

**Vortioxetine versus placebo for treatment of major depressive disorder**

Masoud Behzadifar<sup>1</sup>, Hamidreza Dehghan<sup>1</sup>, Kourosh Saki<sup>2</sup>, Kourosh Sayehmiri<sup>3</sup>, Meysam Behzadifar<sup>4</sup>, Ali Akbari Sari<sup>5\*</sup>

1. Department of Health Technology Assessment, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
2. Shahid Beheshti University of Medical Sciences, Tehran, Iran
3. Department of Health, Ilam University of Medical Sciences, Ilam, Iran
4. Nutritional Health Research Center, Lorestan University of Medical Sciences, Khorramabad , Iran
5. Department of Health Management and Economics, Knowledge Utilization Research Center, Tehran University of Medical Sciences, Tehran, Iran

**\*Corresponding author:** Tel: +98 2188989120 Fax: +98 2166462267

Address: Department of Health Management and Economics, Knowledge Utilization Research Center, Tehran University of Medical Sciences, Tehran, Iran

E-mail: akbarisari@tums.ac.ir

Received; 2015/03/11 revised; 2015/05/27 accepted; 2015/08/16

**Abstract**

**Introduction:** Major depressive disorder is a common mental condition associated with substantial morbidity and economic burden. Approved by the FDA in September 2013 for treatment of episodes of major depressive disorder, Vortioxetine is one of the newer options available in this important area of therapeutics.

**Materials and methods:** A comprehensive literature search (PubMed, the Cochrane library, Scopus, CRD and HTA Database in January 2015) was performed, containing controlled clinical trials that vortioxetine 10 mg/d versus placebo in adults with major depressive disorder.

**Results:** Six controlled clinical trials were included in this meta-analysis. There was a significant difference between the vortioxetine 10 mg/d versus placebo in the Montgomery–Åsberg Depression Rating Scale (MADRS) (P value <0.00001). The results of pooled analysis for diarrhea, dry mouth, dizziness, headache and nausea were also significant (P value <0.00001). Vortioxetine 10 mg/d versus placebo showed a significant difference for nausea, but no significant differences were observed for the other five adverse effects.

**Conclusion:** Therapy with vortioxetine was significantly associated with reduction in depression symptoms from baseline compared to placebo.

**Keywords:** Vortioxetine 10 mg/d, Systematic Review, Meta-analysis, Major Depressive Disorder

**Introduction**

Major depressive disorder (MDD) is characterized essentially by “depressed mood” and “loss of interest or pleasure in nearly all activities” according to the Diagnostic and Statistical Manual of Mental Disorders IV (1). Major depressive disorder is a common mental condition associated with substantial morbidity and

economic burden. The World Health Organization ranks depression as the largest contributor to years lost to disability and the fourth largest contributor to disability-adjusted life-years (2). Signs and symptoms include feelings of guilt, anxiety, fatigue, sleep disturbances, and cognitive and sexual dysfunction

(3). Depression is a serious, common, and a recurring disorder linked to diminished functioning, quality of life, medical morbidity, and mortality (4). There has been a 37.5% increase in health, life years lost to depression over the past two decades (5). Depression was the third-leading cause of the global burden of disease in 2004 and the leading cause of burden of disease in high- and middle-income countries. It is projected to be the leading cause globally in 2030 (6). While effective treatments for depression are available, they are used. Barriers to treatment include geography, socioeconomic status, system capacity, treatment costs (direct and indirect), low mental health literacy, cultural beliefs, and stigma (7, 8). A 2010 study found that 75% of primary care patients with depression in urban areas could identify more than one structural, psychological, cultural, or emotional barrier to accessing behavioral treatments. The rate was substantially higher in rural areas (9). Vortioxetine is one of the newer options available in this important area of therapeutics, that approved by the FDA in September 2013 for treatment of episodes of major depressive disorder (10). More than 30 pharmacotherapy options are available for unipolar depression, including: selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs), bupropion, serotonin antagonist/reuptake inhibitors, second-generation antipsychotics,  $\alpha_2$  antagonists, monoamine oxidase inhibitors (MAOIs), norepinephrine reuptake inhibitors, and tetracyclics. These treatments are meant to reduce mortality and improve quality of life (11). After oral administration, Vortioxetine is absorbed in the gastrointestinal tract and exhibits peak plasma concentrations in about seven to 11 hours ( $T_{max}$ ). Its bioavailability is 75%. Consumption of food

does not affect the bioavailability, and taking vortioxetine with food has not been shown to increase its peak concentration ( $C_{max}$ ) (12). The efficacy of vortioxetine was demonstrated in 6 positive 6 to 8 week randomized, double-blind, placebo-controlled studies, including one study conducted in elderly patients and one maintenance study. These studies demonstrated statistically significant improvements in overall symptoms of depression in adults with MDD based in Montgomery-Asberg Depression Rating Scale (MADRS). (12). The objective of this Meta – analysis was to evaluate the efficacy and safety of vortioxetine 10 mg/d versus placebo in adults with Major depressive disorder.

## Materials and Methods

**Search strategy:** Electronic searches were performed in the Cochrane library, PubMed, Scopus, CRD and HTA Database in January 2015. We also searched ClinicalTrials.gov because it includes the results of both publicly and privately supported clinical studies of humans participants conducted worldwide. Our searches will not be limited by language, publication status or setting. The reference lists of articles and other reviews retrieved in the search or known to the authors will be searched for relevant articles. Unpublished work will be identified by searching the abstract books or websites of two major conferences: the International depressive disorder Conference, the Anxiety Disorders and Depression Conference. An abstract of interest will be assessed in further detail by contacting the authors. We will try to contact the authors of included studies to acquire other data that may either be unpublished or informally published or ongoing and which is related to efficacy of vortioxetine in depression. Data collection and analysis a summary of the identification, screening and inclusion of studies in this review will be presented as a PRISMA (13) (Figure 1).

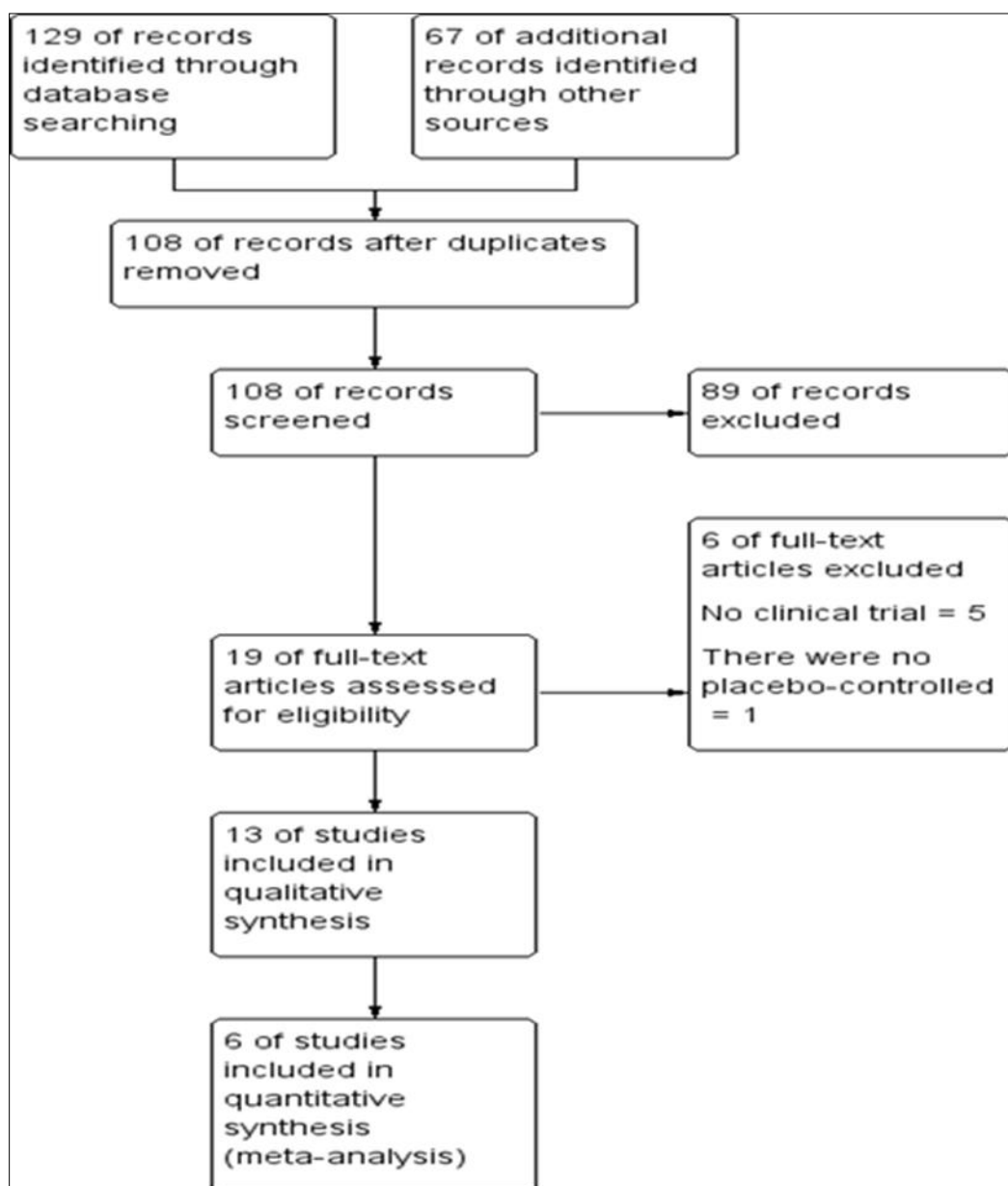


Figure 1. Flow diagram for article selection.

Two review authors (Masoud. B, Meysam. B) Will independently screen and select studies for possible inclusion in the study. First, the titles and abstracts of trials identified from the search will be independently reviewed and pooled for further screening. Secondly, each review author will independently examine the full text of all trials that were identified from the title and abstract scenes. Each reviewer will compile a list of studies that meet the inclusion criteria. The contents of each review author's list will be compared, and any disagreement will be resolved by

discussion and consensus between all of the review authors.

**Inclusion criteria:** Clinical trials testing the efficacy of vortioxetine for the Major depressive disorder were eligible for inclusion. Included studies had to be RCTs comparing vortioxetine with placebo. We considered trials that recruited patients for evaluation of other outcomes if they also met the aforementioned criteria for Major depressive disorder and included data for outcomes of major depressive disorder. Studies were excluded if the main outcome were prevention of relapse or if treatment

outcomes based on rating scales of MDD were not available.

**Data extraction:** We collected data on participant characteristics, treatment details, study procedures, efficacy measures and Adverse Events (AEs). These data included, for example, group (treatment, placebo), size sample, age, sex, duration of treatment, baseline MADRS, doses and study location. A summary of the characteristics of the included studies is presented in Table 1. Outcome data related to the characteristics of the individual trial and the reported results were extracted for each trial. The efficacy measures were the

mean change from baseline in total scores on the MADRS. The MADRS is a ten-item diagnostic questionnaire which psychiatrists use to measure the severity of depressive episodes in patients with mood disorders (14). If studies compared different doses of vortioxetine to the placebo, we only included data comparing the 10 mg/day and placebo doses. For assessed of safety of vortioxetin 10 mg, Data on the number of dropouts (for any reason), lack of efficacy and incidence of AEs were included in the analysis (Table 1).

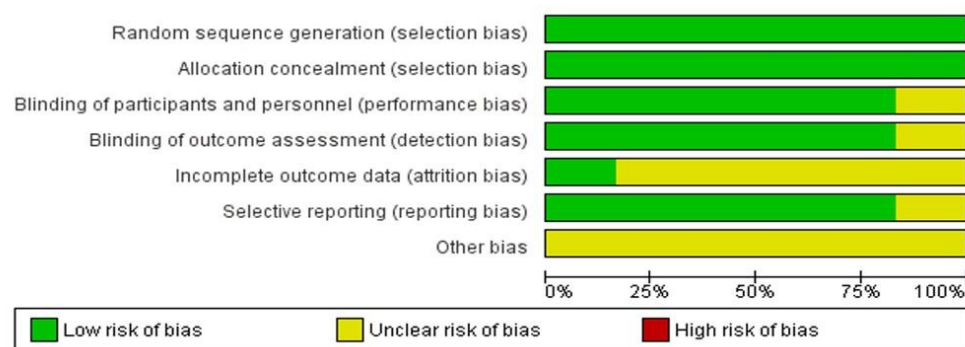
**Table 1.** Summary of the included studies in the Meta-analysis.

Author	Group	Cases	Age (year)	M/F	Baseline MADRS score	Doses	Study location	Entry score by MADRS
Alvarez	T	100	42.3 ±13.1	34:66	34.0±2.8	5,10	Europe/Asia	≥30
	P	105	42.0 ±10.9	36:69	33.9±2.7			
Baldwin	T	151	45.2 ±13.1	51:100	30.4±5.4	2.5,5,10	Europe/Asia	≥26
	P	148	43.4 ±12.5	45:103	29.8±5.1			
Henigsberg	T	140	46.4 ±12.27	55:85	33.1±4.8	1,5,10	Europe/Asia/Africa	≥26
	P	140	46.4 ±12.26	54:86	32.7±4.4			
Jacobsen	T	155	43.1 ±12.04	37:118	32.3±4.5	10,20	USA	≥26
	P	157	42.3 ±11.61	47:110	32.0±4.0			
Mahableshwarkar	T	157	45.2 ±11.94	44:113	34.1±4.1	10,15	USA	≥26
	P	160	46.2 ±11.79	52:108	33.4±4.5			
Trial NCT01255787	T	150	45.7 ±10.90	57:93	31.8±4.0	5,10,20	Europe/Asia	≥26
	P	152	43.6 ±11.57	61:91	31.6±3.6			

T, treatment; P, placebo; M, male; F, female.

**Assessment of risk of bias in included studies:** Quality of studies was rated according to the Cochrane Collaboration's Tool for Assessing Risk of Bias (15), including Random sequence generation (selection bias), Allocation concealment

(selection bias), Blinding of participants and personnel (performance bias), Blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), Selective reporting (reporting bias) and other bias (Figure 2).



**Figure 2.** Assessment of risk of bias in included studies according to the Cochrane Collaboration's Tool.

### Quality assessment of the included studies:

The Jadad score is an instrument used to assess the quality of randomized clinical trials (RCTs). It includes three items as follows: randomization (The study was not randomized or an inappropriate method of randomization was used, the study was described as Randomized, the method of randomization was described and it was appropriate), blindness (The study was not blind or an Inappropriate method of blinding was used, The study was described as double

blind, the method of double blinding was described and it was appropriate), and dropouts (The dropouts were not described in the follow-up, The study contained a description of withdrawals and dropouts). The score standards and the results of our included studies are shown in Table 2, respectively. We are rated as providing good methodological quality based on a Jadad score of 1-5. So the total scores for all included articles indicated a high study quality. The study quality was assessed with Jadad scores (16).



**Table 2.** Jaded score quality assessment of the included studies.

Name study	Years study	Randomization	Blindness	Dropouts	Jaded scores
Alvarez	2012	2	2	1	5
Baldwin	2012	2	2	1	5
Henigsberg	2012	2	2	1	5
Jacobsen	2013	2	2	1	5
Mahableshwarkar	2013	2	2	1	5
Trial NCT01255787	2014	2	2	1	5

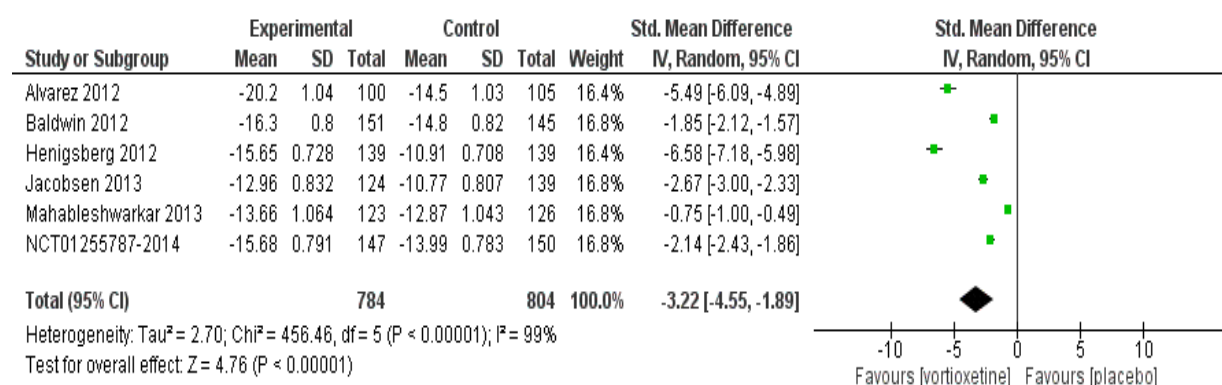
### Statistical analysis

In the review, we assessed MADRS and adverse effects randomized into the vortioxetine 10 mg/day and placebo groups for each trial were statistically combined using by Mantel–Haenszel random effects model. The effects were expressed as standard means different ratios (SMD) with 95% confidence intervals (CIs) and p values. The incidence of adverse effects between the vortioxetine 10 mg/day and placebo groups was also determined using the Mantel–Haenszel model, and the results were expressed as the Odds Ratio (ORs) with the 95 % CI and p values. The heterogeneity across each effect size was evaluated by using the  $I^2$  and Chi-squared tests statistic. This measure evaluates how much of the variance among studies can be attributed to the actual differences among the studies rather than to chance. A magnitude of considerable heterogeneity is usually  $I^2 = 75\%–100\%$  (17). A sensitivity analysis was performed to rule out the possibility

that any single study strongly influenced the pooled effect. Publication bias was assessed by a funnel plot, Egger's test (18), and Begg's rank correlation test (19). Statistical analyses were conducted using Rev Man 5.3 software from the Cochrane Collaboration and Stata 12 software.

### Results

**Efficacy:** Overall, 6 articles met the inclusion criteria and were finally used for this meta-analysis. This article consists Alvarez et al (20), Baldwin et al (21), Henigsberg et al (22), Jacobsen et al (23), Mahableshwarkar et al (24) and trial no NCT01255787 (25). A total of six studies with 1715 patients, 853 in the 10 mg/day Vortioxetine group and 862 patients in the placebo group. The SMD for MADRS with vortioxetine 10 mg compared to placebo was -3.22 with 95% CI [-4.55, -1.89] and P value <0.00001 and heterogeneity for the MADRS scale was  $I^2 = 99\%$  (Figure 3).



**Figure 3.** Forest plot of Standard Different Mean ratios (SMD), 95 % confidence intervals (CIs) in the Montgomery–Åsberg Depression Rating Scale (MADRS).

**Safety:** Drug safety evaluation for symptoms that have been observed in studies was meta-analysis. The most common side effects were diarrhea, dry mouth, dizziness, fatigue, headache and nausea. Results the 10 mg/day vortioxetine compared to placebo showed for diarrhea OR = 0.84 with 95% CI [0.56, 1.27], P value = 0.42, for dry mouth result showed OR = 0.76 with 95% CI [0.49, 1.9], P value = 0.23, for dizziness OR = 1.02 with 95% CI [0.57, 1.83], P value = 0.95, for fatigue OR = 1.01 with 95% CI [0.59, 1.73], P value = 0.97, for headache OR = 0.92 with 95% CI [0.70, 1.22], P value = 0.57 and for nausea OR = 3.89 with 95% CI [2.88, 5.26], P value <0.00001.

**Analysis for publication bias:** Analysis for publication bias in the included studies showed, no publication bias was observed for the MADRS (Egger's test: P= 0.003 respectively, and Begg's test: P= 0.015 respectively) and funnel plots, no publication bias was observed for Adverse Events contain diarrhea, dry mouth, Dizziness, fatigue, headache and nausea analysis in the included studies. (Egger's test: P= 0.229, P= 0.162, P=0.373, P= 0.147, P= 0.488, P= 0.488 respectively and Begg's test: P= 0.188, P= 0.091, P= 0.188, P= 0.188, P= 0.573, P= 0.188, respectively).

**Sensitivity analysis:** A sensitivity analysis not found that the pooled remission rate was significantly influenced when we excluded the study from trial Baldwin et al (21).

## Discussion

The development of vortioxetine, an antidepressant with a novel mechanism of action, which was approved by the FDA in September 2013 for the treatment of major depressive disorder (26). In this meta-analysis, we aimed to evaluate the efficacy and safety of vortioxetine at dose 10 mg in the treatment of MDD by including randomized controlled trials. studies by Katona et al (27), Mahableshwarkar et al (28-29), Jain et al (30) and Boulenger et

al(31) showed that vortioxetine efficacy for treatment Major depressive disorder (MDD). Improved symptoms in patient of major depressive disorder obtained in these studies. The present study supports the efficacy and safety of using vortioxetine 10 mg/d in the treatment Major depressive disorder. We identified six RCTs (1715 patients) for vortioxetine 10 mg/d compared placebo. Five study (Baldwin, Henigsberg, Jacobsen, Mahableshwarkar and Trial NCT01255787) during 8 weeks and a study (Alvarez) has been done during six-week. However, these findings must be interpreted with caution the quality of assessment. The Jadad score is an instrument used to assess the quality of randomized clinical trials was all 5 studies. All the studies according to the specifications (Randomization, Blindness and Dropouts) of the appropriate quality were Jadad.

The quality of the evidence of the six included randomized clinical trial studies, six trials clearly described random sequence generation. In five trials, described blinding of participants and personnel and one study unclear risk of this bias. In five trials blinding of outcome assessment and one study unclear risk of this bias, in one study were described incomplete outcome data and five studies had Selective reporting and five studies unclear risks of this bias.

No statistical evidence was found for publication bias or heterogeneity, and the results remained significant after any one of the trials was removed. The result meta-analysis of SMD suggest that significant differences for MADRS with vortioxetine 10 mg compared to placebo (SMD = -3.22 with 95% CI [-4.55, -1.89] and P value <0.00001). The decrease in depression symptoms seems too associated with 10 mg/d of vortioxetine versus placebo. Clinical trials testing the efficacy of vortioxetine for the short-term treatment (6-8 weeks.) of major depressive disorder were eligible for inclusion. Results of

Adverse events (AEs) showed a significant for nausea OR = 3.89 with 95% CI [2.88, 5.26], P value <0.00001, but no significant differences were observed for the other five adverse effects. AEs discontinuation rates were generally low. It suggested that the negative results in previous double-blind, random-controlled studies may have been due to an inadequate sample size, which can be overcome by the meta-analytic method. These findings indicate that compared to placebo, 20 mg/d mg/day vortioxetine significantly improved depressive symptoms in patients with major depressive disorder. In the randomized clinical analyzed, the common adverse effects of vortioxetine include diarrhea, dizziness, dry mouth, nausea, headache and fatigue. The limitations of this meta-analysis include the following: The inclusion of patients only during the acute phase, which did not enable us to analyze the long-term efficacy and safety of vortioxetine in treating major depressive disorder. The included studies did not include data on the onset time of vortioxetine's efficacy, and thus, we did not compare the onset time between 10 mg/d vortioxetine and placebo. All 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 influenced the results. All included studies did not include the efficacy and adverse effects based on sex; thus, we could not evaluate gender differences. Due to the limited number of the published articles, we did not analyze the efficacy and safety of different doses of vortioxetine in the treatment of major depressive disorder. The small number of included studies and the relatively small sample size, which may influence the reliability of the results. Treatment of depression still remains a challenge, with one of the issues being the diversity of the individual patient symptom profiles, and often residual symptoms persist at the end

of antidepressant treatment (32). However, depression is frequently associated with coronary heart diseases (33), diabetes mellitus (34), stroke (35), pregnancy, and the postpartum period (36). Thus, the use of vortioxetine should also benefit the physical state of these patients. Due to the small number of trials in our meta-analysis, our results warrant additional studies to verify these findings. In the future, additional large-scale and well-designed studies are needed to determine the optimal dose, the most appropriate treatment group, and the efficacy and safety of vortioxetine combined with other antidepressants in treating depression (37-38).

## Conclusion

We found that the vortioxetine 10 mg/d may be effective compared with a placebo for treatment major depressive disorder. The evidence base reported in this review is of very good quality and includes only a small number of studies, which imposes significant limitations for conclusions on both efficacy and potential adverse outcomes. However, our results should be interpreted and translated into clinical practice with caution, effect sizes of the clinical trials included in the present meta-analysis. Adequately powered, well-designed, direct-comparison clinical trials should also be more clearly addressed the comparative efficacy of vortioxetine and different antidepressants. The current meta-analysis of published RCTs has shed light on the benefits of 10 mg/d vortioxetine for the treatment of major depression disorder. Further studies in the future with more ensure that can find this drug in the treatment of depressive patients rated effectiveness.

## Acknowledgement

The authors would like to thank all participants who made this study possible.



## References

1. Pehrson AL, Sanchez C. Altered  $\gamma$ -amino butyric acid neurotransmission in major depressive disorder: a critical review of the supporting evidence and the influence of serotonergic antidepressants. *Drug Des Devel Ther*. 2015; 9(5):603-624.
2. Birnbaum HG, Kessler RC, Kelley D, Ben-Hamadi R, Joish VN, Greenberg PE. Employer burden of mild, moderate, and severe major depressive disorder: mental health services utilization and costs, and work performance. *Depress Anxiety*. 2010; 27(1):78-89.
3. Kennedy SH. Core symptoms of major depressive disorder: relevance to diagnosis and treatment. *Dialogues Clin Neurosci*. 2008; 10(3):271-277.
4. Kessler RC, Bromet EJ. The epidemiology of depression across cultures. *Annu Rev Public Health*. 2013; 34(6):119-138.
5. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman A, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012; 380(9859):2197-223.
6. Jaeger J, Berns S, Uzelac S, Davis-Conway S. Neurocognitive deficits and disability in major depressive disorder. *Psychiatry Res*. 2006; 145(1):39-48.
7. Titov N, Dear BF, Schwencke G, Andrews G, Johnston L, Craske MG, et al. Transdiagnostic internet treatment for anxiety and depression: a randomised controlled trial. *Behav Res Ther*. 2011; 49(8):441-452.
8. Clarke G, Yarrow B. Evaluating the promise of Health IT to enhance/expand the reach of mental health services. *Gen Hosp Psychiatry*. 2013; 35(4):339-344.
9. Mohr DC, Ho J, Duffecy J. Perceived Barriers to Psychological Treatments and Their Relationship to Depression. *J Clin Psychol*. 2010; 66(4):394-409.
10. FDA. Brintellix (vortioxetine): Highlights of Prescribing Information. Brintellix Label. Available at [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/204447s0001bl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204447s0001bl.pdf)
11. McIntyre RS, Lophaven S, Olsen CK. A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. *Int J Neuropsychopharmacol*. 2014; 17(10):1557-1567.
12. McDonagh MS, Peterson K, Balshem H, Helfand M. US Food and Drug Administration documents can provide unpublished evidence relevant to systematic reviews. *J Clin Epidemiol*. 2013; 66(10):1071-81.
13. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche P, Ioannidis J, et al. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. *PLoS Med*. 2009; 6(7):91-100.
14. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979; 134 (4): 382-89.
15. Higgins JPT, Altman DG, Gøtzsche PC. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ: Br Med J*. 2011; 343(114):5928-36.
16. Jadad AR. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996; 17(1):1-12.
17. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ: Br Med J*. 2003; 327(7414):557-560.
18. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test.

- BMJ: Br Med J. 1997; 315(7109):629-634.
19. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994; 50(4):1088–1101.
  20. Alvarez E, Perez V, Dragheim M, Loft H, Artigas F. A double-blind, randomized, placebo-controlled, active reference study of Lu AA21004 in patients with major depressive disorder. *Int J Neuropsychopharmacol*. 2012; 15(5):589-600.
  21. Baldwin DS, 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(7):482-91.
  22. Henigsberg N, Mahableshwarkar AR, Jacobsen P, Chen Y, Thase ME. 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(7):953-9.
  23. Jacobsen PL. 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(5):575-82.
  24. Mahableshwarkar AR, Jacobsen PL, Serenko M, Chen Y, Trivedi MH. 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(5):583-91
  25. Efficacy and Safety Study of Vortioxetine (Lu AA21004) for Treatment of Major Depressive Disorder. Available at <http://clinicaltrials.gov/ct2/show/NCT01255787?term=NCT01255787&rank=1>
  26. D'Agostino A, English CD, Rey JA. Vortioxetine (Brintellix): A New Serotonergic Antidepressant. *Pharmacy and Ther*. 2015; 40(1):36-40.
  27. Katona C, Hansen T, Olsen CK. 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(4):215-23
  28. Jain R, Mahableshwarkar AR, Jacobsen PL. 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(2):313-21.
  29. Mahableshwarkar AR, Jacobsen PL, Chen Y, Serenko M, Trivedi MH. 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(12):2061-70.
  30. Jain R. 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(2):313-21.
  31. Boulenger JP, Loft H, Olsen CK. Efficacy and safety of vortioxetine (Lu AA21004), 15 and 20 mg/day: a randomized, double-blind, placebo-controlled, duloxetine-referenced study in the acute treatment of adult patients with major depressive disorder. *Int Clin Psychopharmacology*. 2014; 29(3):138-149.
  32. Nierenberg AA, Keefe BR, Leslie VC, Alpert JE, Pava JA, Worthington JJ, et

- al. Residual symptoms in depressed patients who respond acutely to fluoxetine. *J Clin Psychiatry*. 1999; 60(4):221-5.
33. Penninx BW, Beekman AT, Honig A, Deeg DJ, Schoevers RA, van Eijk JT, et al. Depression and cardiac mortality: results from a community-based longitudinal study. *Arch Gen Psychiatry*. 2001; 58(3):221-7.
34. Schlienger JL. Type 2 diabetes complications. *Presse Med*. 2013; 42(5): 839–848 .
35. Robinson RG, Spalletta G. Poststroke Depression: A Review .*Canadian j psychiatry*. 2010; 55(6):341-349.
36. Di Florio A, Forty L, Gordon-Smith K. Perinatal episodes across the mood disorder spectrum. *JAMA Psychiatry*. 2013; 70(2):168–175 .
37. 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(1):7-16 .
38. Frank E, Prien RF, Jarrett RB, Keller MB, Kupfer DJ, Lavori PW, et al. Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. *Arch Gen Psychiatry*. 1991; 48(9):851-5.