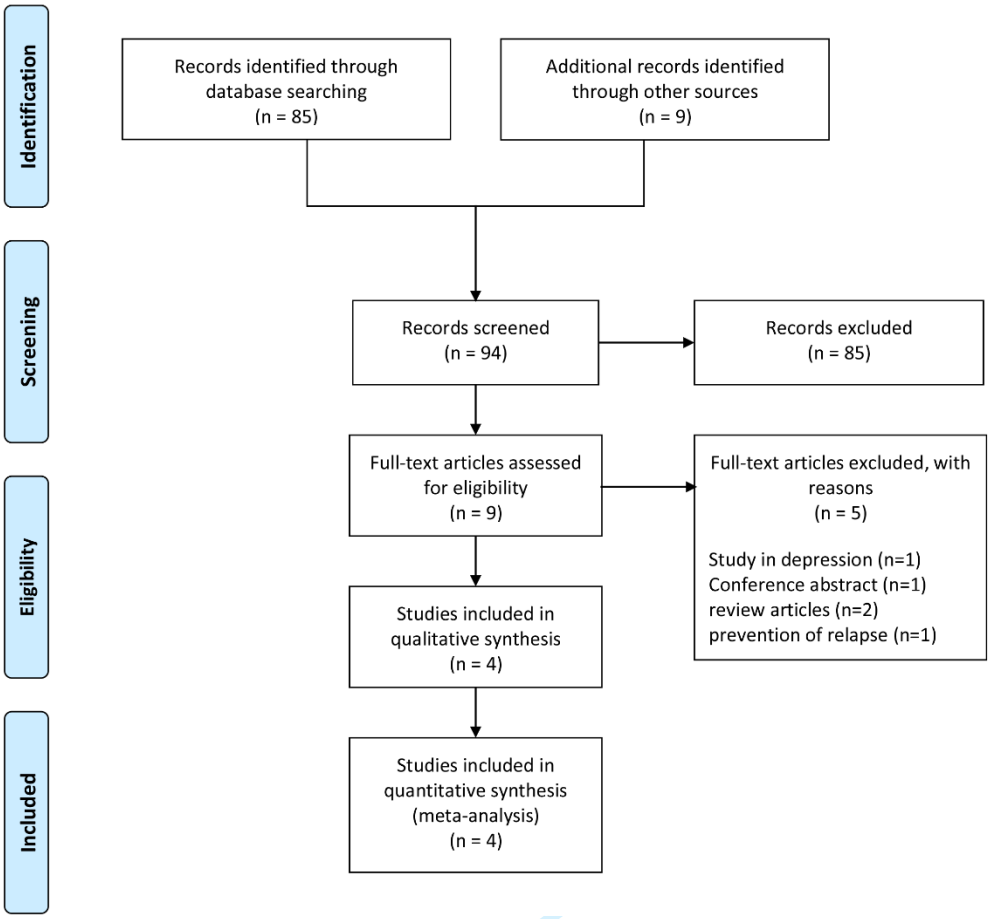


Figure 5

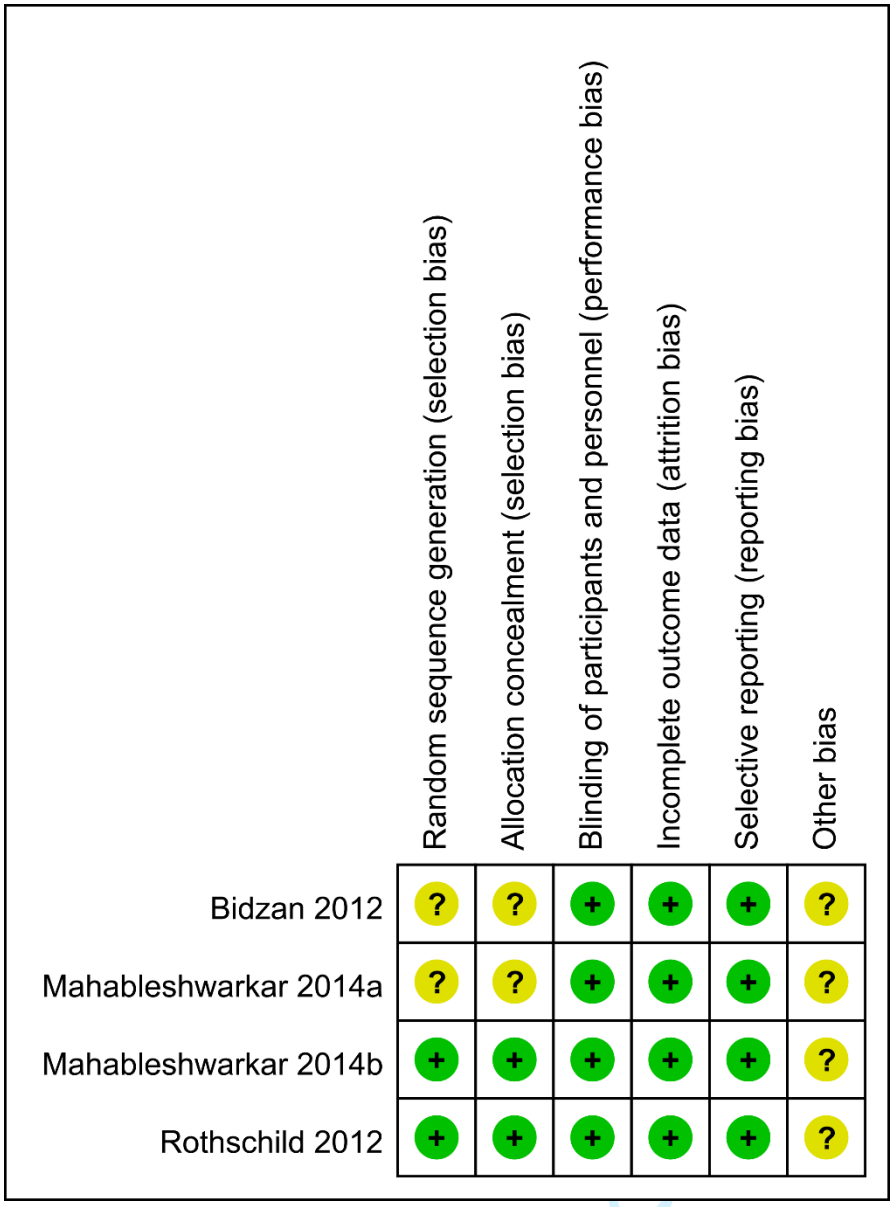
196x128mm (300 x 300 DPI)

Supplementary Table 1: Search Strategy

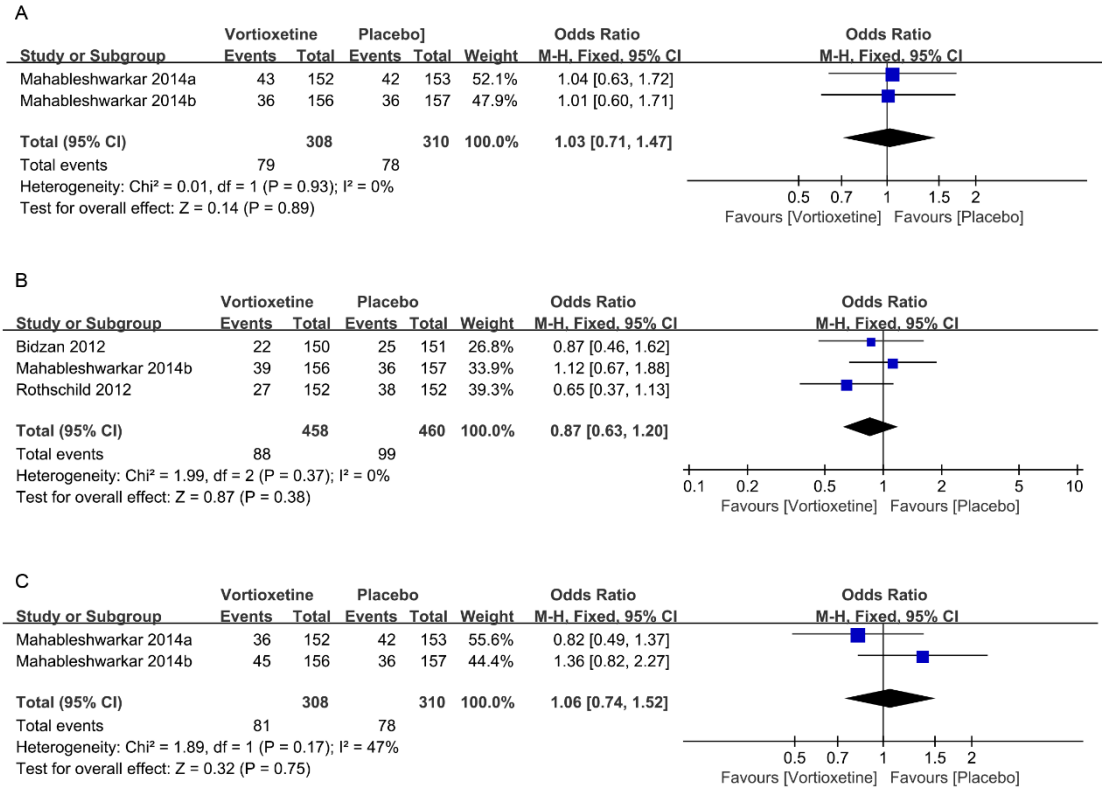
Search Strategy (Pubmed)	
#1	((vortioxetine[Title/Abstract]) OR Lu AA21004[Title/Abstract]) OR Brintellix[Title/Abstract]
#2	((((anxiety[Title/Abstract]) OR anxiety disorder[Title/Abstract]) OR anxiety disorders[Title/Abstract]) OR mood disorder[Title/Abstract]) OR mood disorders[Title/Abstract]
#3	Search "Anxiety Disorders"[Mesh]
#4 (#2 OR #3)	("Anxiety Disorders"[Mesh]) OR (((((anxiety[Title/Abstract]) OR anxiety disorder[Title/Abstract]) OR anxiety disorders[Title/Abstract]) OR mood disorder[Title/Abstract]) OR mood disorders[Title/Abstract])
#5 (#1 OR #4)	((("Anxiety Disorders"[Mesh]) OR (((((anxiety[Title/Abstract/]) OR anxiety disorder[Title/Abstract]) OR anxiety disorders[Title/Abstract]) OR mood disorder[Title/Abstract]) OR mood disorders[Title/Abstract]))) AND (((vortioxetine[Title/Abstract]) OR Lu AA21004[Title/Abstract]) OR Brintellix[Title/Abstract])
#6	Filters: Clinical Trial; Randomized Controlled Trial



Supplementary Figure 1: Search flow for the trial identification and selection process.

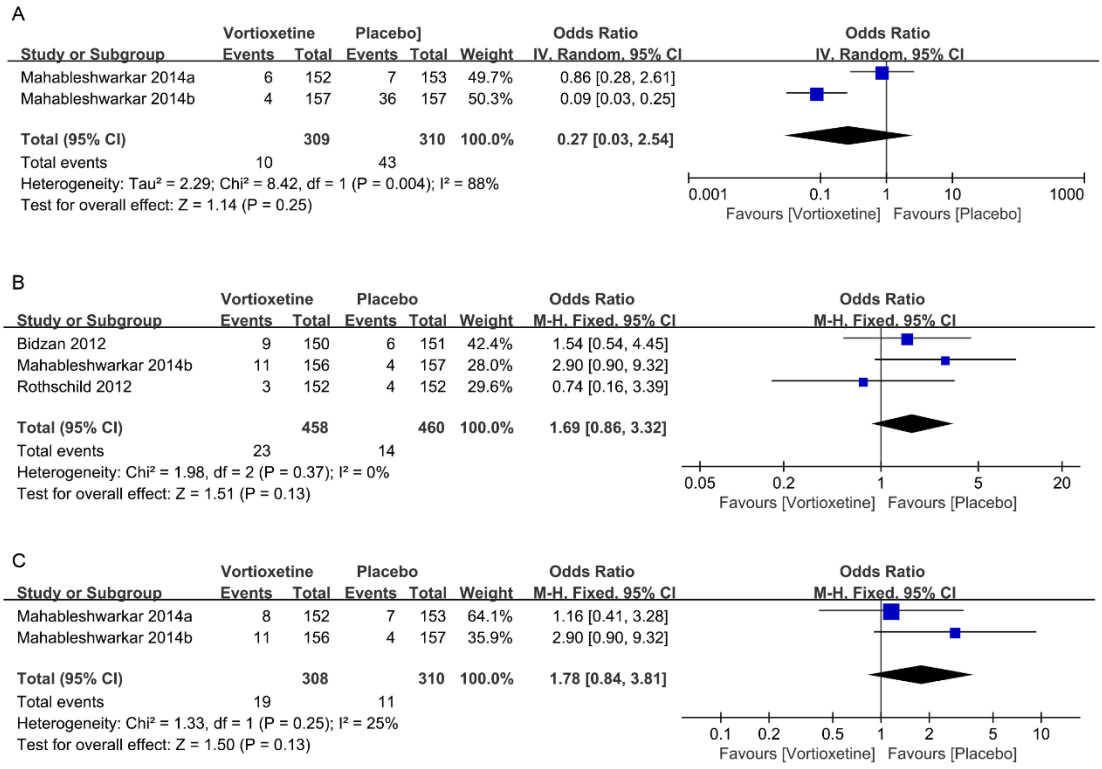


Supplementary Figure 2: Summarized risks of bias for the included studies.



Supplementary Figure 3: Odds ratios (ORs) and 95% confidence intervals (CIs) of the selected studies and the pooled data, comparing the discontinuation rates for any reason, between the vortioxetine and placebo groups.

Notes: (A) 2.5-mg/day vortioxetine versus placebo, (B) 5-mg/day vortioxetine versus placebo, and (C) 10-mg/day vortioxetine versus placebo.



Supplementary Figure 4: Odds ratios (ORs) and 95% confidence intervals (CIs) of the selected studies and the pooled data, comparing the discontinuation rates due to adverse events (AEs), between vortioxetine and placebo groups.

Notes: (A) 2.5-mg/day vortioxetine versus placebo, (B) 5-mg/day vortioxetine versus placebo, and (C) 10-mg/day vortioxetine versus placebo.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3-4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4-5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5-6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5-6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7-8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8-9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	10

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.