The efficacy and safety of 10 mg/day vortioxetine compared to placebo for adult major depressive disorder: a meta-analysis

Jiahuan Zheng, Zhaoyu Wang, Enli Li

Guangdong Provincial Key Laboratory of Biotechnology Candidate Drug Research, School of Biosciences and Biopharmaceutics, Guangdong Pharmaceutical University, Guangdong, Guangzhou 510006.

Abstract:

Background: There is a growing interest in vortioxetine in major depressive disorder (MDD).

Objectives: This meta-analysis aimed to assess the efficacy and safety of 10 mg/day (mg/d) vortioxetine compared to placebo for MDD in adult.

Methods: Eight randomly controlled trials (RCTs) about the treatment of 10 mg/d vortioxetine in adult patients with MDD were identified and 2354 patients were included in meta-analysis.

Results: According to the results, 10 mg/d vortioxetine showed significant differences in response rates (OR=1.88, 95% CI=1.40-2.53, P<0.0001), remission rates (OR=1.54, 95% CI=1.27-1.86, P<0.00001), change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) total score (SMD=-3.50, 95%CI=-4.83 to -2.17, P<0.00001), clinical global Impression-Global Improvement (CGI-I) total score (SMD=-3.40, 95% CI=-4.69 to -2.11, P<0.00001), and change from baseline in Sheehan Disability Scale (SDS) total score (SMD=-2.09, 95% CI=-2.64 to -1.55, P<0.00001). But 10 mg/d vortioxetine was easier induced nausea (OR=4.18, 95% CI=3.21-5.44, P<0.00001) and constipation (OR=1.88, 95% CI=1.14 to 3.09, P=0.01).

Conclusion: 10 mg/d vortioxetine was more effective, but easily induced nausea and constipation when compared to placebo for MDD in adult.

Keywords: Vortioxetine, major depressive disorder, meta-analysis.

DOI: https://dx.doi.org/10.4314/ahs.v19i1.48

Cite as: *Zheng J, Wang Z, E L. The efficacy and safety of 10 mg/day vortioxetine compared to placebo for adult major depressive disorder: a meta-analysis. Afri Health Sci. 2019;19(1). 1716-1726. https://dx.doi. org/10.4314/ ahs. v19i1.48*

Introduction

Depressive disorder is one of serious diseases plaguing mankind[1,2]. It is a chronic and recurring disease with considerable morbidity and mortality in general population[3]. The World Health Organization found that over 350 million people suffered from depression over the whole world and the disease was spread in all age people. Depression impair the quality of life and daily functioning of patients with major depressive disorder (MDD), and at its most severe, depression can lead to suicide. It estimated that over 1 million patients end their life due to the depression every year[4]. Depression is not only the leading cause of disability worldwide, but also the chief factor to lead the world burden of disease.

Corresponding author:
Zhaoyu Wang,
Guangdong Provincial Key Laboratory of Biotechnology Candidate Drug Research, School of Biosciences and Biopharmaceutics, Guangdong Pharmaceutical University
Email: clearconsult@163.com

Vortioxetine is a novel antidepressant that was approved by the U.S. Food and Drug Administration (FDA) recently for the treatment of MDD[5]. It was considered that the activity of vortioxetine was shown through two mechanism: the direct modulation of receptor activity and the inhibition of the serotonin reuptake[6,7]. Some vitro stud-

ies indicated that vortioxetine was the receptor antagonist of 5-HT3 and 5-HT7 receptors, the partial agonist of 5-HT1B receptor, the agonist of 5-HT1A receptor, and the 5-HT transporter inhibitor[8]. In vivo non-clinic studies, vortioxetine can enhance the level of 5-HT, noradrenaline, dopamine, acetylcholine and histamine in specific areas of the brain was demonstrated[9]. However, the effective dosage of vortioxetine for the treatment of MDD was uncertain until now.

The recommended dosage of vortioxetine was 5-20 mg/day (mg/d) at present[10]. Several articles have reported the efficacy of vortioxetine in the dosage of 5 mg/d[11-16,10] mg/d[13,15-20], and 20 mg/d[18,20,21]. And there were a few articles about the dosage of 2.5 mg/d[11,15,17], which was not recommended currently. However, these articles showed inconsistent results. So some people have conducted meta-analysis to assess the efficacy and safety of different dosage vortioxetine. Jie Fu et al.[22] have assessed the difference of efficacy and safety between 5 mg/d vortioxetine and placebo through a meta-analysis, thus they demonstrated that 5 mg/d vortioxetine was more effective but more easier to lead nausea for the treatment of MDD. And it was indicated that 20 mg/d vortioxetine also more effective than placebo by a meta-analysis conducted by Masoud Behzadifar[23]. In this article, we have assessed the efficacy and safety of 10 mg/d vortioxetine in adult MDD for the current meta-analysis based on the newest available data in published studies.

Material and methods

Sources of data

In this systematic and meta-analysis, we searched Pubmed, PsycINFO, Sciencedirect, Google Scholar, Embase, Ebsco, Cochrane Central Register of Controlled Trials and Clinical-Trials.gov using the terms "vortioxetine", "Lu AA21004" or "Brintellix" vs "depression", "mood disorder" or "depressive disorder". All databases were searched from the available date of inception until the latest issue (February 2016). The search was limited to individual randomized controlled trials (RCTs) and had no language restriction.

Selection criteria

Studies were selected for analysis if they met the following criterias: (1) Eligibility was limited to RCTs of MDD; (2) Clinical trials testing the efficacy of vortioxetine for the short term treatment of MDD; (3) the dosage of vortioxetine was 10 mg/d; (4) Studies compared the efficacy and safety of vortioxetine to placebo for the treatment of MDD; (5) Patients in the RCT were diagnosed with MDD according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revised (DSM-IV-TR) and were required to have a Montgomery-Asberg Depression Rating Scale (MADRS)[24] total score≥26, and aged from 18 to 75 years old.

Data extraction

The data (study design, quality criteria, participant characteristics, intervention details, outcome measures, baseline and posttreatment results) were independently extracted by two authors (Jiahuan Zheng and Zhaoyu Wang). Any discrepant data between the two reviewers were resolved by consensus, or, if necessary, by a third reviewer. We selected the following indicators as the outcomes: response, remission, change from baseline in MADRS total score at week 8, clinical global Impression-Global Improvement (CGI-I) total score at week 8, change from baseline in Sheehan Disability Scale (SDS) total score at week 8, and AEs. Response was defined as ≥50% decrease from baseline MADRS total scores, and the remission was defined as the MADRS total scores<10[24]. If the studies compared different doses vortioxetine to placebo, only the 10 mg/d and placebo doses were included in our meta-analysis.

Quality assessment

The study quality was assessed using Jadad five-point scores for RCTs[25]. The key domains were: randomization (0-2 points), blindness (0-2 points), and dropouts (0-1 point). If the study was described as randomized such as "randomly", "random", and "randomization", adding one point to the study; an additional point would be given if the specific item of randomization was described and it was appropriate. At last, a point was deducted if the study did not mention the randomization. This method was also applied to blinding. If there had a description of withdraws or dropouts in the study, adding one point, otherwise, adding zero. The maximum point of a study is five. Studies with a total score of 3 or more were regarded as high study quality.

Statistical analysis

The effect and safety of 10 mg/d vortioxetine on MDD were calculated as differences between the treatment group and the placebo control group using Review Manager 5.1 meta-analysis software. Heterogeneity[26] would be evaluated using the Higgins I2 test before effect size (ES) pooled. when the studies in the group were similar enough (P>0.10), the fixed-effects model was used to assess the results. While the studies were not similar (P<0.10 or I2>50%), the results were assess though random-effects model. The overall effect was tested using a Z-score with significance set at P<0.05. Odd ratio (OR) and 95% confidence intervals (CIs) were calculated for dichotomous data, while standardized mean differences (SMD) and the 95% confidence intervals (CIs) were calculated for continuous data. A sensitivity analysis was performed to study robustness of the meta-analysis consequence and explore the potential sources when high heterogeneity was found. Publication bias was not assessed here since the number of included studies was small.

Results

Study selection process

The process of study selection was shown as the flow chart in Fig. 1. Firstly, 1813 articles were identified from Pubmed, PsycINFO, Sciencedirect, Google Scholar, Embase, Ebsco, Cochrane Central Register of Controlled Trials and Clinical-Trial. gov. And then 1717 articles were removed by reviewing their abstracts and headlines.

Secondly, 67 articles were excluded since they had duplicated citations with others; 10 articles were excluded since that they were the same trials with different publication to others; 6 articles were not included since they were not placebo controlled trials; 1 article was eliminated since it was not a RCT; 2 articles were not included since they were not acute phase studies; 2 articles were finally excluded due to the participants in the trials. At last, 8 RCTs included 2354 patients were met the inclusion criteria and were included in the meta-analysis[19,15,16,13,20,18,27,28]. Fig.1

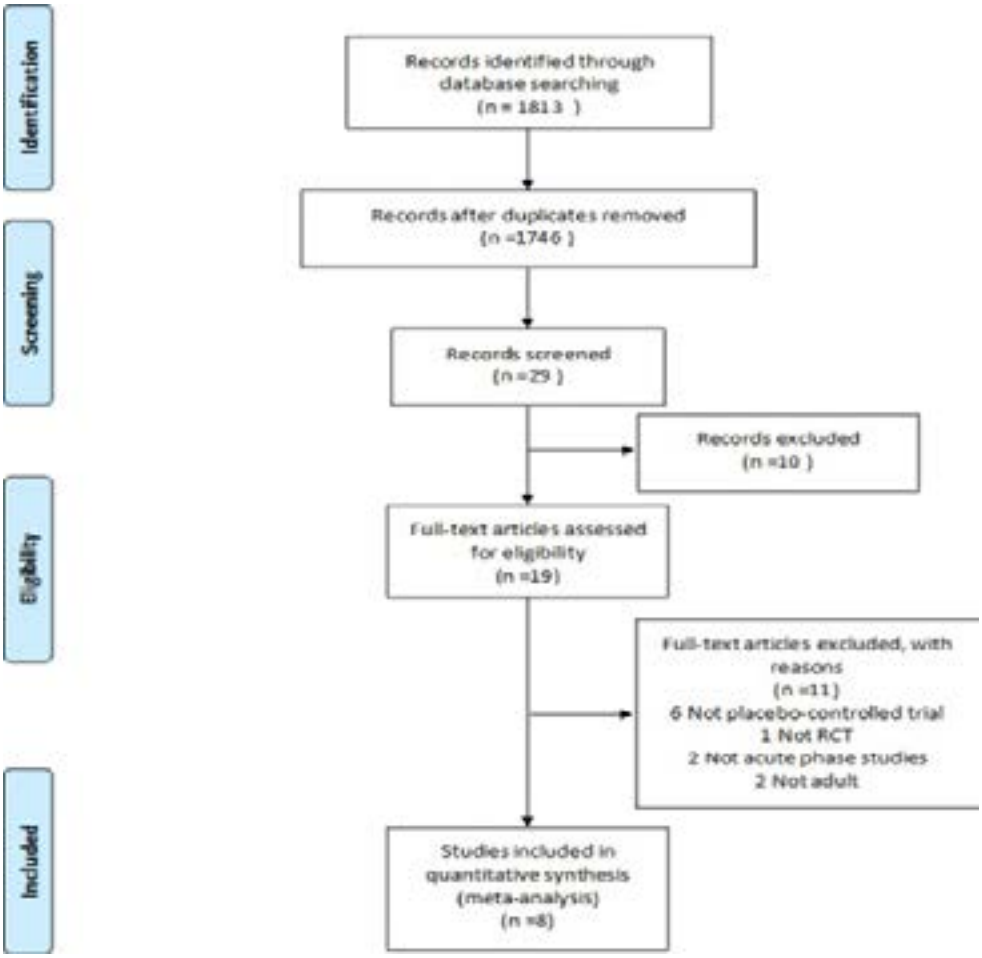

Fig 1. Search flow: trial identification and selection process

Study characteristics

All eight included studies[19,15,16,13,20,18,27,28] were randomized, double-blind, parallel-group, and placebo-controlled trails. Patients in all eight studies were older than 17 years and younger than 75 years. Patients in the vortioxetine group received more than one dosage vortioxetine, whereas patients in the placebo group received a placebo treatment. Homogeneity is a very important variable in the depression level of patients.Hence, only those patients who have a MADRS score≥26 can be included in the RCTs. The baseline MADRS score was at least 26, indicating that patients included in vortioxetine trials were all in the depressed symptom. Details of eight studies were shown in table 1. Quality assessment of the included RCTs was presented in Table 2 and Jadad scores were shown here as well.

Table 1 Characteristic of the included studies

study	Group	Sample size	Age, mean (SD)	Sex, M:F	Duration (weeks)	Baseline MADRS score	Intervention	Region
Atul et al, 2015	Treatment Placebo	157 160	45.2±11.9 46.2±11.8	44:113 52:108	8	34.1±4.1 33.4±4.5	Vortioxetine 10 mg/d placebo	US
David et al, 2012	Treatment Placebo	151 148	45.2±13.1 43.4±12.5	51:100 45:103	8	31.8±3.9 31.7±4.3	Vortioxetine 10 mg/d placebo	Non-US
Enric et al, 2012	Treatment Placebo	101 105	42.3±13.1 42.0±10.9	35:66 36:69	6	34.0±2.8 33.9±2.7	Vortioxetine 10 mg/d placebo	Non-US
Neven et al, 2012	Treatment Placebo	140 140	46.4±12.3 46.4±12.3	55:85 54:86	8	31.6±3.8 30.6±2.9	Vortioxetine 10 mg/d placebo	Non-US
Paula et al, 2015	Treatment Placebo	155 157	43.1±12.0 42.3±11.6	37:118 47:110	8	32.3±4.5 32.0±4.0	Vortioxetine 10 mg/d placebo	US
Roger S. et al, 2014	Treatment Placebo	195 196	45.4±12.2 45.6±12.1	61:134 67:129	8	31.6±3.8 31.3±3.8	Vortioxetine 10 mg/d placebo	USA, Non-US
Trial NCT01355081, 2014	Treatment Placebo	123 124	38.8±11.0 37.6±10.7	69:54 57:67	8	32.5±4.9 32.5±4.5	Vortioxetine 10 mg/d placebo	Japan
Trial NCT01255787, 2013	Treatment Placebo	150 152	45.7±10.90 43.7±11.57	57:93 61:91	10	31.8±4.02 31.6±3.56	Vortioxetine 10 mg/d placebo	Non-US

Table 2 Jadad score of the included studies

Study	Randomization	Blindness	Dropouts	Scores
Atul et al, 2015	1	2	1	4
David et al, 2012	2	1	1	4
Enric et al, 2012	1	1	1	3
Neven et al, 2012	1	2	1	4
Paula et al, 2015	1	2	1	4
Roger S. et al, 2014	2	2	1	5
Trial NCT01355081, 2014	1	1	1	3
Trial NCT01255787, 2013	1	1	1	3

Efficacy

A total eight RCTs with 2354 patients, 1172 in the 10 mg/day vortioxetine group and 1182 patients in the placebo group were included in our meta-analysis. The OR for response rate with 10 mg/d compared to placebo was 1.88 (95% CI=1.40 to 2.53, P<0.0001, Z=4.17, I2=66%) (Fig. 2). Meanwhile, there was a statistically significant difference for remission rate with an OR=1.54 (95% CI=1.27 to 1.86, P<0.00001, Z=4.45, I2=22%) (Fig. 3). The standard mean different ratio (SMD) for MADRS change was -3.50 (95% CI=-4.83 to -2.17, P<0.00001, Z=5.17, I2=99%) (Fig. 4), and the SMD was -3.40 (95% CI=-4.69 to -2.11, P<0.00001, Z=5.16, I2=99%) for CGI-I (Fig. 5), and for SDS change, the SMD was -2.09 (95% CI=-2.64 to -1.55, P<0.00001, Z=7.50, I2=93%) (Fig. 6).

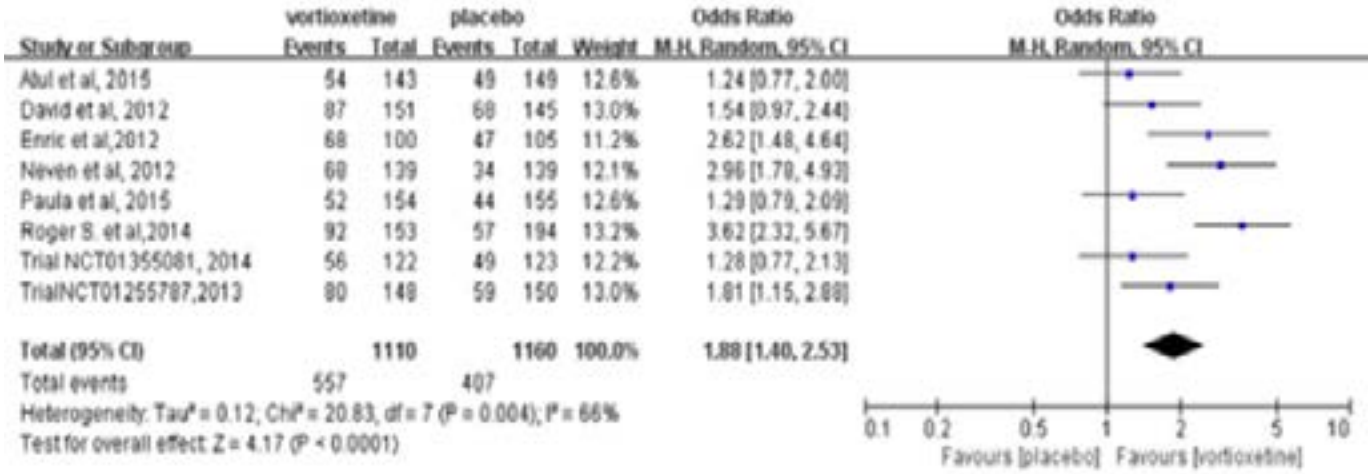

Fig.2 Odds ratios (ORs) and 95% confidence intervals (CIs) of the individual studies and the pooled data for all included studies comparing the response rate between 10 mg/day vortioxetine and placebo

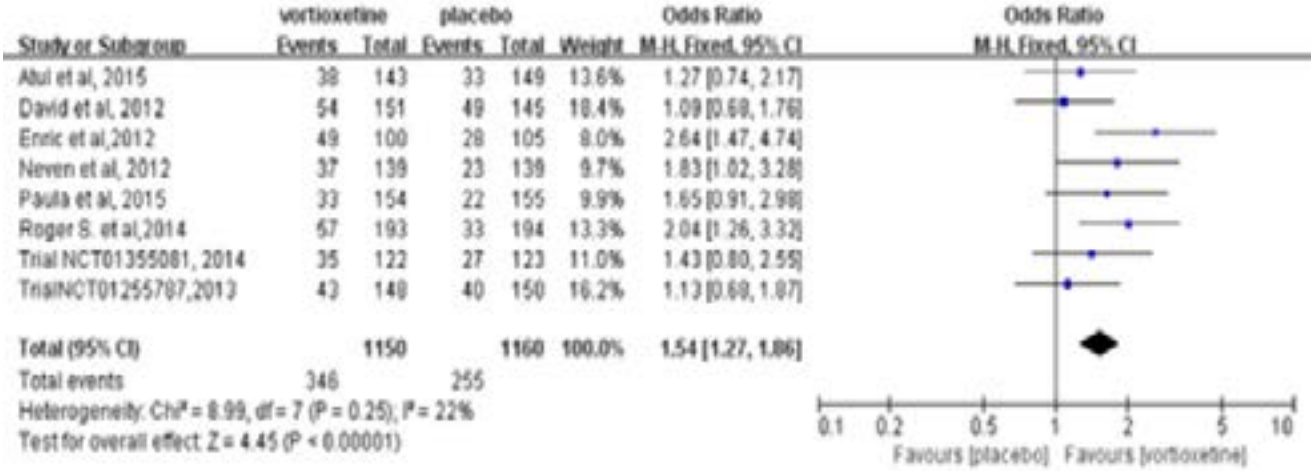

Fig.3 Odds ratios (ORs) and 95%confidence intervals (CIs) of the individual studies and the pooled data for all included studies comparing the remission rate between 10 mg/day vortioxetine and placebo

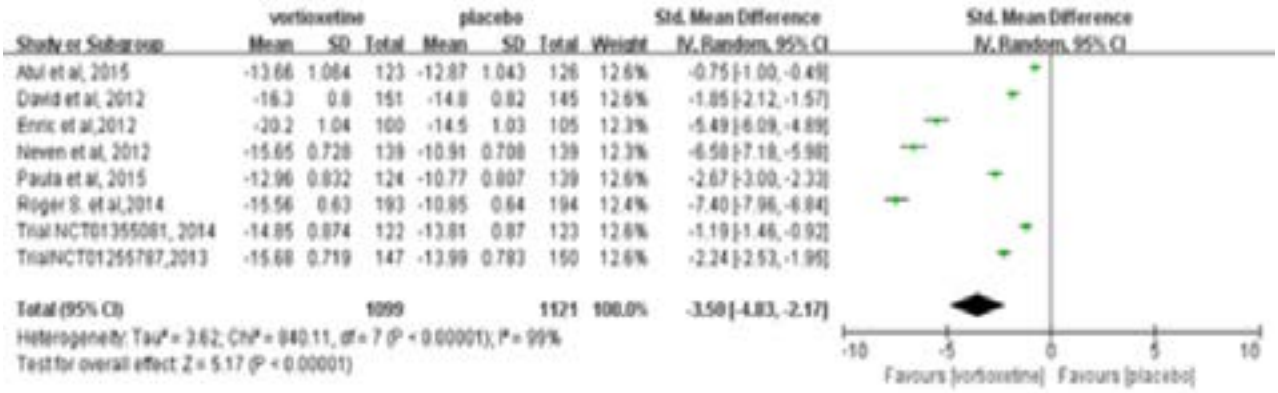

Fig. 4 Standardized mean differences (SMDs) and 95 % confidence intervals (CIs) of the individual studies and the pooled data comparing the change from baseline MADRS score between 10 mg/day vortioxetine and placebo

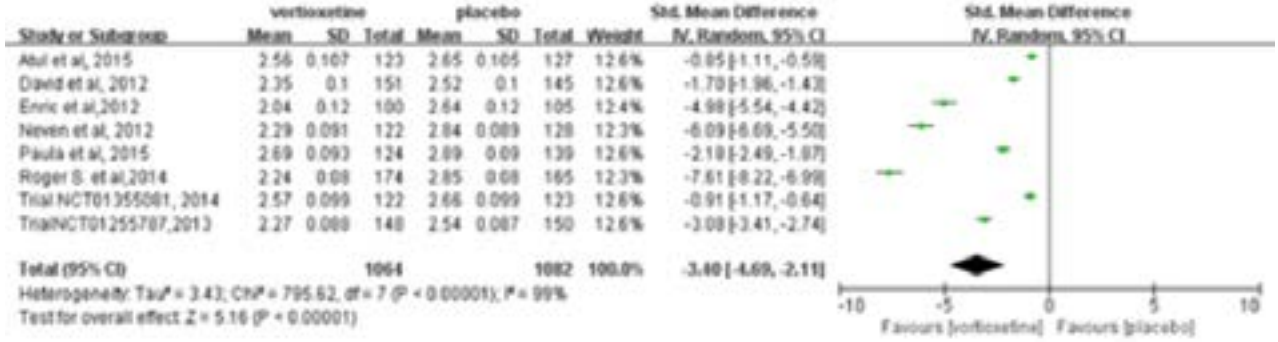

Fig. 5 Standardized mean differences (SMDs) and 95 % confidence intervals (CIs) of the individual studies and the pooled data comparing the CGI-I score between 10 mg/day vortioxetine and placebo

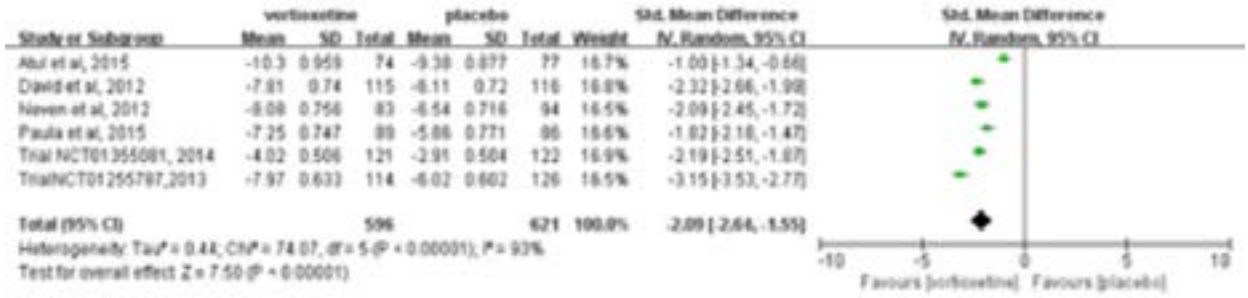

Fig. 6 Standardized mean differences (SMDs) and 95 % confidence intervals (CIs) of the six included studies and the pooled data comparing the change from baseline SDS score between 10 mg/day vortioxetine and placebo

Safety

The common adverse effects related to vortioxetine treatment were nausea, headache, diarrhoea, dizziness, nasopharyngitis, constipation, fatigue, and dry mouth. It was showed that 10 mg/d vortioxetine had extremely significant difference on nausea when compared to placebo (OR=4.18, 95% CI=3.21 to 5.44, P<0.00001, Z=10.62 I2=0%) in results. And the OR was 1.88 (95% CI=1.14 to 3.09, P=0.01, Z=2.49, I2=1%) for constipation. But the others were not observed difference between 10 mg/d vortioxetine and placebo (headache OR=0.94, 95% CI=0.73 to 1.21, P=0.64, Z=0.46, I2=0%; nasopharyngitis OR=0.81, 95% CI=0.58 to 1.15, P=0.24, Z=1.18, I2=0%; diarrhoea OR=1.07, 95% CI=0.75 to 1.52, P=0.71, Z=0.37, I2=1%; dizziness OR=0.95, 95% CI=0.63 to 1.44, P=0.83, Z=0.22, I2=43%; fatigue OR=1.13, 95% CI=0.68 to 1.90, P=0.63, Z=0.48, I2=0%; and dry mouth OR=1.11, 95% CI=0.75 to 1.64, P=0.61, Z=0.51, I2=46%) (Fig. 7).

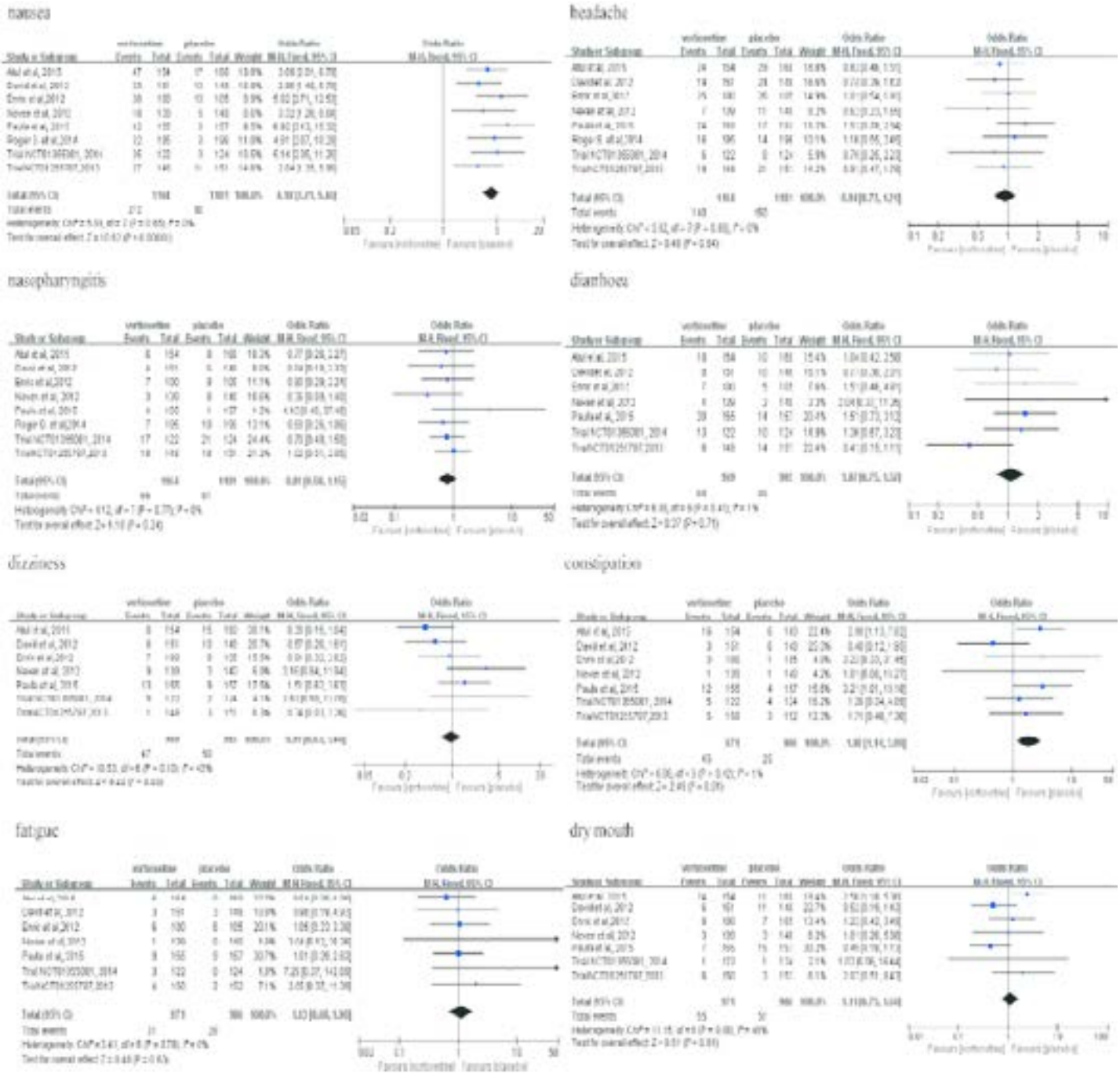

Fig. 7 Odds ratio (OR) and 95% confidence intervals (CIs) of nausea, headache, nasopharyngitis, diarrhoea, dizziness, constipation, fatigue and dry mouth AEs in the included studies

Sensitivity analysis

A sensitivity analysis did not find that the pooled effects of change from baseline MADRS score, CGI-I score and change from baseline SDS score were significantly influenced when we excluded any study one by one.

Discussion

The efficacy and safety of vortioxetine 10 mg/d verse placebo for treatment of MDD was examined in our study including eight RCTs. The present meta-analysis showed that the response and remission of vortioxetine 10 mg/d was greater than placebo. The superior antidepressant efficacy of vortioxetine 10 mg/d compared to placebo were demonstrated in terms of mean change of MADRS score, GCI-I mean score, mean change of SDS score. A sensitivity analysis did not influence the results when we ruled out any study one by one.

MADRS[24] is a scale to measure overall severity of depressive symptoms (such as apparent sadness, reported sadness, inner tension). Higher scores indicate greater severity of symptoms. A decrease is equal or more than 50% in the MADRS total score from baseline is defined as response while remission is defined as a participant with a MADRS total score less than or equal to 10. Our results showed that patients in vortioxetine group had a higher response rate when compared to placebo group, and similarly, the remission rate was also higher in 10 mg/d vortioxetine group than in placebo group. All these results indicated that patients treated with 10 mg/d vortioxetine could receive a better efficacy than patients treated with placebo. Further more, the MADRS score and SDS score were declined more serious and the CGI-I score was lower in the 10 mg/d vortioxetine group. The SDS[29] comprises self-rated items designed to measure impairment and the CGI-I30 assesses the participant's improvement. A decrease in the SDS total score indicates improvement, and the lower CGI-I score who gets, the much improved situation he will have. Thus our results demonstrated the improvement was shown in the 10 mg/d vortioxetine group.

The high heterogeneity (>75%) was found in the pooled trials of the change from baseline MADRS score, CGI-I score, and change from baseline SDS score, though we designed the inclusion criteria when we selected proper studies. The sensitively analysis did not influence the results which indicate that there was no single study can decide the pooled ES and the high heterogeneity. Many factors could contribute to the high heterogeneity such as the difference of patients' region and age. And the duration of patients taking drugs in different trial was difference, which may also a contribution to the heterogeneity. The gender of patients was also a key factor to influence the improvement of depression since that women were easier to experience depression than men[31]. It also contributed to the heterogeneity that the data of women and men were not separated to analyze respectively in our meta-analysis.

The incidence rate of nausea and constipation in the 10 mg/d vortioxetine group were significantly higher than placebo group in our analysis, which mean 10 mg/d vortioxetine would easily lead patients to feel nausea or constipation. Jie Fu et al.[19] and Masoud Behzadifar et al.[32] have ever reported that vortioxetine was easier in leading patients experience nausea. It may be a reason that patients refuse to take vortioxetine.

Conclusion

The current meta-analysis of published RCTs indicated that 10 mg/d vortioxetine was more effective than placebo for the treatment of adult major depressive disorder. But the patients in 10 mg/d vortioxetine group can easier to experience nausea and constipation.

Conflicts of interest

The authors declare that we have no conflict of interest.

Acknowledgements

The authors gratefully acknowledge financial support from the National Natural Science Foundation of China (31201236).

References

1. Smith K. Mental health: A world ofdepression. *Nature*. 2014; 515:181.

2. Yuan K S, Zheng J X, Yang D T, et al. Self-Assembly of Au@Ag Nanoparticles on Mussel Shell To Form Large-Scale 3D Supercrystals as Natural SERS Substrates for the Detection of Pathogenic Bacteria. *ACS Omega*. 2018; 3:2855–2864.

3. Mutlu O, Gumuslu E, Ulak G, et al. Effects of fluoxetine, tianeptine and olanzapine on unpredictable chronic mild stress-induced depression-like behavior in mice. *Life Sci*. 2012;91:1252-1262.
4. Available at: http://www.who.int/mediacentre/factsheets/fs369/en/.
5. FDA. Brintellix (vortioxetine): Highlights of Prescribing Information. Brintellix Label. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204447s000lbl.pdf.
6. Pehrson A L, Cremers T, Betry C, et al. Lu AA21004, a novel multimodal antidepressant, produces regionally selective increases of multiple neurotransmitters--a rat microdialysis and electrophysiology study. *Eur Neuropsychopharmacol*. 2013;23:133-145.
7. Bang-Andersen B, Ruhland T, Jørgensen M, et al. Discovery of 1-2-(2,4-Dimethylphenylsulfanyl)phenylpiperazine (Lu AA21004): A Novel Multimodal Compound for the Treatment of Major Depressive Disorder. *J Med Chem*. 2011;54:3206-3221.
8. Mork A, Pehrson A, Brennum L T, et al. Pharmacological effects of Lu AA21004: a novel multimodal compound for the treatment of major depressive disorder. *J Pharmacol Exp Ther*. 2012;340:666-675.
9. Gibb A, Deeks ED. Vortioxetine: first global approval. *Drugs*. 2014;74:135-145.
10. Chen G, Lee R, Hojer A M, et al. Pharmacokinetic drug interactions involving vortioxetine (Lu AA21004), a multimodal antidepressant. *Clin Drug Investig*. 2013;33:727-736.
11. Mahableshwarkar A R, Jacobsen P L, Chen Y. A randomized, double-blind trial of 2.5 mg and 5 mg vortioxetine (Lu AA21004) versus placebo for 8 weeks in adults with major depressive disorder. *Curr Med Res Opin*. 2013;29:217-226.
12. Jain R, Mahableshwarkar A R, Jacobsen P L, et al. A randomized, double-blind, placebo-controlled 6-wk trial of the efficacy and tolerability of 5 mg vortioxetine in adults with major depressive disorder. *Int J Neuropsychopharmacol*. 2013;16:313-321.
13. Henigsberg N, Mahableshwarkar A R, Jacobsen P, et al. A randomized, double-blind, placebo-controlled 8-week trial of the efficacy and tolerability of multiple doses of Lu AA21004 in adults with major depressive disorder. *J Clin Psychiatry*. 2012;73:953-959
14. Katona C, Hansen T, Olsen C K. A randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder. *Int Clin Psychopharmacol*. 2012;27:215-223
15. BaldwinD S, Loft H, Dragheim M. A randomised, double-blind, placebo controlled, duloxetine-referenced, fixed-dose study of three dosages of Lu AA21004 in acute treatment of major depressive disorder (MDD). *Eur Neuropsychopharmacol*. 2012;22:482-491.
16. Alvarez E, Perez V, Dragheim M, et al. A double-blind, randomized, placebo-controlled, active reference study of Lu AA21004 in patients with major depressive disorder. *Int J Neuropsychopharmacol*. 2012;15:589-600.
17. Mahableshwarkar A R, Jacobsen P L, Serenko M, et al. A randomized, double-blind, fixed-dose study comparing the efficacy and tolerability of vortioxetine 2.5 and 10 mg in acute treatment of adults with generalized anxiety disorder. *Hum Psychopharmacol*. 2014;29:64-72.
18. McIntyre R S, Lophaven S, Olsen C K. A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. *Int J Neuropsychopharmacol*. 2014;17:1557-1567.
19. Mahableshwarkar A R, Jacobsen P L, Serenko M, et al. A randomized, double-blind, placebo-controlled study of the efficacy and safety of 2 doses of vortioxetine in adults with major depressive disorder. *J Clin Psychiatry*. 2015;76:583-591
20. Jacobsen P L, Mahableshwarkar A R, Serenko M, et al. A randomized, double-blind, placebo-controlled study of the efficacy and safety of vortioxetine 10 mg and 20 mg in adults with major depressive disorder. *J Clin Psychiatry*. 2015;76:575-582.
21. Mahableshwarkar A R, Jacobsen P L, Chen Y, et al. A randomized, double-blind, duloxetine-referenced study comparing efficacy and tolerability of 2 fixed doses of vortioxetine in the acute treatment of adults with MDD. *Psychopharmacology (Berl)*. 2015;232:2061-2070.
22. 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.
23. Behzadifar M, Dehghan H, Saki K, et al. Evaluation Efficacy and Safety of Vortioxetine 20mg/d versus Placebo for Treatment Major Depressive Disorder: A Sys-

tematic Review and Meta-Analysis of Randomized Controlled Trials. *Pharmacology & Pharmacy*. 2015;06:221-231.
24. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134:382–389.
25. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Control Clin Trials*. 1996;17:1-12.
26. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557-560.
27. ClinicalTrials.gov. Efficacy Study of Vortioxetine (Lu AA21004) for Treatment of Major Depressive Disorder, Takeda. Updated November 4, 2014 Available at: https://clinicaltrials.gov/ct2/show/NCT01355081?term=NCT01355081&rank=1.
28. ClinicalTrials.gov. Efficacy and Safety Study of Vortioxetine (Lu AA21004) for Treatment of Major Depressive Disorder, Takeda. Updated October 25, 2013 Available at: https://clinicaltrials.gov/ct2/show/results/NCT01255787?term=NCT01255787&rank=1.
29. Arbuckle, R, Frye, MA, Brecher, M, et al. The psychometric validation of the Sheehan Disability Scale (SDS) in patients with bipolar disorder. *Psychiatry Res*. 2009;165:163-174.
30. Kadouri A, Corruble E, Falissard B. The improved Clinical Global Impression Scale (iCGI): development and validation in depression. *BMC Psychiatry*. 2007;7:1-7.
31. Gibson P A, Baker E H, Milner A N. The role of sex, gender, and education on depressive symptoms among young adults in the United States. *J Affect Disord*. 2016;189:306-313.
32. Behzadifar M, Keshavarzi A, Tofighian A, et al. Efficacy and Safety of Vortioxetine and Duloxetine 60 mg Compared Placebo for the Treatment of Major Depressive Disorder: A Systematic Review and Meta-Analysis. *J Behav Brain Sci*. 2015;5: 430-439.