Journal of Behavioral and Brain Science, 2015, 5, 430-439
Published Online September 2015 in SciRes. http://www.scirp.org/journal/jbbs
http://dx.doi.org/10.4236/jbbs.2015.510041

Efficacy and Safety of Vortioxetine and Duloxetine 60 mg Compared Placebo for the Treatment of Major Depressive Disorder: A Systematic Review and Meta-Analysis

Masoud Behzadifar[1], Abouzar Keshavarzi[2], Abed Tofighian[1], Mohammad Rastian[1], Mohammad Zobidi[1], Ali Akbari Sari[3*]

[1]Department of Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[2]Shiraz University of Medical Sciences, Shiraz , Iran
[3]Department of Health Management and Economics, Tehran University of Medical Sciences, Tehran, Iran
Email: [*]akbarisari@tums.ac.ir

Received 8 August 2015; accepted 7 September 2015; published 10 September 2015

Abstract

Background: Major depressive disorder is a serious public health problem affecting the lives of millions in the worldwide and leading causes of disability and disease. This study aimed to evaluate the efficacy and safety of Vortioxetine and Duloxetine 60 mg compared to placebo for the treatment of major depressive disorder. Method: We searched the Cochrane library, Pub Med, CRD, Scopus, and Central Register of Controlled Trials to January 2015. We also searched Clinical-Trials.gov, International depressive disorder Conference and the Anxiety Disorders and Depression Conference. We identified that five randomized clinical trials were ultimately included in a Meta analysis. Data analysis was conducted by Standardized Mean Differences (SMD) for Montgomery-Åsberg Depression Rating Scale (MADRS), and Odds Ratio (OR) for adverse events. The SMD and OR reported by 95% CI. Results: Results showed statistical significance in the MADRS for Vortioxetine (SMD = −3.29; 95% CI −4.47 to −2.10; I^2 = 99.3%) and for Duloxetine 60 mg (SMD = −6.35; 95% CI −8.84, −3.87; I^2 = 99.3%). Results showed that the Vortioxetine 2.5, 5, 10, 15, 20 mg and overall compared to placebo showed a significance for Nausea and no significance for diarrhea, dry mouth, dizziness, fatigue and headache. Also results of Duloxetine 60 mg showed a significant effect for dry mouth, dizziness, fatigue and nausea. Conclusion: It is necessary to do more studies so as to better assess and much more powerful than the evidence for the use of this drug in the treatment of depression.

[*]Corresponding author.

How to cite this paper: Behzadifar, M., *et al*. (2015) Efficacy and Safety of Vortioxetine and Duloxetine 60 mg Compared Placebo for the Treatment of Major Depressive Disorder: A Systematic Review and Meta-Analysis. *Journal of Behavioral and Brain Science*, **5**, 430-439. http://dx.doi.org/10.4236/jbbs.2015.510041

Keywords

Vortioxetine, Duloxetine 60 mg, Placebo, Major Depressive Disorder, Systematic Review, Meta-Analysis

1. Introduction

Major depressive disorder (MDD) is a serious public health problem affecting the lives of millions in the worldwide and leading causes of disability and disease [1]. This disease causes disorder in social, mental and physical functions of patients [2]. It is estimated that depressive disorder will have the first place disease burden in developing countries in the 2020. According to reports of the World Health Organization (WHO), about 350 million people worldwide suffer from major depressive illness [3]. Major depressive disorders are common mental health conditions which are thought to be caused by an imbalance in serotonin (5-HT) and nor epinephrine in addition to multiple situational, cognitive, and medical factors [4]. Patients with major depressive disorder often have such symptoms or signs: low pleasure usual activities, depressed mood, changes in sleeping or eating, fatigue, suicidal thoughts and difficulty concentrating [5]. Antidepressants play important role in the treatment of patients with depression and can often cause adverse effects [6]. In patients with major depression disorder, these diseases are reported: Parkinson's disease, rheumatic arthritis, asthma, cancer, backs problems, chronic obstructive pulmonary disease (COPD), migraine, stroke, heart disease, diabetes mellitus, epilepsy, multiple sclerosis, and inflammatory bowel disease [7]. Vortioxetine, an antidepressant for the treatment of major depressive disorder, was approved by the Food and Drug Administration (FDA) in 2013. Vortioxetine is a selective serotonin reuptake inhibitor (SSRI) that binds to the presynaptic serotonin reuptake site, increasing the level of serotonin (5-HT) in the neuronal synapse and selectively binding to a variety of other serotonin receptors. It selectively binds to and acts as an antagonist of 5-HT3, 5-HT1D and 5-HT7 receptors, as a partial agonist to 5-HT1B receptors, and as an agonist of 5-HT1A receptor [8]. Duloxetine 60 mg, is an antidepressant which was approved for the treatment of major depressive disorder in 2004, and inhibits the neuronal uptake of serotonin and nor epinephrine, with a negligible affinity for other neuronal receptors, and this dual inhibition mechanism is believed to underlie its therapeutic effects [9]. In this study, Meeker *et al*., results showed Vortioxetine was significantly more effective than placebo for acute treatment of major depressive disorder (MDD). Although treatment effect estimates varied substantially between studies, a dose effect was not observed. Vortioxetine doesn't appear to be more effective, and is potentially less effective than an SNRI [10]. This study aimed to evaluate the efficacy and safety of Vortioxetine and Duloxetine 60 mg compared to placebo for the treatment of major depressive disorder.

2. Methods

2.1. Search Strategy

The aim of this paper was to evaluate the efficacy and safety of Vortioxetine and Duloxetine 60 mg compared placebo for the treatment of major depressive disorder.

In this systematic and meta-analysis, we searched the Cochrane library, Pub Med, CRD, Scopus, Central Register of Controlled Trials to January 2015. We also searched ClinicalTrials.gov, International depressive disorder Conference and the Anxiety Disorders and Depression Conference. Our searches will not be limited by language, publication status or setting. The findings (data collection, summary and analysis of the identification) of this systematic review are reported according this systematic review and the results will be presented as a PRISMA [11], which are shown in **Figure 1**.

2.2. Inclusion Criteria

We used randomized clinical trials (RTC) to investigate the efficacy and safety Vortioxetine and Duloxetine 60 mg compared to placebo (Vortioxetine and Duloxetine 60 mg and placebo in a three-arm study). Adult pa-

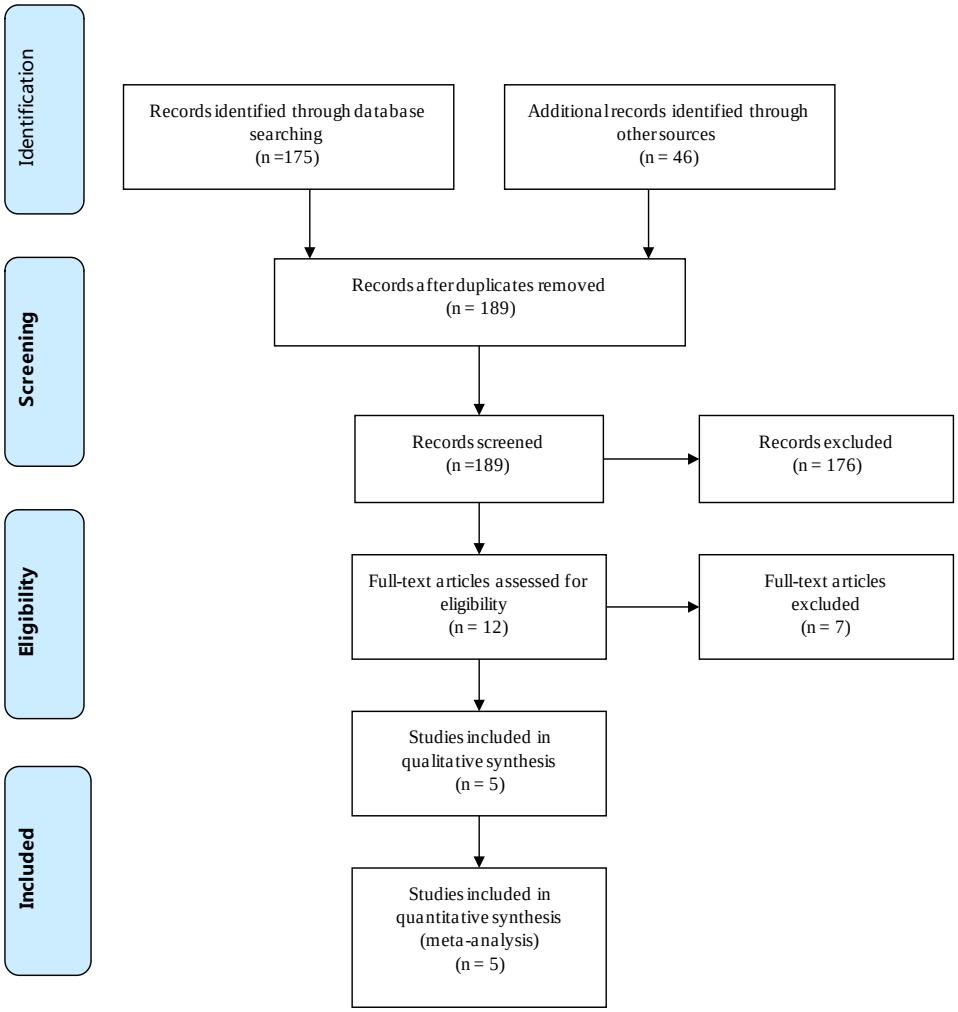


Figure 1. Flowchart of included studies in meta-analysis.

tients of both genders man and women with a primary diagnosis of major depressive disorder according to the diagnostic and statistical manual of mental disorder 4 the Ed – Text revision criteria were invluded [12]. Studies were excluded if the main outcome was prevention of relapse or if treatment outcomes based on rating scales of major depressive disorder were not available.

2.3. Data Extraction

In order to extract the data, two reviewers independently identified the "main outcome measure" and extracted data for each trial using a standard recording approach. First, screening the titles and abstracts of RCTs. Secondly, review author will independently full text of all trials. Compares the contents of each review author's list, and conflicts were resolved by discussion. We collected data on treatment details, study procedures, participant characteristics, efficacy measures and adverse events (AEs). These data included arms (Vortioxetine, Duloxetine 60 mg, and placebo), size sample, age, sex, and duration of treatment, baseline MADRS and doses and study location. Outcome data related to the characteristics of the individual trial and the reported results were extracted for each trial. In the study, we assessed Montgomery Åsberg Depression Rating Scale (MADRS), and adverse effects contain diarrhea, dry mouth, dizziness, fatigue, headache and nausea included in meta-analysis..

2.4. Quality Assessment

Quality assessment studies included the review by the Cochrane Collaboration "Risk of bias" [13], which were

shown in **Table 1**.

2.5. Quality of RCTs Included

The study quality was assessed with Jadad scores. This instrument was used to assess the quality of RCT [14].

It includes three items as follows: randomization, blinding and dropouts. The score standards and the results of our included studies are shown in **Table 2**, respectively. We're 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.

2.6. Statistical Analysis

In the study, the Montgomery Åsberg Depression Rating Scale (MADRS) [15] were reported in studies and adverse effects of Vortioxetine and Duloxetine 60 mg compared to placebo were statistically combined using the Mantel-Haenszel random effects model. The effect sizes were expressed as SMD (Standardized Mean Differences) [16]. The assessment of adverse effects was also determined using the Mantel-Haenszel model [17], and the results were expressed as the OR (Odds Ratio). The SMD and OR reported by 95% CI (confidence intervals) and P values. Heterogeneity across each effect size was evaluated by using the I^2 and Chi-squared test statistic [18]. 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 % [19]. To assess the Publication bias by a funnel plot, Egger's test [20], and Begg's [21] rank correlation test were used. All the statistical analyses were performed by using Review Manager (Rev Man 5.3) software and Stata 11 software.

3. Results

This study evaluated the efficacy, safety of Vortioxetine and Duloxetine 60 mg compared to placebo for treatment of major depressive disorder in patients. The literature search resulted in a total of 189 records after duplicates

Table 1. Risk of bias graph of the included studies.

Items	Author				
	Baldwin-2012	Katona - 2012	Boulenger-2013	Mahableshwarkar -2013	Mahableshwarkar-2014
Random sequence generation (selection bias)	L	L	L	L	L
Allocation concealment (selection bias)	L	L	L	L	L
Blinding of participants and personnel (performance bias)	L	L	L	L	L
Blinding of outcome assessment (detection bias)	L	L	L	L	L
Incomplete outcome data (attrition bias)	L	U	U	U	U
Selective reporting (reporting bias)	L	U	L	L	L
Other bias	U	U	L	U	U

L = low risk of bias; U = unclear risk of bias; H = high risk of bias.

Table 2. Jadad score quality assessment of the included studies in meta-analysis.

Name study	Year	Randomization	Blindness	Dropouts	Jaded scores
Baldwin	2012	2	2	1	5
Katona	2012	2	2	1	5
Boulenger	2013	2	2	1	5
Mahableshwarkar	2013	2	2	1	5
Mahableshwarkar	2014	2	2	1	5

were removed. Of these, 176 were excluded because they did not meet inclusion criteria, and 12 candidate trials were assessed for eligibility. We identified five randomized clinical trials with a total of 3039 patients fulfilled the inclusion criteria for treatment MDD. **Table 3** summarizes the characteristics and findings of the included studies. Randomized clinical trials ranged in size from 452 to 755 participants. All five trials were Vortioxetine, Duloxetine 60 mg and placebo in the three arms. Trials ranged studied more than one Vortioxetine dose ranging from 2.5 to 20 mg and Duloxetine 60 mg dose was 60 mg. According to jaded scores five included trials indicated a high study quality.

Table 3. Characteristics of included studies.

Authors	Arms	Mean age	Duration (wk)	Sample size	Baseline MADRS score	Study location	Entry score by MADRS	Year of publication	References
Baldwin			8			Europe-Asia	≥26	2012	[22]
	Placebo	43.4		145	29.8 ± 5.1				
	VTX 2.5 mg	46		155	29.6 ± 5.8				
	VTX 5 mg	44.7		155	31.3 ± 5.8				
	VTX 10 mg	45.2		151	30.4 ± 5.4				
	DLX 60 mg	45.3		149	29.9 ± 5.8				
Katona			8			Usa-Europe-Asia	≥26	2012	[23]
	Placebo	70.3		145	29.4 ± 5.1				
	VTX 5 mg	70.5		156	29.2 ± 5				
	DLX 60 mg	70.9		151	28.5 ± 4.9	Usa	≥26	2013	
Mahablashwarkar			8						[24]
	Placebo	42.6		153	29.5 ± 6.1				
	VTX 2.5 mg	42.6		153	29.8 ± 5.4				
	VTX 5 mg	43.1		153	29.8 ± 4.5				
	DLX 60 mg	42.7		152	29.4 ± 4.4				
Boulenger			8			Europe	≥26	2013	[25]
	Placebo	48.1		158	31.5 ± 3.6				
	VTX 15 mg	47		151	31.8 ± 3.4				
	VTX 20 mg	46.2		151	31.2 ± 3.4				
	DLX 60 mg	45.6		147	31.2 ± 3.5				
Mahablashwarkar			8			Usa	≥26	2014	[26]
	Placebo	42.4		161	31.6 ± 4.18				
	VTX 15 mg	43.1		147	31.9 ± 4.08				
	VTX 20 mg	42.8		154	32 ± 4.36				
	DLX 60 mg	43.4		152	32.9 ± 4.39				

VTX = Vortioxetine; DLX = Duloxetine 60 mg.

3.1. Efficacy Vortioxetine and Duloxetine 60 mg Compared to Placebo

Five trials [22]-[26] compared Vortioxetine to placebo for response using the MADRS scale. As shown in **Figure 2(a)**, compared to placebo, response rates were not significant for Vortioxetine 2.5 mg (SMD = −1.11; 95% CI −2.34, 0.13; I^2 = 98%), significant for Vortioxetine 5 mg (SMD = −2.61; 95% CI −5.22 to −0.00; I^2 = 99.5%), significant for Vortioxetine 10 mg (SMD = −1.85; 95% CI −2.12 to −1.58; I^2 = 0), no significant for Vortioxetine 15 mg (SMD = −4.42; 95% CI −9.74 to 0.90; I^2 = 99.6%), significant for Vortioxetine 20 mg (SMD = −6.20; 95% CI −12.08 to −0.31; I^2 = 99.5%), and significant for total Vortioxetine (SMD = −3.29; 95% CI −4.47 to −2.10; I^2 = 99.3%). Heterogeneity was very high for most of the dose comparisons. Five trials compared Duloxetine 60 mg to placebo for response using the MADRS scale. As shown in **Figure 2(b)**, compared to placebo, response rates were no significant for Duloxetine 60 mg 60 mg (SMD = −6.35; 95% CI −8.84, −3.87; I^2 = 99.3%).

3.2. Safety Vortioxetine and Duloxetine 60 mg Compared to Placebo

Table 4 summarizes pooled adverse events (AEs) absolute Odds Ratio for each vortioxetine and Duloxetine 60 mg compared to placebo. The most frequently reported adverse events were diarrhea, dry mouth, dizziness, fatigue, headache and nausea. Results showed that vortioxetine 2.5, 5, 10, 15, 20 mg and overall compared to placebo have a significant effective for Nausea and no significant for diarrhea, dry mouth, dizziness, fatigue and headache. Results also showed that duloxetine 60 mg compared to placebo has a significant effective for dry mouth, dizziness, fatigue and nausea.

3.3. Publication Bias

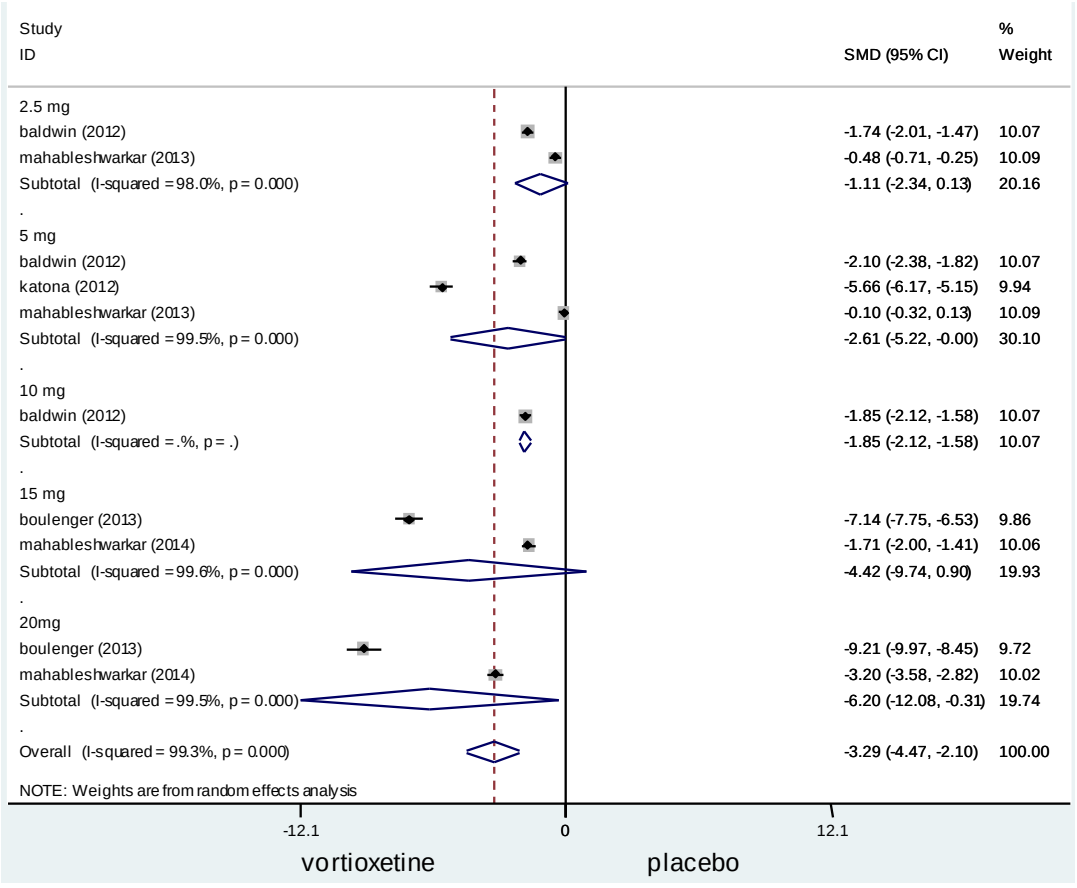
Publication bias for five studies was detected by drawing Egger's funnel plot in the meta-analysis. Result showed significantly for publication bias (p = 0.000) (**Figure 3**).

4. Discussion

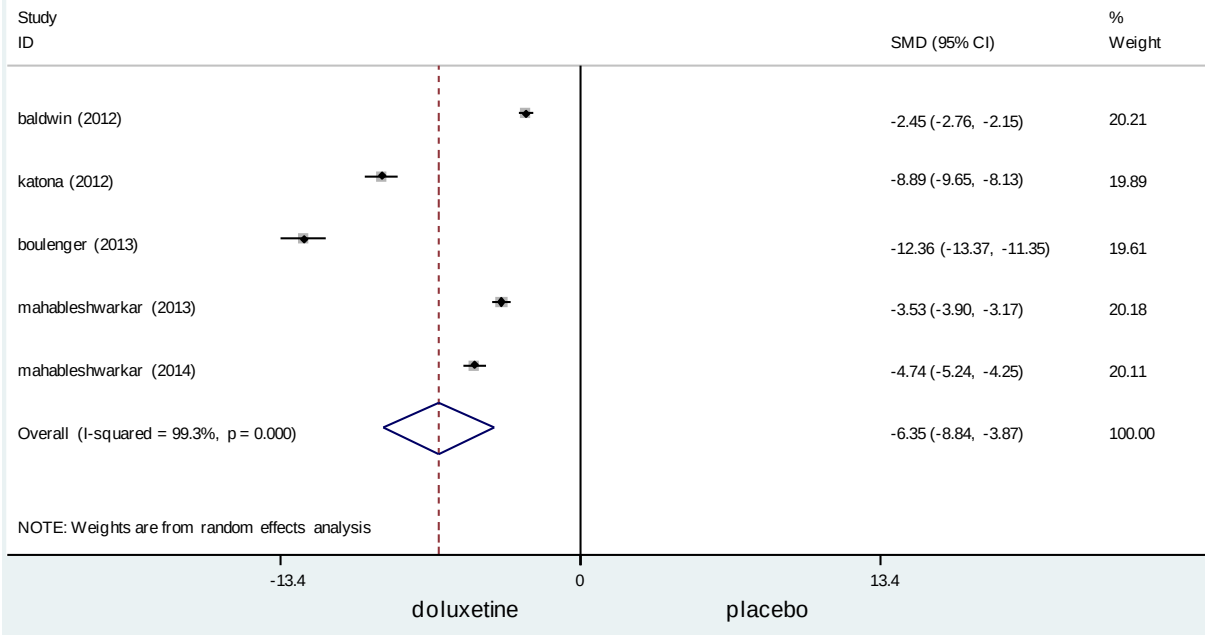
In this systematic review and meta-analysis, we include 5 studies in the meta-analysis. They include Vortioxetine, Duloxetine 60 mg and placebo. Results on relevant clinical efficacy and safety outcomes were included. Study quality was assessed and results were pooled by using random effect meta-analyses where applicable. A sensitivity analysis did not influence the results. The present meta- analysis demonstrated the superior efficacy of overall Vortioxetine compared placebo in MADRS for the treatment of major depressive disorder. The decrease in depression symptoms seems to be associated with Vortioxetine compared placebo. Results of meta-analysis demonstrated the of Duloxetine 60 mg compared placebo in MADRS. In the clinical studies analyzed, the common adverse effects of Vortioxetine compared to placebo, included diarrhea, dry mouth, dizziness, fatigue,

Table 4. Pooled adverse events (AEs) in the included studies.

Drug Adverse effects	Vortioxetine 2.5 mg	Vortioxetine 5 mg	Vortioxetine 10 mg	Vortioxetine 15 mg	Vortioxetine 20 mg	Overall	Duloxetine 60 mg 60 mg
Diarrhea	0.58 [0.29 - 1.15]	0.69 [0.34 - 1.41]	0.77 [0.30 - 2.01]	1.84 [0.76 - 4.41]	1.53 [0.79 - 2.96]	0.97 [0.66 - 1.44]	1.44 [0.98 - 2.13]
Dry mouth	0.92 [0.31 - 2.73]	1.17 [0.70 - 1.95]	0.52 [0.19 - 1.43]	0.97 [0.51 - 1.85]	1.60 [0.89 - 2.87]	1.10 [0.83 - 1.46]	2.75 [1.51 - 5.01]
Dizziness	0.98 [0.44 - 2.19]	0.98 [0.51 - 1.87]	0.57 [0.20 - 1.61]	1.57 [0.33 - 7.44]	1.81 [0.29 -11.25]	1.14 [0.72 - 1.82]	2.54 [1.57 - 4.12]
Fatigue	0.50 [0.15 - 1.69]	1.23 [0.56 - 2.69]	0.98 [0.19 - 4.93]	1.76 [0.72 - 4.32]	0.44 [0.02 - 9.20]	0.84 [0.39 - 1.80]	3.12 [1.88 - 5.19]
Headache	0.98 [0.62 - 1.55]	0.80 [0.47 - 1.37]	0.74 [0.39 - 1.42]	1.42 [0.87 -2.32]	1.27 [0.72 - 2.23]	1.01 [0.80 - 1.27]	1.07 [0.77 - 1.48]
Nausea	1.83 [1.12 - 2.99]	2.87 [1.94 - 4.23]	2.90 [1.46 - 5.78]	3.73 [2.42 - 5.76]	4.00 [2.60 - 6.14]	3.04 [2.47 - 3.37]	4.93 [3.75 - 6.60]



(a)



(b)

Figure 2. Forest plot of Standardized Mean Differences (SMD) and 95% confidence intervals (CIs) of change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS Vortioxetine (a) and Duloxetine 60 mg (b) compared to placebo in the included studies.

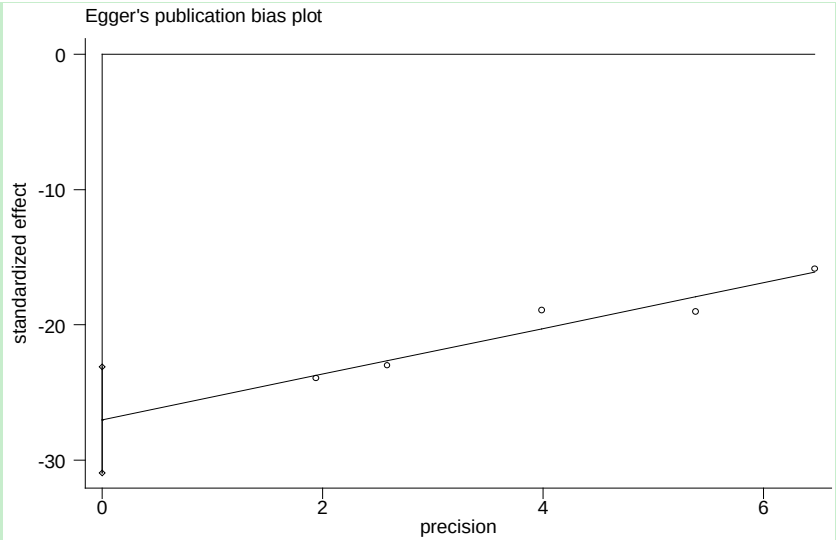


Figure 3. Egger's funnel plot for publication bias.

headache and nausea. This meta-analysis showed that vortioxetine more easily induced nausea when compared with placebo, but there were no significant differences among the other five common side effects. Results also showed the common adverse effects of duloxetine 60 mg compared to placebo more commonly induced dry mouth, dizziness, fatigue and nausea. It seems that the effectiveness of the Vortioxetine and Duloxetine 60 mg in particular improves disease symptoms of major depressive disorder. Of course, the consequences of the improvement are measured in the Vortioxetine. The choice of vortioxetine or duloxetine 60 mg by a physician for the treatment of major depressive disorder and illness depends on the conditions and characteristics of the patient.

Considering the number of studies in this meta-analysis, we can say Vortioxetine drug is effective in the treatment of depression, but more studies to be done if in the future. And this drug, compared with other drugs that are currently used to treat depression, can be a better judgment about the effectiveness of the drug.

There are at least six limitations to this systematic review: 1. All included studies were supported by the Takeda company, Ltd., as part of a joint clinical development program with H. Lundbeck, which may have influenced the results; 2. Due to the limited number of the published and unpublished studies, we did not analyze the efficacy and safety of different doses of vortioxetine in the treatment of major depressive disorder; 3. The inclusion of patients was only during the acute phase (8 weeks), which did not enable us to analyze finding the long-term efficacy and safety of vortioxetine and douloxetine 60 mg in treating major depressive disorder; 4. All included studies in meta-analysis did not include the efficacy and adverse effects based on sex and we could not evaluate gender differences; 5. Primary meta-analyses had significant heterogeneity; this was resolved by subgroup studies by racial composition; 6. 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 treatment of major depressive disorder. However, major depressive disorder (MDD) is frequently associated with heart diseases [27], diabetes [28], stroke, pregnancy, and the postpartum period [29] [30]. Vortioxetine should also benefit the physical state of these patients.

5. Conclusion

We find that Vortioxetine and Duloxetine 60 mg are significantly more effective than placebo for acute treatment of major depressive disorder (MDD). Vortioxetine also appears to be effective for treating symptoms of major depressive disorder. Some researchers' suggestions concerning the place of vortioxetine treatment for adults with major depressive disorder are provided.

Acknowledgments

The authors are grateful to Dr. Hamidreza Dehghan, Dr. Korush Saki, Dr. Ehrampoush, Dr. Mosadegh, Dr.

Dastgerdi, Dr. Maryam Saran and Meysam Behzadifar for their useful advice.

Conflict of Interest

The authors have no conflicts of interest.

Authors' Contributions

Masoud Behzadifar and Ali Akbari Sari are responsible for the study concept, design, and literature searching. Masoud Behzadifar and Mohammad Rastian are responsible for data analysis and interpretation. Abouzar Keshavarzi, Abed Tofighian and Mohammad Zobidi draft the paper. All authors participate in the analysis and interpretation of data and approve the final paper.

References

[1] Alvarez, E., Perez, V., Dragheim, M., Loft, H. and Artigas, F. (2011) A Double-Blind, Randomized, Placebo-Controlled, Active Reference Study of Vortioxetine in Patients with Major Depressive Disorder. *International Journal of Neuropsychopharmacology*, **15**, 589-600. http://dx.doi.org/10.1017/S1461145711001027

[2] Bridge, J.A., Birmaher, B., Iyengar, S., Barbe, R.P. and Brent, D.A. (2009) Placebo Response in Randomized Controlled Trials of Antidepressants for Pediatric Major Depressive Disorder. *American Journal of Psychiatry*, **166**, 42-49. http://dx.doi.org/10.1176/appi.ajp.2008.08020247

[3] Murray, C.J.L. and Lopez, A.D. (1997) Alternative Projections of Mortality and Disability by Cause 1990-2020: Global Burden of Disease Study. *The Lancet*, **349**, 1498-1504. http://dx.doi.org/10.1016/S0140-6736(96)07492-2

[4] Liu, M.T., Maroney, M.E. and Hermes-De Santis, E.R. (2015) Levomilnacipran and Vortioxetine: Review of New Pharmacotherapies for Major Depressive Disorder. *World Journal of Pharmacology*, **4**, 17-30. http://dx.doi.org/10.5497/wjp.v4.i1.17

[5] Khan, A., Bhat, A., Kolts, R., Thase, M.E. and Brown, W. (2010) Why Has the Antidepressant-Placebo Difference in Antidepressant Clinical Trials Diminished over the Past Three Decades? *CNS Neuroscience and Therapeutics*, **16**, 217-226. http://dx.doi.org/10.1111/j.1755-5949.2010.00151.x

[6] Henigsberg, N., Mahableshwarkar, A., Jacobsen, P., Chen, Y.Z. and Thase, M.E. (2012) 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. *The Journal of Clinical Psychiatry*, **73**, 953-959. http://dx.doi.org/10.4088/JCP.11m07470

[7] Khin, N.A., Chen, Y.-F., Yang, Y., Yang, P.L. and Laughren, T.P. (2011) Exploratory Analyses of Efficacy Data from Major Depressive Disorder Trials Submitted to the US Food and Drug Administration in Support of New Drug Applications. *The Journal of Clinical Psychiatry*, 72, 464-472. http://dx.doi.org/10.4088/JCP.10m06191

[8] Pehrson, A.L., Cremers, T., Bétry, C., van der Hartb, M.G.C., Jørgensena, L., Madsen, M., *et al*. (2013) Lu AA21004, a Novel Multimodal Antidepressant, Produces Regionally Selective Increases of Multiple Neurotransmitters—A Rat Microdialysis and Electrophysiology Study. *European Neuropsychopharmacology*, **23**, 133-145. http://dx.doi.org/10.1016/j.euroneuro.2012.04.006

[9] Harada, E., Schacht, A., Koyama, T., Marangell, L.B., Tsuji, T. and Escobar, R. (2015) Efficacy Comparison of Duloxetine and SSRIs at Doses Approved in Japan. *Neuropsychiatric Disease and Treatment*, **11**, 115-123. http://dx.doi.org/10.2147/NDT.S72642

[10] Meeker, A.S., Herink, M.C., Haxby, D.G. and Hartung, D.M. (2015) The Safety and Efficacy of Vortioxetine for Acute Treatment of Major Depressive Disorder: A Systematic Review and Meta-Analysis. *Systematic Reviews*, **4**, 21. http://dx.doi.org/10.1186/s13643-015-0001-y

[11] Liberati, A., Altman, D.G., Tetzlaff, J., Mulrow, C., Gøtzsche, P.C., Ioannidis, J.P.A., *et al*. (2009) The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. *PLoS Medicine*, **6**, e1000100. http://dx.doi.org/10.1371/journal.pmed.1000100

[12] Trull, T.J., Vergés, A., Wood, P.K., Jahng, S. and Sher, K.J. (2012) The Structure of Diagnostic and Statistical Manual of Mental Disorders (4th Edition, Text Revision) Personality Disorder Symptoms in a Large National Sample. *Personality Disorders*, **3**, 355-369. http://dx.doi.org/10.1037/a0027766

[13] Higgins, J.P., Altman, D.G., Gøtzsche, P.C., Jüni, P., Moher, D., Oxman, A.D., *et al*. (2011) The Cochrane Collaboration's Tool for Assessing Risk of Bias in Randomised Trials. *British Medical Journal*, **343**, Article ID: d5928. http://dx.doi.org/10.1136/bmj.d5928

[14] Jadad, A.R., Moore, R.A., Carroll, D., Jenkinson, C., Reynolds, D.J., Gavaghan, D.J. and Mc Quay, H.J. (1996) Assessing the Quality of Reports of Randomized Clinical Trials: Is Blinding Necessary? *Controlled Clinical Trials*, **17**,

1-12. http://dx.doi.org/10.1016/0197-2456(95)00134-4

[15] Zimmerman, M., Chelminski, I. and Posternak, M. (2004) A Review of Studies of the Montgomery-Asberg Depression Rating Scale in Controls: Implications for the Definition of Remission in Treatment Studies of Depression. *International Clinical Psychopharmacology*, **19**, 1-7. http://dx.doi.org/10.1097/00004850-200401000-00001

[16] White, I.R. and Thomas, J. (2005) Standardized Mean Differences in Individually-Randomized and Cluster-Randomized Trials, with Applications to Meta-Analysis. *Clinical Trials*, **2**, 141-151. http://dx.doi.org/10.1191/1740774505cn081oa

[17] Jose, S., George, P.S. and Mathew, A. (2008) Assessment of Confounding and Interaction Using the Mantel-Haenszel Risk Estimation Method. *Asian Pacific Journal of Cancer Prevention*, **9**, 323-325.

[18] Huedo-Medina, T.B., Sánchez-Meca, J., Marín-Martínez, F. and Botella, J. (2006) Assessing Heterogeneity in Meta-Analysis: Q Statistic or I2 Index? *Psychological Methods*, **11**, 193-206. http://dx.doi.org/10.1037/1082-989X.11.2.193

[19] Higgins, J.P.T. and Green S. (2011) Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0. The Cochrane Collaboration. http://www.cochrane-handbook.org

[20] Egger, M., Smith, G.D., Schneider, M. and Minder, C. (1997) Bias in Meta-Analysis Detected by a Simple, Graphical Test. *British Medical Journal*, **315**, 629-634. http://dx.doi.org/10.1136/bmj.315.7109.629

[21] Begg, C.B. and Mazumdar, M. (1994) Operating Characteristics of a Rank Correlation Test for Publication Bias. *Biometrics*, **50**, 1088-1101. http://dx.doi.org/10.2307/2533446

[22] Baldwin, D.S., Loft, H. and Dragheim, M. (2012) 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). *European Neuropsychopharmacology*, **22**, 482-491. http://dx.doi.org/10.1016/j.euroneuro.2011.11.008

[23] Katona, C., Hansen, T. and Olsen, C.K. (2012) 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. *International Clinical Psychopharmacology*, **27**, 215-223. http://dx.doi.org/10.1097/YIC.0b013e3283542457

[24] Mahableshwarkar, A.R., Jacobsen, P.L. and Chen, Y. (2013) 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. *Current Medical Research and Opinion*, **29**, 217-226. http://dx.doi.org/10.1185/03007995.2012.761600

[25] Boulenger, J.P., Loft, H. and Olsen, C.K. (2014) 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. *International Clinical Psychopharmacology*, **29**, 138-149. http://dx.doi.org/10.1097/YIC.0000000000000018

[26] Mahableshwarkar, A.R., Jacobsen, P.L., Chen, Y., Serenko, M. and Trivedi, M.H. (2015) 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*, **232**, 2061-2070. http://dx.doi.org/10.1007/s00213-014-3839-0

[27] Penninx, B.W., Beekman, A.T., Honig, A., Deeg, D.J., Schoevers, R.A., van Eijk, J.T. and van Tilburg, W. (2001) Depression and Cardiac Mortality: Results from a Community-Based Longitudinal Study. *Archives of General Psychiatry*, **58**, 221-227. http://dx.doi.org/10.1001/archpsyc.58.3.221

[28] Schlienger, J.L. (2013) Type 2 Diabetes Complications. *La Presse Médicale*, **42**, 839-848. http://dx.doi.org/10.1016/j.lpm.2013.02.313

[29] Di Florio, A., Forty, L., Gordon-Smith, K., Heron, J., Jones, L., Craddock, N. and Jones, I. (2013) Perinatal Episodes across the Mood Disorder Spectrum. *JAMA Psychiatry*, **70**, 168-175. http://dx.doi.org/10.1001/jamapsychiatry.2013.279

[30] Fu, J. and Chen, Y. (2015) The Efficacy and Safety of 5 mg/d Vortioxetine Compared to Placebo for Major Depressive Disorder: A Meta-Analysis. *Psychopharmacology*, **232**, 7-16. http://dx.doi.org/10.1007/s00213-014-3633-z