Efficacy and safety of vortioxetine (Lu AA21004) in the treatment of adult patients with major depressive disorder: A systematic review and a meta-analysis of randomized controlled trials

SHAN GAO[1*], XINGXING XIE[2*], LING FAN[2] and DEMING ZHANG[3]

[1]Department of Pharmacy, Chengdu Second People's Hospital, Chengdu, Sichuan 618000; Departments of [2]Pharmacy and [3]Neurosurgery, Yaan People's Hospital, Yaan, Sichuan 625000, P.R. China

Received January 31, 2023; Accepted August 16, 2023

DOI: 10.3892/etm.2023.12214

Abstract. Vortioxetine is a novel drug for the treatment of major depressive disorder (MDD). It has been reported that vortioxetine exhibits positive effect on the acute stage of MDD, while it can effectively prevent the recurrence of MDD during the maintenance period. Currently, the results of systematic reviews on vortioxetine are insufficient since several efficacy measures, such as the 24-Items Hamilton Rating Scale for Depression (HADRS-24) total score and other safety factors have not been evaluated. Therefore, the present study aimed to evaluate the efficacy and safety of different doses of vortioxetine on the treatment of adult patients with MDD via assessing more efficacy and safety indicators. The clinical, double-blind, parallel and randomized controlled trials (RCTs) on the effect of vortioxetine on MDD were retrieved from PubMed\Medline, EBSCO, Embase, Cochrane Library, OVID, Web of Science and clinical trial registration websites from database inception to November 2022. A total of two investigators independently screened the included references and independently evaluated their quality. The meta-analysis was performed using Revman 5.0 software. The present systematic review was registered in PROSPERO (registration no. CRD42018106343). In the present study 11 RCTs were included, with a total of 4,908 adult patients with MDD. More specifically, 1,158 patients were included in the 5-mg vortioxetine group, 736 in the 10-mg group, 298 in the 15-mg group, 864 in the 20-mg group and 1,852 in the placebo group. All 11 studies were randomized, double-blinded and parallel control trials, and all publications were evaluated as high quality. The meta-analysis results showed that patients in the 5-, 10- and 20-mg vortioxetine groups exhibited significantly higher Montgomery-Asberg Depression Rating Scale (MADRS) response (≥50%) and remission (≤10%) rates compared with the placebo group ($P<0.05$). The pooled analysis also revealed a statistically significant change in the total score of HADRS-24, MADRS, Sheehan Disability Scale (SDS), Clinical Global Impression Scale-Improvement (CGI-I) and HADRS-24 response rate in the 10- and 20-mg vortioxetine groups compared with the placebo group ($P<0.05$). However, no statistically significant changes in the total score of HADRS-24, MADRS, SDS, CGI-I and HADRS-24 response rate were obtained in the 5-mg group compared with the placebo group ($P>0.05$). Furthermore, the most common adverse events were nausea, hyperhidrosis, insomnia and vomiting, the incidence of which was increased with higher doses of vortioxetine. Overall, the results suggested that vortioxetine administration at doses of 5-20 mg was significantly effective and safe compared with placebo in the treatment of MDD. However, 5 mg vortioxetine displayed no difference in the HADRS-24, MADRS, SDS and CGI-I total scores, and HADRS-24 response rate. Furthermore, patient treatment with increasing vortioxetine doses was associated with good tolerance and high safety. Nevertheless, more multi-center, high-quality and long-term RCTs are still needed to support the aforementioned findings.

Correspondence to: Professor Deming Zhang, Department of Neurosurgery, Yaan People's Hospital, 358 Chenghou Street, Yaan, Sichuan 625000, P.R. China
E-mail: 261317915@qq.com

*Contributed equally

Abbreviations: MDD, major depressive disorder; MADRS, Montgomery-Asberg Depression Rating Scale; SDS, Sheehan Disability Scale; CGI-I, Clinical Global Impression Scale-Improvement; HADRS-24, 24-Items Hamilton Rating Scale for Depression; FDA, Food and Drug Administration; CI, confidence interval; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; BMI, body mass index; RR, risk ratio; MD, mean difference; M-H, Mantel-Haenszel; REM, random-effect model; SMI, serious mental illness

Key words: major depressive disorder, efficacy, safety, vortioxetine, systematic review

Introduction

Depression is a common mood disorder, which is characterized by mood swings, chaos at work, difficulties in learning, eating disorders, lack of interest in daily activities and entertainment, insomnia or excessive sleep, restlessness, excitement, fatigue, feeling of worthlessness, difficulties in thinking

or concentrating and suicidal thoughts or behaviors. It has been reported that depression can increase the incidence and mortality from somatic diseases (1-3). In 2010, there were ~298 million patients suffering from depression worldwide, while the annual incidence of depression is estimated to be ~50%. Therefore, the rising incidence of depression has become a serious challenge in medical research (4,5).

Currently, first-line antidepressant drugs mainly include serotonin re-uptake inhibitors and selective 5-HT-norepinephrine re-uptake inhibitors (6). However, the underlying mechanism of action of vortioxetine differs from other drugs, since it generally acts in a mixed manner via modulating receptor activity and inhibiting the re-uptake of neurotransmitters. Vortioxetine exerts its pharmacological activity *in vivo* via 5-hydroxytryptamine type 3 (5-HT3) receptor, 5-HT7 receptor and 5-hydroxytryptamine (serotonin) receptor 1D (5-HT1D) antagonism, 5-HT1B receptor partial agonism, 5-HT1A receptor agonism and 5-HT transporter inhibition (7,8). Interestingly, a previous study demonstrated that vortioxetine had no effect on norepinephrine and dopaminergic neurons virtually (9). Additionally, another study showed that vortioxetine could effectively treat patients with acute-phase depression, while it could also effectively prevent recurrence during the maintenance phase (10).

On September 30th, 2013, vortioxetine was approved by the US Food and Drug Administration (FDA) for the treatment of adults with depression. The drug is provided in doses of 5, 10, 15 and 20 mg (11). Previous randomized controlled trials (RCTs) and systematic reviews in different databases revealed that vortioxetine displayed improved efficacy and safety compared with the positive drugs paroxetine and venlafaxine, or placebo (12-14). However, the results of the aforementioned studies were considered insufficient, since the different doses of vortioxetine and outcome measures were limited. The two other meta-analysis about vortioxetine also provided few outcomes and safety evaluation. Sufficient outcome evaluation could provide more suggestions to physicians. With the advancement of clinical trials and the increased demand for patient medication, it is necessary to re-evaluate the efficacy and safety of vortioxetine as an increasingly popular first-line drug for the treatment of depression in adults. The re-evaluation of its clinical efficacy and safety has also gained increasing attention from psychiatrists and clinical pharmacists in several countries. Therefore, in terms of systematic reviews, collecting more detailed data from clinical trials on vortioxetine via evaluating more factors associated with the efficacy and safety of different doses of vortioxetine could provide the necessary evidence for decision-making on medical treatments and clinical applications.

Materials and methods

The present study was performed and reported according to the Cochrane Handbook for Systematic Reviews of Interventions, which is used for conducting systematic reviews and meta-analyses for observational studies (15,16), as well as the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement (17). To account for any data that could be missing from the final analysis, the results were assessed using the Last Observation Carried Forward method.

Study eligibility criteria. The clinical trials that met the following criteria were included in the present study meta-analysis: i) Double-blind, parallel-controlled and randomized clinical trials; ii) Adult patients suffering from major depressive disorder (MDD), dysthymic disorder and other psychotic disorders according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (18), DSM-IV Text Revision (19) and/or ICD-10 Classification of Mental and Behavioral Disorders (20-22); iii) Patients treated with 5, 10, 15 or 20 mg/once per day (QD) vortioxetine and placebo; iv) The efficacy outcome was determined based on the changes in the total scores of the 24-Items Hamilton Rating Scale for Depression (HADRS-24) (23), Sheehan Disability Scale (SDS) (24), Montgomery-Asberg Depression Rating Scale (MADRS) (25) and Clinical Global Impression Scale-Improvement (CGI-I) (26), and changes in HADRS-24 response rate, and MADRS response (≥50%) and remission (≤10%) rates, from baseline; and v) The safety outcome was defined as the rate of discontinuation due to adverse effects (>5%).

The exclusion criteria were as follows: i) Systematic reviews; ii) Review articles; iii) Case-control studies; iv) Animal studies; v) Comments; vi) Studies with incomplete data; vii) Case reports; viii) Studies where inappropriate statistical methods were used; ix) Duplicate publications; and x) studies that the diagnostic criteria were not reported.

Data sources and searching strategy. Literature search was performed on PubMed\Medline, EBSCO, Embase, Cochrane library, OVID and Web of Science from database inception to November 2022. There were no limits in terms of language, race, sex and nationality. Potentially relevant unpublished data were searched on ClinicalTrials.gov, the FDA web site (Drugs@FDA; https://www.accessdata.fda.gov/), Chinese Clinical Trial Registry (http://www.chictr.org.cn/), European Union Drug Regulating Authorities Clinical Trials (https://eudract.ema.europa.eu/index.html), World Health Organization and International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/). All studies were hand-searched for randomized clinical trials that met the inclusion criteria. The search terms were as follows: 'vortioxetine', 'brintellix', 'Lu AA21004', 'placebo', 'MDD', 'dysthymic disorder', 'adult patients', 'efficacy', 'safety ', 'tolerability', 'clinical trial', 'randomized controlled trial', 'RCT', 'double-blind' and 'parallel-controlled'. The PubMed search string used was as follows: '(vortioxetine or brintellix or Lu AA21004 or trintellix) and (placebo) and (MDD or dysthymic disorder) and (adult patients) and (efficacy) and (safety or tolerability) and (clinical trial or randomized controlled trial or RCT) and (double-blind) and (parallel-controlled) and (human or humans)'. In addition, the Embase search string used was the following: '(vortioxetine*.ti or brintellix*.ti or Lu AA21004*.ti or Trintellix*.ti) and (MDD*.ti or dysthymic disorder*.ti) and (adult patients*.ti) and (efficacy*.ti) and (safety*.ti or tolerability*.ti) and (clinical trial*.ti or randomized controlled trial*.ti or RCT*.ti) and (double-blind*.ti) and (parallel-controlled*.ti) and (human*.ti or humans*.ti)'.

Study selection. Each search was performed separately, and each study was downloaded as a separate file using Endnote X6. To minimize selection bias, two researchers (SG and XX)

independently screened the titles, abstracts and full texts of each article and data were extracted based on the pre-defined eligibility criteria. The above two researchers evaluated the quality of the literature. In case of disagreement, a third researcher (LF) was involved to reach consensus.

Data extraction. Two researchers (SG and XX) extracted the study characteristics, baseline characteristics of patients, including age, body mass index (BMI), race, HADRS-24 total score, MADRS total score, CGI-I total score and race, interventions and outcome measures, including efficacy [HADRS-24 total score change, SDS total score change, MADRS total score change, CGI-I total score change, HDRS-24 response rate, MADRS response rate (≥50%) and MADRS remission rate (≤10%)], and safety (adverse effects) outcomes.

Quality assessment. The quality of literature was evaluated using the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0) for assessing risk of bias in RCTs (27). The evaluation components included random sequence generation, allocation concealment, blinding, analysis of incomplete outcome data and intention-to-treat analysis, while there was no selective reporting or other bias. Each item was defined as 'yes' (low risk of bias), 'no' (high risk of bias) or 'unclear'.

Statistical analysis. All outcomes were evaluated using Revman 5.3 software (http://www.cochrane.org/). Risk ratios (RR) with 95% confidence intervals (CIs) were calculated for dichotomous outcomes, such as response and remission rates. Continuous outcomes, such as scale score, are expressed as the mean difference (MD). The I^2 statistic was calculated to estimate heterogeneity using Review Manager. $I^2 \leq 50\%$ was considered to indicate that the studies were homogeneous and a fixed effect model with the Mantel-Haenszel (M-H) method was performed. Otherwise, the random-effect model (REM) was adopted (28). Publication bias was assessed by visually inspecting funnel plots (29).

Results

Literature search and study characteristics. After duplicates were removed, a total of 262 studies were screened. Among them, 248 were excluded, since they did not meet the inclusion criteria based on *in vitro* studies, animal studies, trials with healthy volunteers and review articles. The remaining 14 studies were assessed according to the pre-determined inclusion criteria. Finally, 11 RCTs were included in the meta-analysis. The studies evaluated the efficacy and safety of vortioxetine via randomizing adult patients into different study arms with different doses of vortioxetine (Fig. 1) (30-39) with the exception of one study (40). As shown in Table I, in nine studies patients were treated with vortioxetine for eight weeks (30,31,33-39), while in the remaining two studies for six weeks (32,40). The main characteristics of patients included in the 11 studies (30-40), such as age, race, BMI, CGI-I and MADRS basic scores were well described. The demographic or clinical characteristics between trials were equivalent to the baseline. In the selected studies, 4,098 adult patients with MDD were treated with vortioxetine and 1,852 with placebo.

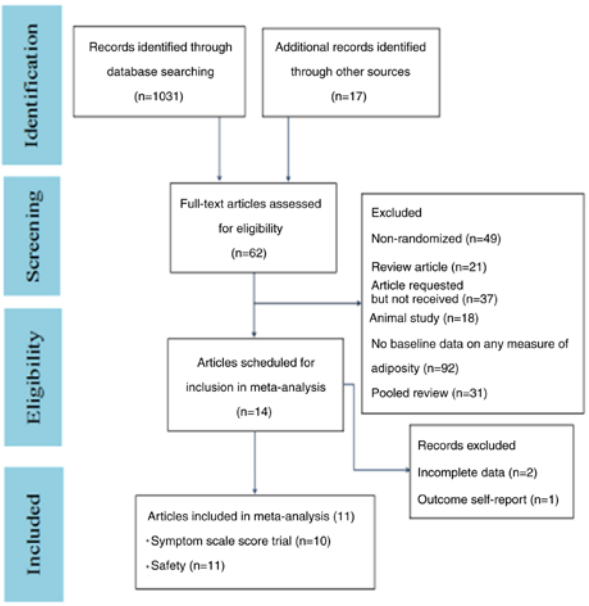

Figure 1. PRISMA flowchart of study selection.

The bias risk assessment demonstrated that there was a low risk of bias in randomization and blinding. However, the presence of other biases, such as recruitment bias and clinical settings-related bias could not be ruled out (Fig. 2).

Efficacy outcomes. To evaluate the efficacy of vortioxetine on MDD, the changes in the total scores of HADRS-24, MADRS, SDS and CGI-I, and the HADRS-24 and MADRS response rates (≥50%) and those in MADRS remission rate (≤10%) were retrieved from the included studies. The HADRS-24 response rate, MADRS response rate (≥50%) and MADRS remission rate (≤10%) were considered as the primary efficacy outcomes. In addition, the HADRS-24, MADRS, SDS and CGI-I total score changes were considered as the secondary efficacy outcomes. The effect of vortioxetine (5, 10, 15 and 20 mg) compared with placebo on the response of patients with MDD was assessed via measuring the changes in the total scores of HADRS-24, MADRS, SDS and CGI-I, and in HADRS-24 response rate, MADRS response rate (≥50%) and MADRS remission rate (≤10%) at 8 or 6 weeks. Patients were considered to be the measure index responders when reduced total scores from baseline at the end of the study were obtained. The present study analysis revealed the following results: i) In the 5-mg vortioxetine group vs. the placebo group, no statistically significant difference was observed in terms of HADRS-24, MADRS, SDS and CGI-I total score change, and HADRS-24 response rate ($P>0.05$). However, the MADRS response (≥50%; M-H RR=1.57; 95% CI=1.23-1.99) and remission (≤10%; M-H RR=1.28; 95% CI=1.10-1.49; $I^2=49\%$) rates were significantly enhanced in the 5-mg vortioxetine dose group compared with the placebo group ($P<0.05$). ii) In the 10-mg vortioxetine group vs. the placebo group, a statistically significant difference was observed in the total scores of HADRS-24 [MD=-4.93; 95% CI=-5.12-(-4.76)], MADRS [MD=-3.65; 95% CI=-5.61-(-1.69)], SDS [MD=-1.54; 95% CI=-1.76-(-1.32)] and CGI-I [MD=-0.58; 95% CI=-0.64-(-0.52)], and in HDRS-24 response rate (M-H RR=2.16; 95% CI=1.52-3.05), MADRS

Table I. Basic characteristics of literatures (Baseline/mean ± SD).

Study	Interventions	Patients (n)	Age, years	Body mass, index kg/m^2	CGI-S score	HDRS-24 total score	MADRS total score	Treatment duration (weeks)	Race	Outcome measure
Henigsberg *et al* (30)	Vorti 5-mg	140	47.3±12.0	26.4±5.1	Not	32.1±5.04	30.6±2.83	8	White, Black,	①②③④
2012	Vorti 10-mg	140	46.4±12.3	26.2±4.6	reported	33.1±4.77	31.6±3.83		Asian, Other	⑤⑥⑦⑧
	Placebo	140	46.4±12.3	26.4±4.6	32.7±4.40	30.6±2.89				
Nishimura *et al* (31)	Vorti 5-mg	144	44.2±11.89	25.06±5.43	4.7±0.65	Not	31.6±3.67	8	Asian	⑤⑥⑦
2018	Vorti 10-mg	150	45.7±10.9	25.93±5.46	4.7±0.66	reported	31.8±4.02			
	Vorti 20-mg	154	44.0±11.79	24.82±5.21	4.7±0.65		31.7±3.73			
	Placebo	152	43.6±11.57	24.82±5.13			31.6±3.56			
Jain *et al* (32)	Vorti 5-mg	300	42.5±13.0	30.5±8.2	Not	32.7±5.4	42.5±13.0	6	White, Black,	①②③④
2013	Placebo	300	42.4±12.7	30.8±7.7	reported	32.2±5.5	42.4±12.7		Asian, American Indian/Alaskan, Pacific Inlander	⑤⑥⑧
McIntyre *et al* (33)	Vorti 10-mg	195	45.4±12.2	Not	4.60±0.62	Not	45.4±12.2	8	Not reported	②④⑥⑦
2014	Vorti 20-mg	207	46.1±11.8	reported	4.62±0.58	reported	46.1±11.8			
	Placebo	196	45.6±12.1		4.55±0.63		45.6±12.1			
Mahablesh warkar, *et al* (34)	Vorti 2.5-mg	153	42.6±12.9	29.5±7.5	4.6±0.62	29.8±5.4	42.6±12.9	8	White, Black,	①③④⑤
2013	Vorti 5-mg	153	43.1±13.9	31.4±8.8	4.6±0.65	29.0±5.6	43.1±13.9		Asian, American Indian/Alaskan, Pacific Inlander	⑥⑧
	Placebo	153	42.6±13.8	29.6±7.3	4.5±0.62	29.5±6.1	42.6±13.8			
Baldwin *et al* (35)	Voeti 2.5-mg	155	46.0±12.5	Not	4.8±0.7	29.6±5.8	46.0±12.5	8	Asian	②⑧
2012	Vorti 5-mg	157	44.7±13.1	reported	4.8±0.7	31.3±5.8	44.7±13.1			
	Vorti 10-mg	151	45.2±13.1		4.8±0.7	30.4±5.4	45.2±13.1			
	Placebo	148	43.4±12.5		4.8±0.7	29.8±5.1	43.4±12.5			
Katona *et al* (36)	Vorti 5-mg	156	70.5±4.8	Not	4.8±0.7	29.2±5.0	70.5±4.8	8	Not Reported	①⑤⑥⑦
2012	Placebo	145	70.3±4.4	reported	4.7±0.7	29.4±5.1	70.3±4.4			⑧
Mahablesh warkar *et al* (37)	Vorti 20-mg	198	44.2±12.2	Not	4.6±0.6	Not	44.2±12.2	8	Black, Asian,	②④⑧
2015	Placebo	194	45.0±12.1	reported	4.6±0.6	reported	45.0±12.1		Other	
Boulenger *et al* (38)	Vorti 15-mg	151	47.0±14.6	Not	4.9±0.6	Not	47.0±14.6	8	Not Reported	⑥⑦⑧
2014	Vorti 20-mg	151	46.2±13.4	reported	4.8±0.7	reported	46.2±13.4			
	Placebo	158	48.1±13.1		4.9±0.7		48.1±13.1			
Mahablesh warkar *et al* (39)	Vorti 15-mg	147	43.1±12.28	31.3±7.48	4.5±0.55	Not	43.1±12.28	8	White, Black,	⑥⑦⑧
2015	Vorti 20-mg	154	42.8±12.40	30.9±7.63	4.5±0.60	reported	42.8±12.40		Asian, Native American/ Alaskan native	
	Placebo	161	42.4±12.55	31.1±7.88	4.6±0.58		42.4±12.55			

Table I. Continued.

Study	Interventions	Patients (n)	Age, years	Body mass, index kg/m^2	CGI-S score	HDRS-24 total score	MADRS total score	Treatment duration (weeks)	Race	Outcome measure
Alvarez *et al* (40) 2012	Vorti 5-mg	108	43.8±11.6	Not reported	5.2±0.7	29.9±5.4	43.8±11.6	6	Not reported	⑧
	Vorti 10-mg	100	42.3±13.1		5.1±0.7	29.3±5.6	42.3±13.1			
	Placebo	105	42.0±10.9		5.1±0.7	29.7±5.0	42.0±10.9			

LOCF, last observation carried forward; HDRS-24, 24-item Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; SDS, Sheehan Disability Scale; CGI-I, Clinical Global Impression Scale-Improvement; Vorti, Vortioxetine; ①HDRS-24(LOCF), 24-item Hamilton Depression Rating Scale; ②MADRS(LOCF), Montgomery-Asberg Depression Rating Scale; ③SDS(LOCF), Sheehan Disability Scale; ④CGI-I(LOCF), Clinical Global Impression Scale-Improvement; ⑤, HDRS-24 response rate; ⑥, MADRS remission rate; ⑦, MADRS response rate; ⑧, Safety.

Figure 2. Risk of bias summary: Judgements of review authors about each risk of bias item for each included study.

response rate (≥50%; M-H RR=1.44; 95% CI=1.15-1.81; I^2=39%) and MADRS remission rate (≤10%; M-H RR=1.61; 95% CI=1.38-1.89; I^2=34%; P<0.05). iii) The HADRS-24, MADRS, SDS, CGI-I total scores and HDRS-24 response rate were not reported for the 15-mg vortioxetine group. However, there was no statistically significant difference in the MADRS response (≥50%) and remission rates (≤10%) between the two groups (P>0.05) (4). Consistently, in the 20-mg vortioxetine group vs. placebo, the HADRS-24 and SDS total score changes, and the HADRS-24 response rate were not reported. A statistically significant difference was obtained between the above groups in terms of the total scores of MADRS [MD=-2.30; 95% CI=-2.45-(-2.15)] and CGI-I [MD=-0.58; 95% CI=-1.13-(-0.02)], MADRS response rate (≥50%; M-H RR=1.55; 95% CI=1.07-2.23) and MADRS remission rate (≤10%; M-H RR=1.54; 95% CI=1.17-2.03; all P<0.05). Details of efficacy and heterogeneity assessment are presented in Table II and Figs. S1-4.

Safety outcomes. Subsequently, a parallel, independent meta-analysis was performed. The meta-analysis of the 11 articles included 16 adverse reactions, including nausea, headache, nasopharyngitis, dizziness, diarrhea, constipation, dry mouth, insomnia, adverse events (AEs) leading to discontinuation, serious AEs (SAEs), fatigue, hyperhidrosis, decreased appetite, somnolence, vomiting and upper respiratory tract infection, with a total adverse drug reaction rate of 5%. Therefore, the analysis revealed that compared with the placebo group: i) A statistically significant difference was observed in the onset of nausea (response rate, M-H RR=2.48; 95% CI=1.99-3.10; I^2=0%) in the 5-mg vortioxetine

Table II. Comparison of therapeutic effect analysis in each trial group.

	HADRS-24 total score change (MD)	MADRS total score change (MD)	SDS total score change (MD)	CGI-I total score change (MD)	HADRS-24 response rate (RR)	MADRS response rate (≥50%) (RR)	MADRS remission rate (≤10%) (RR)
Vortioxetine 5-mg vs. Placebo	-7.46 (-16.69 to 1.77) Z=1.58; (P=0.11) 4 trials	-2.07 (-4.37 to 0.23) Z=1.76 (P=0.08); 3 trials	-0.27 (0.94 to 0.40) Z=0.79 (P=0.43); 3 trials	-0.22 (0.48 to 0.03) Z=1.71 (P=0.09); 3 trials	1.34 (1.00 to 1.80) Z=1.96 (P=0.05); 4 trials	1.57 (1.23 to 1.99) Z=3.66 (P<0.05); 3 trials	1.28 (1.10 to 1.49)[a] Z=3.13 (P<0.05); 5 trials
Vortioxetine 10-mg vs. Placebo	-4.93 (-5.12 to -4.74) Z=52.18 (P<0.05); 1 trial	-3.65 (-5.61 to -1.69) Z=3.65 (P<0.05); 3 trials	-1.54 (-1.76 to -1.32) Z=13.86 (P<0.05); 1 trial	-0.58 (-0.64 to -0.52) Z=19.35 (P<0.05); 2 trials	2.16 (1.52 to 3.05) Z=4.34 (P<0.05); 1 trial	1.44 (1.15 to 1.81)[a] Z=3.13 (P<0.05); 3 trials	1.61 (1.38 to 1.89)[a] Z=5.88 (P<0.05); 3 trials
Vortioxetine 15-mg vs. Placebo	Not reported	Not reported	Not reported	Not reported	Not reported	1.36 (0.75 to 2.47) Z=1.00 (P=0.32); 2 trials	1.41 (0.91 to 2.19) Z=1.53 (P=0.13); 2 trials
Vortioxetine 20-mg vs. Placebo	Not reported	-2.30 (-2.45 to -2.15) Z=30.37 (P<0.05); 1 trial	Not reported	-0.58 (-1.13 to -0.02) Z=2.02 (P<0.05); 2 trials	Not reported	1.55 (1.07 to 2.23) Z=2.32 (P<0.05); 4 trials	1.54 (1.17 to 2.03) Z=3.06 (P<0.05); 4 trials

HDRS-24, 24-item Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; SDS, Sheehan Disability Scale; CGI-I, Clinical Global Impression Scale-Improvement; [a]$I^2 \leq 5$; MD, Mean Difference; R, Risk Ratio.

group. However, no difference was observed in headache, nasopharyngitis, dizziness, diarrhea, constipation, dry mouth, insomnia, AEs leading to discontinuation, SAEs, fatigue, hyperhidrosis, decreased appetite, somnolence and vomiting, between the two groups (P>0.05). ii) A statistically significant difference was obtained in nausea (response rate, M-H RR 3.02; 95% CI, 2.16=4.23; I^2=0%) and hyperhidrosis (response rate, M-H RR=4.65; 95% CI=1.36-15.95; I^2=0%) between the 10-mg vortioxetine group compared with the placebo group. No differences in the remaining AEs were recorded (P>0.05). iii) In the 15-mg vortioxetine group, a statistically significant difference was only obtained in nausea (response rate, M-H RR=3.12; 95% CI=2.18-4.46; I^2=0%), compared with the placebo group, and not for the other AEs (P>0.05). iv) In the 20-mg vortioxetine group, a statistically significant difference in nausea (response rate, M-H RR=3.39; 95% CI=2.54-4.51; I^2=0%), insomnia (response rate, M-H RR=2.25; 95% CI=1.09-4.68; I^2=22%) and vomiting (response rate, M-H RR=13.42; 95% CI=1.78-101.37) was observed. There were no statistically significant differences in headache, nasopharyngitis, dizziness, diarrhea, constipation, dry mouth, AEs leading to discontinuation, SAEs, fatigue, decreased appetite, vomiting and upper respiratory tract infection between the two groups (P>0.05). The details of AE assessment are demonstrated in Table III and Figs. S5-8. Furthermore, the visual inspection of funnel plots revealed low obvious publication bias (Fig. 3).

Discussion

Summary of findings. It has been reported that serious mental illness (SMI), such as depression, bipolar disorder and schizophrenia, not only seriously affects patient's interpersonal relationships, work and independent living capabilities, but also is a significant risk factor for increasing the prevalence and mortality of somatic diseases (41). Previous studies verified that patients with SMI were at a higher risk of developing acute organ dysfunction (42) and their life expectancy was lower by an average of 20 years compared with the general population (2). Among the aforementioned conditions, cardiovascular diseases, cancer and diseases of the endocrine system, such as diabetes and obesity, and respiratory system have become the main cause of SMI-related death (43). Numerous studies suggested that cardiovascular diseases were the most common diseases among patients with SMI, characterized by relatively high mortality rate (44,45). Among them, the lifetime prevalence rate of myocardial infarction, angina pectoris and stroke were ~30% (46). Cognitive dysfunction is common in patients with MDD, while it has been reported that cognitive impairment may persist after the relief of depressive symptoms (47). Since cognitive impairment is the most significant residual symptom and can reduce the quality of life of patients with MDDs, persistent cognitive impairment may prevent full recovery from depressive episodes. Several scholars have advocated 'remission of cognitive function'

Table III. Comparison of safety analysis in each trial group.

	Vortioxetine 5-mg	Vortioxetine 10-mg	Vortioxetine 15-mg	Vortioxetine 20-mg
Nausea	2.48% (1.99 to 3.10%)[a] I^2=0%; 7 trials	3.02% (2.16 to 4.23%)[a] I^2=0%; 4 trials	3.12% (2.18 to 4.46%)[a] I^2=0%; 2 trials	3.39% (2.54 to 4.51%)[a] I^2=0%; 4 trials
Headache	1.01% (0.82 to 1.25%) I^2=4%; 6 trials	0.89% (0.67 to 1.20%) I^2=0%; 4 trials	1.36% (0.89 to 2.08%) I^2=0%; 2 trials	1.19% (0.88 to 1.60%) I^2=0%; 4 trials
Nasopharyngitis	1.24% (0.84 to 1.84%) I^2=0%; 4 trials	0.81% (0.52 to 1.27%) I^2=0%; 4 trials	0.65% (0.24 to 1.74%) 1 trial	0.95% (0.62 to 1.46%) I^2=0%; 3 trials
Dizziness	1.00% (0.72 to 1.40%) I^2=0%; 7 trials	1.20% (0.72 to 2.01%) I^2=35%; 4 trials	1.53% (0.35 to 6.60%) I^2=78%; 2 trials	1.70% (0.82 to 3.52%) I^2=52%; 4 trials
Diarrhea	0.95% (0.52 to 1.73%) I^2=61%; 5 trials	0.75% (0.43 to 1.29%) I^2=34%; 3 trials	1.87% (1.04 to 3.38%) I^2=33%; 2 trials	1.13% (0.54 to 2.39%) I^2=59%; 4 trials
Constipation	1.00% (0.60 to 1.68%) I^2=0%; 5 trials	1.12% (0.49 to 2.60%) I^2=25%; 3 trials	0.87% (0.35 to 2.13%) 1 trial	1.73% (0.89 to 3.37%) I^2=0%; 2 trials
Dry mouth	1.20% (0.86 to 1.68%) I^2=0%; 6 trials	0.99% (0.55 to 1.80%) I^2=31%; 3 trials	0.97% (0.54 to 1.76%) I^2=0%; 2 trials	1.42% (0.92 to 2.18%) I^2=23%; 4 trials
Insomnia	1.46% (0.83 to 2.58%) I^2=0%; 4 trials	1.05% (0.50 to 2.23%) I^2=0%; 3 trials	0.68% (0.23 to 2.02%) 1 trial	2.25% (1.09 to 4.68%)[a] I^2=22%; 2 trials
AE leading to discontinuation	0.35% (0.07 to 1.70%) 1 trial	2.38% (0.94 to 6.03%) 1 trial	Not reported	1.72% (0.60 to 4.92%) I^2=58%; 2 trials
Any SAE	2.10% (0.19 to 22.88%) 1 trial	3.06% (0.32% to 29.09%); 1 trial	Not reported	5.03% (0.60 to 42.57%); 1 trial
Fatigue	1.07% (0.58 to 1.97%) I^2=0%; 4 trials	1.08% (0.44 to 2.66%) I^2=0%; 2 trials	1.57% (0.45 to 5.45%) 1 trial	1.31% (0.36 to 4.78%) 1 trial
Hyperhidrosis	1.58% (0.75 to 3.31%) I^2=0%; 4 trials	4.65% (1.36 to 15.95%)[a] I^2=0%; 2 trials	0.87% (0.27 to 2.80%) 1 trial	0.08% (0.00 to 1.42%) 1 trial
Decreased appetite	2.07% (0.73 to 5.92%) I^2=0%; 3 trials	0.47% (0.04 to 5.14%) 1 trial	Not reported	2.92% (0.31 to 27.86%) 1 trial
Somnolence	1.16% (0.58 to 2.32%) I^2=0%; 3 trials	0.94% (0.28 to 3.19%) 1 trial	Not reported	Not reported
Vomiting	1.28% (0.45 to 3.63%) I^2=0%; 2 trials	1.32% (0.43 to 4.07%) 1 trial	7.57% (0.94 to 60.80%); 1 trial	13.42% (1.78 to 101.37%)[a] 1 trial
Upper respiratory tract infection	Not reported	Not reported	0.49% (0.17 to 1.38%) 1 trial	0.75% (0.31 to 1.82%) 1 trial

[a]P<0.05. AE, adverse effect; SAE, serious AE.

as a novel target for the treatment of MDD. Chen *et al* (48) confirmed that the changes in the number of dendritic spines, dendritic spine density, dendritic length and branching in the hippocampus could promote the maturation of hippocampal dendritic spines and improve cognitive function in animals, thus indicating that they could also potentially affect cognitive function in humans. Another study suggested that vortioxetine could increase histamine levels in the cerebral cortex and hippocampus, and it could indirectly improve cognitive function via regulating serotonin in the vegetarian system (49).

In the present systematic review, 11 randomized, double-blind, placebo-controlled trials were included based on the inclusion and exclusion criteria (30-40). Subsequently, an evidence-based medical evaluation of the efficacy and safety of the four vortioxetine preparation doses (5, 10, 15 and 20 mg) was carried out. All 11 studies showed that the methodological assessments performed were of high quality, with a low risk of bias, thus verifying that this was a systematic review with high data credibility. Additionally, all included studies displayed favorable general-data consistency and baseline balance, while they were comparable. Furthermore, the heterogeneity of several indicators in the reference material was assessed by Q test. In the efficacy assessment, there were varying degrees of heterogeneity in each group (5, 10, 15 and 20 mg). Due to the heterogeneity (I^2>50%) in the reference material and since all the clinical research data were valid, the weight ratio difference analysis of the relevant effect indicators could not accurately exclude heterogeneous sources. Therefore, to evaluate the efficacy of each indicator in the four groups (5-, 10-, 15- and 20-mg vortioxetine groups), a meta-analysis using a fixed effect model was performed for only a few indicators (MADRS remission rate in the 5- and 10-mg vortioxetine groups and

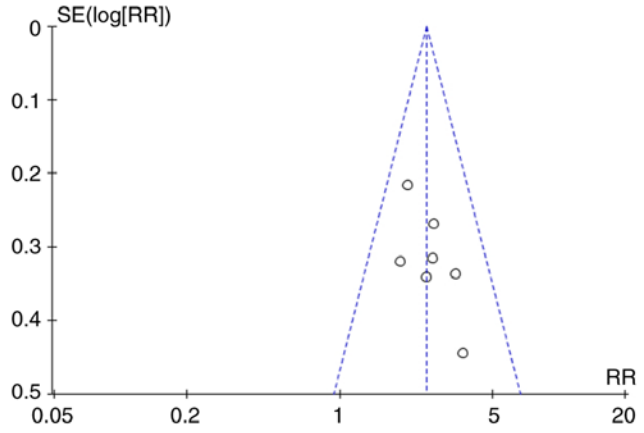

Figure 3. Publication bias for vortioxetine in all included studies.

MADRS response rate in the 10-mg vortioxetine group), while the remaining indicators were assessed by a REM. For patients with depression, who were initially treated with 5 mg vortioxetine QD, the results revealed that there was a significant difference in the MADRS response and remission rates at the end of the treatment period. In addition, the clinical symptom scores of patients in the 10- and 20-mg QD vortioxetine groups were markedly changed with increasing dosage. Compared with the placebo group, there was a significant difference in symptom scores and response rates ($P<0.05$). However, data processing revealed that the data from five indicators, namely HADRS-24 total score, MADRS total score, SDS total score, CGI-I total score and HADRS-24 response rate, were missing for the 15-mg QD vortioxetine group. Therefore, only the data for two indicators, namely MADRS response rate and MADRS remission rate, were used for the combined analysis in this group. There was no statistically significant difference between the aforementioned two indicators in the 15-mg QD vortioxetine group compared with the placebo group ($P>0.05$), possibly due to the effect of reference source, selection and publication bias. Therefore, a descriptive analysis was performed, and a single double-blind RCT showed that patient treatment with 15 mg vortioxetine QD could significantly improve symptom score (39). The aforementioned results were consistent with those reported by Meeker *et al* (50), which verified that patient treatment with 5, 10, 15 or 20 mg vortioxetine could significantly affect the response and remission rates. In the present study, the results also showed that administration of 5, 10, 15 or 20 mg vortioxetine could notably alter HADRS-24, MADRS, SDS and CGI-I total scores, and the HADRS-24 response rate compared with placebo. However, the results also demonstrated that treatment with 5 mg vortioxetine had no effect on HADRS-24, MADRS, SDS and CGI-I total scores, and HADRS-24 response rate, compared with placebo. There was an effort to use the subgroup analysis due to the heterogeneity, but the included research in every efficacy outcome measure is no more than four, therefore the subgroup analysis cannot solve heterogeneity ($I^2>50\%$), Finally, it was decided not to use the subgroup analysis. Nevertheless, more high-quality clinical studies are urgently needed to further investigate and confirm the aforementioned findings.

In terms of safety evaluation, an independent merged meta-analysis on 16 adverse reactions, namely nausea, headache, nasopharyngitis, dizziness, diarrhea, constipation, dry mouth, insomnia, AEs leading to discontinuation, SAEs, fatigue, hyperhidrosis, decreased appetite, somnolence, vomiting and upper respiratory tract infection was carried out. The total incidence rate of AEs in the 11 included studies was >5% (30-40). The results revealed that nausea, hyperhidrosis, insomnia and vomiting were more common in all trial vortioxetine groups (5, 10, 15 and 20 mg) compared with placebo. Regarding the association between AEs and vortioxetine dosage, no absolute linear association was found in this evaluation system. However, this result could be greatly affected by bias and the completeness of the data. Therefore, further high-quality clinical studies are required to verify the aforementioned results.

Moreover, there have been two systematic reviews about vortioxetine (51,52); the study conducted by Zhang *et al* (51) only the response rate, remission rate and tolerability were analyzed, which is insufficient. In the study conducted by Thase *et al* (52), the safety outcomes were not analyzed. In addition, in the present study more and new outcome measures were analyzed. The efficiency outcome measures not only contained MADRS response rate, MADRS remission rate, but also HADRS-24, MADRS, SDS, CGI-I and HADRS-24 response rate. The safety outcome measure was also substantial. Although the conclusion was different, Zhang *et al* (51) considered that vortioxetine is more advantageous over placebo in treating MDD among adults, while the present study revealed that there was no statistical difference between vortioxetine 5-mg and placebo in HADRS-24, MADRS, SDS, CGI-I total score change and HADRS-24 response rate. Overall, the present study provided sufficient outcome measure, new conclusions compared with other meta-analysis of vortioxetine and could offer significant information to clinicians who prescribe vortioxetine to patients suffering from SMI.

Limitations. Even though the included studies in the present meta-analysis were strictly screened according to the inclusion and exclusion criteria, a rigorous standardized quality evaluation was conducted for the grouped 11 references. There were nevertheless certain limitations. The following deficiencies still exist in the meta-analysis of the system evaluation and effect indicators: i) In multiple databases, there could be omissions in the collection of references due to the retrieval strategy applied; ii), Since two researchers reviewed the references in an independent and parallel way according to the inclusion and exclusion criteria, the risk of reference selection bias during the screening of reference material should not be excluded; iii) Screening results from relevant clinical trial registration websites were unsatisfactory. For several grey references and evidence from non-traditional sources, the query results may not be a strong supplement for the required entry data due to the effects of confidentiality agreements. Therefore, a particular degree of publication bias risk could be included in the analysis. iv) Since the 11 studies included into the analysis were all in English, the risk of language bias could not be avoided. However, the aforementioned risks could be present in any systematic review and meta-analysis. The strict and careful reference screening

and quality assessment, and the appropriate methodological handling can guarantee scientific, complete and accurate results with high clinical reference value.

The present systematic review demonstrated that 5-20 mg was significantly effective compared with placebo in the treatment of MDD. However, treatment of patients with 5 mg vortioxetine displayed no difference in the HADRS-24, MADRS, SDS and CGI-I total scores, and HADRS-24 response rate. Interestingly enough, increased vortioxetine doses were associated with improved tolerance and high safety. Considering the potential bias and confounding of the studies included in this meta-analysis, more well-conducted and large-scale RCTs are needed to confirm the findings of the present study.

Acknowledgements

Not applicable.

Funding

The present study was supported by the Science and Technology Plan Fund from Yaan Science and Technology Bureau (grant no. 22KJJH0039).

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

SG, LF, XX and DZ designed the study, collected the data, undertook the statistical analyses, drafted the manuscript and contributed equally to this work. SG and XX participated in the review of the study, performed the statistical analyses, helped to interpret data and drafted the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Hirschfeld RM: Differential diagnosis of bipolar disorder and major depressive disorder. J Affect Disord 169 (Suppl 1): S12-S16, 2014.
2. DE Hert M, Correll CU, Bobes J, Cetkovich-Bakmas M, Cohen D, Asai I, Detraux J, Gautam S, Möller HJ, Ndetei DM, *et al*: Physical illness in patients with severe mental Disorders. I. Prevalence, impact of medications and disparities in health care. World Psychiatry 10: 52-77, 2011.
3. Grigoriadis S, VonderPorten EH, Mamisashvili L, Eady A, Tomlinson G, Dennis CL, Koren G, Steiner M, Mousmanis P, Cheung A, *et al*: The effect of prenatal antidepressant exposure on neonatal adaptation: A systematic review and meta-analysis. J Clin Psychiatry 74: e309-e320, 2013.
4. Hair P, Cameron F and Garnock-Jones KP: Levomilnacipran extended-release: First global approve. Drugs 73: 1639-1645, 2013.
5. Sartorius N: Comorbidity of mental and physical disorders: A main challenge to medicine in the 21st century. Psychiatr Danub 25 (Suppl 1): S4-S5, 2013.
6. He S, Yang XM and Li HF: Levomilnacipran: A new drug for treatment of major depressive disorder. Chin J New Drugs Clin Rem 34: 418-422, 2015.
7. Bang-Andersen B, Ruhland T, Jørgensen M, Smith G, Frederiksen K, Jensen KG, Zhong H, Nielsen SM, Hogg S, Mørk A and Stensbøl TB: Discovery of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine (Lu AA21004): A novel multimodal compound for the treatment of major depressive disorder. J Med Chem 54: 3206-3221, 2011.
8. Pehrson AL, Cremers T, Bétry C, van der Hart MG, Jørgensen L, Madsen M, Haddjeri N, Ebert B and Sanchez C: Lu AA21004, a novel multimodal antidepressant, produces regionally selective increases of multiple neurotransmitters a rat microdialysis and electrophysiology study. Eur Neuropsychopharmacol 23: 133-145, 2013.
9. Gibb A and Deeks ED: Vortioxetine: First global approval. Drugs 74: 135-145, 2014.
10. Boulenger JP, Loft H and Florea I: A randomized clinical study of Lu AA21004 in theprevention of relapse in patients with major depressive disorder. J Psychopharmacol 26: 1408-1416, 2012.
11. FDA. Vortioxetine(EB/OL). http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204447s000lbl.pdf, 2013-09-30.
12. Li G, Wang X and Ma D: Vortioxetine versus duloxetine in the treatment of patients with major depressive disorder: A Meta-analysis of randomized controlled trials. Clin Drug Investig 36: 509-517, 2016.
13. Pae CU, Wang SM, Han C, Lee SJ, Patkar AA, Masand PS and Serretti A: Vortioxetine: A meta-analysis of 12 short-term, randomized, placebo-controlled clinical trials for the treatment of major depressive disorder. J Psychiatry Neurosci 40: 174-186, 2015.
14. Baldwin DS, Chrones L, Florea I, Nielsen R, Nomikos GG, Palo W and Reines E: The safety and tolerability of vortioxetine: Analysis of data from randomized Placebo-controlledtrials and open-label extension studies. J Psychopharmacol 30: 242-252, 2016.
15. Page MJ and Moher D: Evaluations of the uptake and impact of the preferred reporting items for systematic reviews and Meta-analysis (PRISMA) statement and extensions: A scoping review. Syst Rev 6: 263, 2017.
16. Sandini M, Mattavelli I, Nespoli L, Uggeri F and Gianotti L: Systematic review and meta-analysis of sutures coated with triclosan for the prevention of surgical site infection after elective colorectal surgery according to the PRISMA statement. Medicine (Baltimore) 95: e4057, 2016.
17. Panic N, Leoncini E, de Belvis G, Ricciardi W and Boccia S: Evaluation of the endorsement of the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement on the quality of published systematic review and meta-analyses. PLoS One 8: e83138, 2013.
18. Durak S, Ercan ES, Ardic UA, Yuce D, Ercan E and Ipci M: Effect of methylphenidate on neurocognitive test battery: An evaluation according to the diagnostic and statistical manual of mental disorders, fourth edition, subtypes. J Clin Psychopharmacol 34: 467-474, 2014.
19. Shabsigh R and Rowland D: The Diagnostic and statistical manual of mental distal disorders, Fouth edition, text revision as an appropriate diagnostic for premature ejaculation. J Sex Med 4: 1468-1478, 2007.
20. Faiad Y, Khoury B, Daouk S, Maj M, Keeley J, Gureje O and Reed G: Frequency of use of the international classification of diseases ICD-10 diagnostic categories for mental and behavioural disorders across world regions. Epidemiol Psychiatr Sci 11: 1-9, 2017.
21. Janca A, Ustün TB, Early TS and Sartorius N: The ICD-10 symptom checklist: A companion to the ICD-10 classification of mental and behavioural disorders. Soc Psychiatry Psychiatr Epidemiol 28: 239-242, 1993.

22. International Advisory Group for the Revision of ICD-10 Mental and Behavioural Disorders: A conceptual framework for the revision of the ICD-10 classification of mental and behavioural disorders. World Psychiatry 10: 86-92, 2011.
23. Khan A, Lewis C and Lindenmayer JP: Use of non-parametric item response theory to develop a shortened version of the Positive and Negative Syndrome Scale (PANSS). BMC Psychiatry 11: 178, 2011.
24. Garcia-Caballero A, Torrens-Lluch M, Ramírez-Gendrau I, Garrido G, Vallès V and Aragay N: The efficacy of motivational intervention and cognitive-behavioral therapy for pathological gambling. Adicciones 30: 219-224, 2018 (In English, Spanish).
25. Health Quality Ontario: Psychotherapy for Major depressive disorder and generalized anxiety disorder: A health technology assessment. Ont Health Technol Assess Ser 17: 1-167, 2017.
26. Hedges DW, Brown BL and Shwalb DA: A direct comparison of effect sizes from the clinical global impression-improvement scale to effect sizes from other rating scales in controlled trials of adult social anxiety disorder. Hum Psychopharmacol 24: 35-40, 2009.
27. Higgins JPT and Green S, (eds.): Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration, Available from: http://handbook.cochrane.org, (Updated March 2011).
28. Berhan A and Barker A: Vortioxetine in the treatment of adult patients with major depressive disorder: A meta-analysis of randomized double-blind controlled trials. BMC Psychiatry 14: 276-283, 2014.
29. Braga VL, Rocha LPDS, Bernardo DD, Cruz CO and Riera R: What do Cochrane systematic reviews say about probiotics as preventive interventions? Sao Paulo Med J 135: 578-586, 2017.
30. Henigsberg N, Mahableshwarkar AR, Jacobsen P, Chen Y and 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 73: 953-959, 2012.
31. Nishimura A, Aritomi Y, Sasai K, Kitagawa T and Mahableshwarkar AR: Randomized, double-blind, placebo-controlled 8-week trial of the efficacy, safety, and tolerability of 5, 10, and 20 mg/day vortioxetine in adults with major depressive disorder. Psychiatry Clin Neurosci 72: 64-72, 2018.
32. Jain R, Mahableshwarkar AR, Jacobsen PL, Chen Y and Thase ME: 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 16: 313-321, 2013.
33. McIntyre RS, Lophaven S and Olsen CK: A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. Int J Neuropsychopharmacol 17: 1557-1567, 2014.
34. Mahableshwarkar AR, Jacobsen PL and 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 29: 217-226, 2013.
35. Baldwin DS, Loft H and 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 22: 482-491, 2012.
36. Katona C, Hansen T and 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 27: 215-223, 2012.
37. Mahableshwarkar AR, Zajecka J, Jacobson W, Chen Y and Keefe RS: A randomized, placebo-controlled, active-reference, double-blind, flexible-dose study of efficacy of vortioxetine on cognitive function in major depressive disorder. Neuropsychopharmacology 40: 2025-2037, 2015.
38. Boulenger JP, Loft H and 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 Psychopharmacol 29: 138-149, 2014.
39. Mahableshwarkar AR, Jacobsen PL, Chen Y, Serenko M and 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) 232: 2061-2070, 2015.
40. Alvarez E, Perez V, Dragheim M, Loft H and Artigas F: A double-blind, randomized, placebo-controlled, active reference study of Lu AA21004 in patients with major depressive disorder. Int J Neuropsychopharmacol 15: 589-600, 2012.
41. Ma XR, Hou CL and Xia FJ: Present situation and challenges of somatic syndromes in patients with serious mental illness. Chin J Behav Med Brain Sci 23: 181-183, 2014.
42. Shen HN, Lu CL and Yang HH: Increased risks of acute organ dysfunction and mortality in intensive care unit patients with schizophrenia: A nationwide population-based study. Psychosom Med 73: 620-626, 2011.
43. Lawrence D and Kisely D: Inequalities in healthcare provision for people with severe mental iuness. J Psychopharmacol 24 (4 Suppl): S6l-S68, 2010.
44. Ritchie S and Muldoon L: Cardiovascular preventive care for patients with serious mental illness. Can Fam Physician 63: e483-e487, 2017.
45. Kilbourne AM, Welsh D, McCarthy JF, Post EP and Blow FC: Quality of care for cardiovascular disease-related conditions in patients with and without mental disorders. J Gen Intern Med 23: 1628-1633, 2008.
46. Zhao G, Ford ES, Dhingra S, Li C, Strine TW and Mokdad AH: Depression and anxiety among US adults: Associations with body mass index. Int J Obes (Lond) 33: 257-266, 2009.
47. Waller JA, Chen F and Sanchez C: Vortioxetine promotes maturation of dendritic spines in vitro: A comparative study in hippocampal cultures. Neuropharmacology 103: 143-154, 2016.
48. Chen F, du Jardin KG, Waller JA, Sanchez C, Nyengaard JR and Wegener G: Vortioxetine promotes early changes in dendritic morphology compared to fluoxetine in rat hippocampus. Eur Neuropsychopharmacol 26: 234-245, 2016.
49. Smagin GN, Song D, Budac DP, Waller JA, Li Y, Pehrson AL and Sánchez C: Histamine may contribute Tovortioxetine's procognitive effects; possibly through an orexigenic mechanism. Prog Neuropsychopharmacol Biol Psychiatry 68: 25-30, 2016.
50. Meeker AS, Herink MC, Haxby DG and Hartung DM: The safety and efficacy of vortioxetine for acute treatment of major depressive disorder: A systematic review and meta-analysis. Syst Rev 4: 21, 2015.
51. Zhang X, Cai Y, Hu X, Lu CY, Nie X and Shi L: Systematic review and meta-analysis of vortioxetine for the treatment of major depressive disorder in adults. Front Psychiatry 13: 922648, 2022.
52. Thase ME, Mahableshwarkar AR, Dragheim M, Loft H and Vieta E: A meta-analysis of randomized, placebo-controlled trials of vortioxetine for the treatment of major depressive disorder in adults. Eur Neuropsychopharmacol 26: 979-993, 2016.

Copyright © 2023 Gao et al. This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.