Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology) *2025 26(1):26-38*
www.jzus.zju.edu.cn; www.springer.com/journal/11585
E-mail: jzus_b@zju.edu.cn

Research Article

https://doi.org/10.1631/jzus.B2400470

Clinical efficacy and safety of vortioxetine as an adjuvant drug for patients with bipolar depression

Chunxiao DAI[1,2*], Yaoyang FU[2*], Xuanwei LI[3*], Meihua LIN[3], Yinbo LI[4], Xiao LI[3], Keke HUANG[3], Chengcheng ZHOU[4], Jian XIE[2✉], Qingwei ZHAO[3✉], Shaohua HU[1,5,6,7,8,9,10✉]

[1]*Department of Psychiatry, the First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China*
[2]*Department of Clinical Psychology, Hangzhou First People's Hospital, Hangzhou 310006, China*
[3]*Department of Clinical Pharmacy, the First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China*
[4]*Fuyang Third People's Hospital, Hangzhou 311402, China*
[5]*Nanhu Brain-Computer Interface Institute, Hangzhou 311100, China*
[6]*The Zhejiang Key Laboratory of Precision Psychiatry, Hangzhou 310003, China*
[7]*School of Brain Science and Brain Medicine, and MOE Frontier Science Center for Brain Science and Brain-Machine Integration, Zhejiang University School of Medicine, Hangzhou 310012, China*
[8]*Brain Research Institute of Zhejiang University, Hangzhou 310003, China*
[9]*The State Key Lab of Brain-Machine Intelligence, Zhejiang University, Hangzhou 310003, China*
[10]*Zhejiang Engineering Center for Mathematical Mental Health, Hangzhou 310003, China*

Abstract: Objective: Whether vortioxetine has a utility as an adjuvant drug in the treatment of bipolar depression remains controversial. This study aimed to validate the efficacy and safety of vortioxetine in bipolar depression. Methods: Patients with bipolar II depression were enrolled in this prospective, two-center, randomized, 12-week pilot trial. The main indicator for assessing treatment effectiveness was a Montgomery-Asberg Depression Rating Scale (MADRS) of ⩾50%. All eligible patients initially received four weeks of lurasidone monotherapy. Patients who responded well continued to receive this kind of monotherapy. However, no-response patients were randomly assigned to either valproate or vortioxetine treatment for eight weeks. By comprehensively comparing the results of MADRS over a period of 4–12 weeks, a systematic analysis was conducted to determine whether vortioxetine could be used as an adjuvant drug for treating bipolar depression. Results: Thirty-seven patients responded to lurasidone monotherapy, and 60 patients were randomly assigned to the valproate or vortioxetine group for eight weeks. After two weeks of combined valproate or vortioxetine treatment, the MADRS score in the vortioxetine group was significantly lower than that in the valproate group. There was no difference in the MADRS scores between the two groups at 8 and 12 weeks. The incidence of side effects did not significantly differ between the valproate and vortioxetine groups. Importantly, three patients in the vortioxetine group appeared to switch to mania or hypomania. Conclusions: This study suggested that lurasidone combination with vortioxetine might have potential benefits to bipolar II depression in the early stage, while disease progression should be monitored closely for the risk of switching to mania.

Key words: Bipolar II depression; Lurasidone; Vortioxetine; Combination

1 Introduction

Bipolar disorder (BD) is a common psychiatric disease affecting 1%–2% of the global population (Clemente et al., 2015). Depressive episodes comprise 72% of the disease duration for BD-I and 81% for BD-II in BD (Goldberg et al., 2009). Patients with BD-II are more likely to experience depressive episodes that disrupt their social functioning, life quality, social relationships, and occupational performance than those with hypomania (Post, 2016; Dome et al.,

✉ Jian XIE, srxjian@163.com
Qingwei ZHAO, qwzhao@zju.edu.cn
Shaohua HU, dorhushaohua@zju.edu.cn
* The three authors contributed equally to this work
Chunxiao DAI, https://orcid.org/0009-0006-2496-1887
Yaoyang FU, https://orcid.org/0000-0002-4961-0374
Xuanwei LI, https://orcid.org/0000-0003-2830-1596
Jian XIE, https://orcid.org/0000-0002-6680-7558
Qingwei ZHAO, https://orcid.org/0000-0002-7201-0588
Shaohua HU, https://orcid.org/0000-0003-0570-670X

Received Sept. 11, 2024; Revision accepted Nov. 28, 2024; Crosschecked Dec. 17, 2024

2019). Managing bipolar depression remains a major challenge for clinicians because of the complex nature of bipolarity (Mitchell et al., 2008; McIntyre and Calabrese, 2019). As we all know, BD is a mental disease with multi-dimensional symptoms, involving powerful emotions, cognitive impairment, behavioral and other related symptoms and phenotypes. The corresponding pathological changes are complex neurotransmitter and receptor dysfunction. Further clinical evidence suggests that several atypical antipsychotics are effective in the treatment of the acute phase of bipolar depression, which also lays the foundation for these drugs to be recommended as first-line treatment in national treatment guidelines (Loebel et al., 2014a; Suttajit et al., 2014). The US Food and Drug Administration (FDA) has approved four atypical antipsychotics for treating bipolar depression: quetiapine, lurasidone (LUR), cariprazine, and a combination of fluoxetine with olanzapine (McIntyre et al., 2013). The mechanism of action of these antipsychotics may be related to the complex pharmacological mechanism of multi-target and multi-receptor regulation of serotonergic, dopaminergic and other pathways, which improves the multi-dimensional symptoms of bipolar depression (Fountoulakis et al., 2024). However, the accumulated evidence of treatment options in bipolar II depression is insufficient. Only quetiapine and extended-release quetiapine have been approved for the treatment of this type (Mitchell et al., 2008; McIntyre et al., 2013; Calabrese et al., 2021). In addition, BD prognosis is complicated by cardiometabolic problems and immunological abnormalities associated with the disease or its treatment, substantially reducing patients' life expectancy (Crump et al., 2013; Forte et al., 2015; Yalin and Young, 2020). Therefore, more effective and safer intervention is imminent.

The atypical antipsychotic drug LUR, is a potent antagonist of dopamine-2 (D2), serotonin 2A (5-HT2A), and 5-HT7 receptors, and a partial agonist of 5-HT1A receptor. The serotonergic receptor action of LUR appears to be effective in alleviating depression and promoting cognition, and the D2 blockade may act as a protective mechanism and reduce the risk of switching to mania/hypomania (Greenberg and Citrome, 2017). LUR was successively approved by the FDA and recommended in the 2018 Canadian Network for Mood and Anxiety Treatment (CANMAT) and the International Society for Bipolar Disorders (ISBD) guidelines for the acute bipolar depressive episode (Yatham et al., 2018). It was established as efficacious for monotherapy and an adjunct to lithium or valproate (VAL). LUR is devoid of antihistaminic or anticholinergic activity, and therefore it is well tolerated, with minimal effects on weight and metabolic parameters (Ishibashi et al., 2010; Ketter et al., 2016). However, these results were based on studies conducted exclusively on patients with BD-I, and hence may not be generalizable to BD-II. The efficacy and safety of LUR in BD-II require further validation. Currently, using antidepressants to treat bipolar depression remains controversial due to the limited evidence of their efficacy and the potential risk of switching to mania or inducing rapid cycling. This issue particularly affects BD-II patients who have more frequent and longer depressive episodes and a higher risk of suicide attempts than those with BD-I (Pacchiarotti and Verdolini, 2021). Notably, several systematic reviews and meta-analyses have demonstrated that antidepressants may be safe with moderate efficacy when administered adjunctively with mood-stabilizing pharmacological agents, such as lithium, lamotrigine, and second-generation antipsychotics, especially in BD-II (Tondo et al., 2013; Grande et al., 2016; McGirr et al., 2016; Liu et al., 2017). However, the efficacy and safety of antidepressants as adjuvants with new mechanisms of action need to be urgently evaluated.

Vortioxetine (VOR) is a novel multimodal antidepressant with unique modulation systems that directly affect various 5-HT receptors and inhibit their transporters (Bang-Andersen et al., 2011; Mørk et al., 2012). It is effective against a broad spectrum of depressive symptoms (Cipriani et al., 2018; de Diego-Adelino et al., 2022). Current clinical experience for VOR points to a low risk of switching to mania in patients with major depressive disorder, and several recent meta-analyses have shown no information on the risk of a hypomanic/manic switch induced by VOR in patients with major depressive disorder (Berhan and Barker, 2014; Pae et al., 2015). In September 2019, 4.87 million patients (approximately 20 million patients treated for three months) treated with VOR were included in the Periodic Safety Update Report, with 51 cases of hypomania and 322 cases of mania. According to this data, the conversion rate of VOR is approximately 1 per 10000 patient-years or 1 per 40000 patients. Given the advantages of VOR in treating major depressive disorders, it is vital to study its efficacy in BD-II depressive episodes and the risk of switching to mania. Therefore, the present study aimed to validate

the clinical efficacy and safety of VOR as an adjuvant therapy in patients who do not respond to LUR monotherapy.

2 Patients and methods

2.1 Patients

The patient inclusion criteria were as follows: (a) 18 to 65 years of age; (b) meeting the diagnostic criteria for BD-II as per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), and being required to have a current major depressive episode (Kaltenboeck et al., 2016); (c) a score of ≥20 on the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979); and (d) a Young Mania Rating Scale (YMRS) score of ≤14 at screening and baseline (Young et al., 1978; DelBello et al., 2017). The Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) was conducted to exclude patients characterized by the following: (a) meeting DSM-5 criteria for a current or lifetime schizophrenia and related psychotic disorder diagnosis; (b) a medically unstable condition; (c) previous intolerance to LUR or currently using LUR at a study baseline or within three months of the study; (d) borderline personality disorder; (e) substance use disorder within the past six months; (f) intellectual disability and autism spectrum disorder; (g) no capacity to provide informed, written consent; and (h) having taken any psychotropics for four consecutive weeks before the enrollment. Additional exclusion criteria included a history of electroconvulsive therapy (ECT) within the past three months, participation in an investigational drug trial within 30 d before the start of the trial, pregnancy and lactation, and women of childbearing potential without adequate contraception.

2.2 Study design

This prospective, two-center, randomized, 12-week pilot study aimed to compare the combination therapy of the VAL group and the VOR group regarding MADRS total score reduction. Eligible patients initially received LUR monotherapy for four weeks. At the end of the first phase, those who had achieved a ≥50% improvement compared with the baseline in MADRS total score continued the monotherapy with LUR. No-response patients with a <50% reduction in the MADRS total score were randomly assigned to either the LUR combined with VAL or LUR combined with VOR group for eight weeks. The randomization list was computer-generated and blinded to both the investigators and the patients. The dose of LUR administered in the first two weeks was routinely titrated. The patients who met the inclusion criteria began open-label treatment with 20 mg/d of LUR on Days 1–3 and 40 mg/d on Days 4–7, and then received flexible dosing of 20–120 mg/d. After four weeks, patients in the VAL group received a flexible 500–1000 mg/d dose of sodium VAL. The patients in the VOR group started taking VOR at a variable dose of 5–20 mg/d. At Weeks 5–12, the dose of LUR was varied and adjusted based on the patient's tolerance and response (20–120 mg/d). The second stage of the study lasted for eight weeks. Propranolol (20–30 mg/d) was administered as required for akathisia. The concomitant use of alprazolam (0.4–1.2 mg/d) was permitted for insomnia.

2.3 Efficacy

Efficacy assessments were conducted at baseline and weekly intervals throughout the experiment. To further evaluate the potential of VOR as an adjuvant for bipolar II depressive episodes, the patients who did not respond to 4-week LUR monotherapy were randomly administered VOR or VAL. The primary efficacy endpoint was the mean change in the MADRS total score between the VAL and VOR groups from Week 4 to Week 12. The score of MADRS, a 10-item scale with a total score ranging from 0 to 60, was assessed by a qualified site-based rater at each time-point. Treatment response was defined as achieving ≥50% reduction in MADRS total score from baseline. Additional efficacy parameters included changes in the Hamilton Rating Scale for Depression (24-items) (HAMD-24), Hamilton Anxiety Rating Scale (HAMA), and Young Mania Rating Scale (YMRS) scores from baseline to Week 12.

2.4 Therapeutic drug monitoring

In order to measure the serum concentration of the LUR, 5 mL venous blood samples were taken into ethylene diamine tetraacetic acid (EDTA) Vacutainer tubes under steady-state conditions after 14 and 28 d of LUR treatment. The blood samples were obtained between 12 h post-dose and before the first daily drug intake and processed immediately by centrifugation. The serum concentrations of LUR were determined at

the laboratories for therapeutic drug monitoring (TDM) by high-performance liquid chromatography (HPLC) and ultraviolet (UV) detection. Both methods were validated and checked for accuracy.

2.5 Risk of switching to mania/hypomania

Treatment-emergent switching to mania or hypomania was recorded at each time point. We extended the clinical follow-up period by four weeks to assess the mania/hypomania symptoms through telephone follow-ups at Week 16. Treatment-emergent mania (TEM) or treatment-emergent hypomania was defined a priori as a YMRS score of ⩾16 on any two consecutive visits or at the final assessment (McIntyre et al., 2020), or if an adverse event of mania or hypomania fulfilled DSM-5 criteria.

2.6 Statistical analysis

Data were analyzed using SPSS software version 27. Descriptive statistics were presented as mean± standard error of the mean (SEM) for quantitative values and frequency (percentage) for qualitative values. The Kolmogorov-Smirnov test was used to test for the normality of data. Differences were compared using paired-sample *t*-test. The homogeneity of variance was evaluated using an evenness test. Pearson's and Chi-square tests were applied to analyze the correlation between quantitative and qualitative variables. Statistical significance was set at $P<0.05$. The intent-to-treat population included randomly assigned patients who received at least one dose of the studied medication and had a baseline and at least one post-baseline MADRS, HAMD-24, HAMA, and YMRS total scores. A generalized linear mixed model was performed using the maximum likelihood (ML) method to analyze the primary efficacy variable: the change from Week 4 to Week 12 in the MADRS, HAMD-24, HAMA, and YMRS total scores. Furthermore, Pearson's correlation analysis was conducted to evaluate the correlation between short-term efficacy and serum LUR concentrations.

3 Results

3.1 Patients

In total, 126 patients were screened for eligibility, of which 100 met the inclusion criteria and were included in the study (10 did not meet the entry criteria and 16 withdrew consent). The trial consisted of two stages, as shown in Fig. 1. During the first stage, all participants were treated by monotherapy with LUR; three patients (3.0%, 3/100) switched to mania and eventually were excluded. In the first stage, the response and no-response groups depended on the reduction of the MADRS total score compared to the baseline. Response was defined as a ⩾50% reduction in the score, and these patients continued to receive the monotherapy with LUR. Sixty no-response patients who showed a <50% reduction of the MARDS score were randomly divided into the VAL and VOR groups. During the second stage, 27, 28, and 18 patients completed the 12-week treatment in the LUR, VAL, and VOR groups, respectively.

The baseline characteristics of all patients are summarized in Table 1. The age, education, illness duration, and body mass index (BMI) for the patients were (21.17±0.81) years, (11.83±0.30) years, (44.14±5.23) months, and (21.40±0.41) kg/m^2, respectively. The HAMD-24, HAMA, MADRS, and YMRS total scores for patients at the enrolment were 23.94±0.41, 16.96±0.51, 24.80±0.42, and 5.62±0.34, respectively.

Table 1 Characteristics of the enrolled patients on baseline

Variables	Value (*n*=100)
Age (years)	21.17±0.81
Sex (M/F)	33/67
Duration (months)	44.14±5.23
BMI (kg/m^2)	21.40±0.41
Marital status (unmarried/married/divorced)	85/13/2
Education (years)	11.83±0.30
HAMD-24 (Week 0)	23.94±0.41
HAMA (Week 0)	16.96±0.51
MADRS (Week 0)	24.80±0.42
YMRS (Week 0)	5.62±0.34

Data are expressed as mean±standard error of the mean (SEM) or number of patients. M: male; F: female; BMI: body mass index; HAMD-24: Hamilton Rating Scale for Depression (24-items); HAMA: Hamilton Anxiety Rating Scale; MADRS: Montgomery-Asberg Depression Rating Scale; YMRS: Young Mania Rating Scale.

3.2 Characteristics of response and no-response patients at the end of the first stage

Notably, all patients were treated with LUR monotherapy for four weeks. Furthermore, 37 (37.0%, 37/100) and 60 (60.0%, 60/100) patients were assigned to the response (LUR) and no-response groups, respectively, based on whether the MADRS score reduction rate was ⩾50% or lower. Patients in the response group

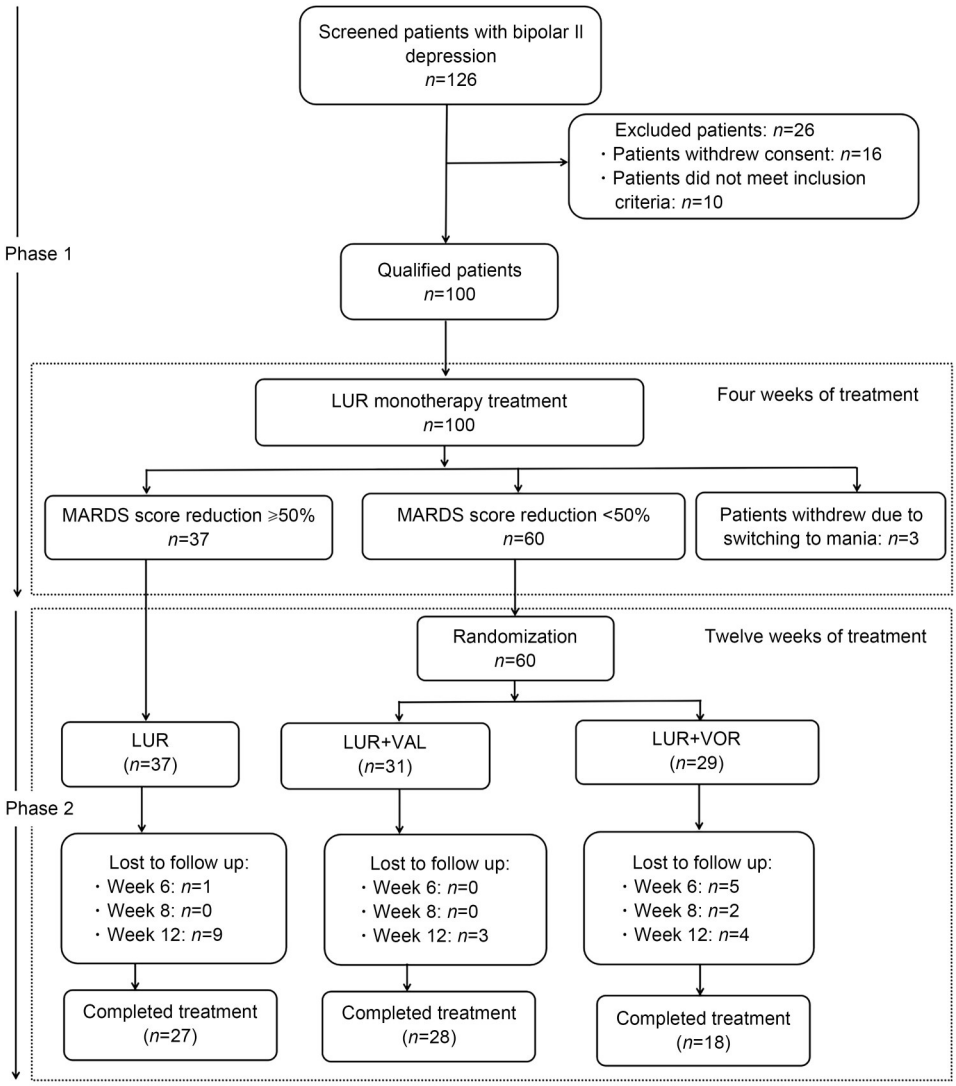

Fig. 1 Enrolment and randomization. LUR: lurasidone; VAL: valproate; VOR: vortioxetine; MADRS: Montgomery-Asberg Depression Rating Scale.

had significantly longer education time than those in the no-response group ((12.92±0.51) years vs. (11.33±0.36) years, t=2.598, P=0.011). The two groups had no significant differences in age, sex, disease duration, BMI, or marital status (Table 2).

During the 4-week LUR monotherapy, the primary efficacy endpoint MADRS total score declined in both groups at every visit, while significant differences between the response and no-response groups were observed at Week 4 (Week 2: 14.48±1.08 vs. 16.86±0.84, P=0.081; Week 4: 7.72±0.67 vs. 18.16±0.53, P<0.001). The mean changes from baseline to Week 4 in HAMD-24 were 13.32±1.05 vs. 16.31±0.82 (P=0.025, Week 2) and 8.47±1.02 vs. 17.94±0.79 (P<0.001, Week 4), those in HAMA were 10.13±1.01 vs. 12.44±0.79 (P=0.07, Week 2) and 6.37±0.88 vs. 12.84±0.68 (P<0.001, Week 4), and those in YMRS were 3.13±0.52 vs. 4.63±0.41 (P=0.023, Week 2) and 2.59±0.52 vs. 4.54±0.41 (P=0.003, Week 4). The total scores in the response group were significantly lower than those in the no-response group at the Week 4 time-point. In addition, the two groups had significant different HAMD-24 and YMRS total scores at the Week 2 time-point (Fig. 2).

3.3 Correlation of lurasidone serum concentrations with the 4-week monotherapy efficacy

Within the naturalistic setting of a routine TDM service at the First Affiliated Hospital, Zhejiang

Table 2 Characteristics of patients in the response group vs. no-response group at baseline

Variables	Response (n=37)	No-response (n=60)
Age (years)	23.30±1.48	20.17±0.95
Sex (female)	27 (73.0%)	39 (65.0%)
Sex (male)	10 (27.0%)	21 (35.0%)
Duration (months)	48.35±7.05	43.66±7.17
BMI (kg/m^2)	21.95±0.81	20.98±0.44
Marital status (unmarried)	30 (81.1%)	52 (86.7%)
Marital status (married)	6 (16.2%)	7 (11.7%)
Marital status (divorced)	1 (2.7%)	1 (1.7%)
Education (years)	12.92±0.51	11.33±0.36*

Data are expressed as mean±standard error of the mean (SEM) or number (percentage) of patients. * P<0.05.

University School of Medicine, 74 patients underwent serum concentration measurements of LUR in Week 2 and 80 patients in Week 4. Among the 74 patients who received the TDM service in Week 2, 29 (39.2%, 29/74) achieved a MADRS reduction proportion of ≥50% after four weeks of treatment with LUR, with a mean dose of (43.44±2.82) mg/d, and 45 no-response patients (60.8%, 45/74) had a similar mean dose of (43.11±1.55) mg/d (P=0.910; Fig. 3a). The serum concentrations of LUR were (5.78±0.95) and (4.55±0.45) ng/mL, respectively, for the response and no-response groups (P=0.196). In Week 4, 80 patients had received TDM. In total, 33 patients (41.2%, 33/80) responded to the 4-week monotherapy of LUR, with a mean dose of (44.85±1.90) mg/d, while 47 (58.8%, 47/80) failed to respond, with a similar dose of (49.79±1.79) mg/d (P=0.067). The TDM results showed similar concentrations for the two groups (response (6.25±0.89) ng/mL vs. no-response (6.50±0.78) ng/mL, P=0.836; Fig. 3b). Spearman correlation analysis revealed no significant correlation between LUR concentration and the MADRS reduction rate (r=0.117, P=0.303; Fig. 3c).

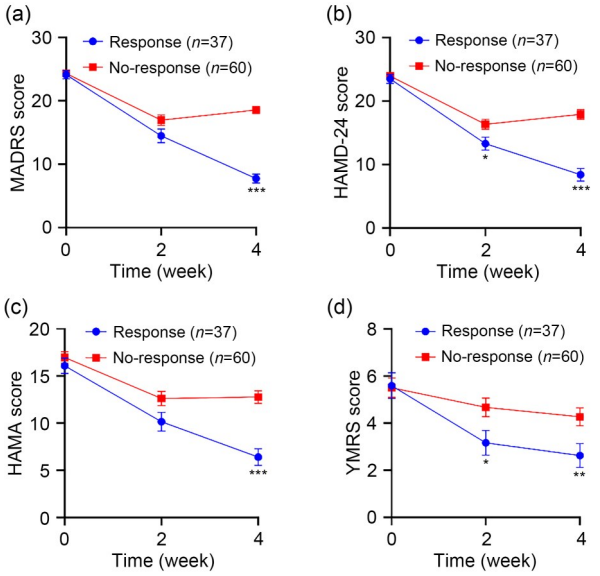

Fig. 2 Changes in the MADRS (a), HAMD-24 (b), HAMA (c), and YMRS (d) scores of the response and no-response groups during lurasidone monotherapy after four weeks of treatment. Response group: the MADRS score reduction rate was ≥50%; No-response group: the MADRS score reduction rate was <50%. Data are expressed as mean±standard error of the mean (SEM). * P<0.05, ** P<0.01, *** P<0.001, vs. the no-response group. MADRS: Montgomery-Asberg Depression Rating Scale; HAMD-24: Hamilton Rating Scale for Depression (24-items); HAMA: Hamilton Anxiety Rating Scale; YMRS: Young Mania Rating Scale.

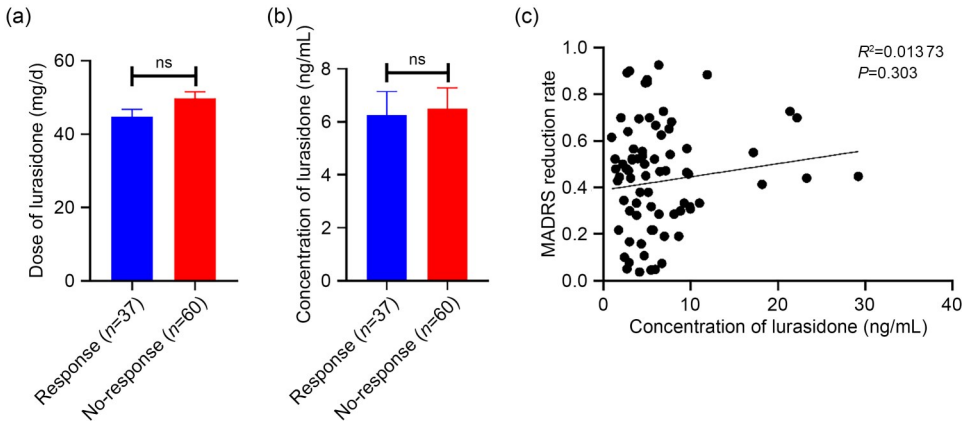

Fig. 3 Correlation of lurasidone serum concentrations with the 4-week monotherapy efficacy. Dose (a) and concentration (b) of lurasidone in the response and no-response groups during the 4-week lurasidone monotherapy treatment. Data are expressed as mean±standard error of the mean (SEM). ns: not significant (P>0.05). (c) Pearson's correlation coefficient was used to analyze the correlation between serum lurasidone concentration and drug efficacy.

3.4 Efficacy of combined vortioxetine therapy in bipolar II depression

After a 4-week monotherapy with LUR, 37 (37.0%, 37/100) response patients continued this monotherapy. At the same time, 60 no-response patients were assigned to the VAL (31 patients) or the VOR group (29 patients). The patients' demographics and clinical characteristics are shown in Table 3. The two groups had no significant differences at baseline in age, sex, BMI, years of education, or disease duration (P>0.05; Table 3). Two groups had no significant differences in the HAMD-24, HAMA, or MADRS score at the end of the 4-week monotherapy or the beginning of the combined treatment (P>0.05). There was a statistically significant difference in the YMRS score between the two groups (VAL: 5.77±0.73 vs. 3.31±0.48, P=0.007); however, both groups scored within the normal rating range. The VAL treatment group showed a significant improvement in their YMRS scores during the 8-week follow-up period (P<0.001), highlighting the inherent characteristics of VAL as a mood stabilizer (Fig. 4d). After a 2-week combination treatment with VAL or VOR, the mean MADRS score in the VOR group (11.93±1.06) decreased significantly compared to the VAL group (15.02±0.94) at the end of Week 6 (Fig. 4a). However, there were no significant differences in the HAMD-24, HAMA, or YMRS total score. In the subsequent two weeks, the MADRS score in the VAL group declined significantly, to a value (10.92±1.04) close to that in the VOR group (12.20±1.23) by the end of the eighth week (P=0.424; Fig. 4a). There were no significant differences in the HAMD-24, HAMA, or YMRS total score between the two groups at the end of the eighth week (Figs. 4b–4d). At the final visit (12 weeks), the MADRS, HAMD-24, HAMA, or YMRS total score showed no significant differences between the two groups (Fig. 4).

3.5 Adverse events

The study completion rates were 73.0% (27/37), 90.3% (28/31), and 62.1% (18/29) in the LUR, VAL, and VOR groups, respectively. The proportion of patients who discontinued treatment due to any adverse event was <20% in each treatment group, which was similar in the LUR (13.5%, 5/37), VAL (16.1%, 5/31), and VOR groups (13.8%, 4/29) (P>0.05).

Treatment-emergent adverse events (TEAEs) reported with an incidence of >5% in at least one group are listed in Table 4. No significant differences were observed in the incidence of adverse effects between the VAL and VOR groups (P>0.05).

Table 3 Demographic and clinical characteristics between the valproate (VAL) and vortioxetine (VOR) groups

Variables	VAL (n=31)	VOR (n=29)
Age (years)	19.39±1.12	20.97±1.55
Sex (female)	22 (71.0%)	17 (58.6%)
Sex (male)	9 (29.0%)	12 (41.4%)
Duration (months)	32.16±7.18	54.03±13.43
BMI (kg/m^2)	21.32±0.72	20.63±0.50
Marital status (unmarried)	28 (90.3%)	24 (82.8%)
Marital status (married)	3 (9.7%)	4 (13.8%)
Marital status (divorced)	0 (0.0%)	1 (3.4%)
Education (years)	11.42±0.47	11.24±0.57
HAMD-24 (Week 4)	16.65±1.20	18.24±1.23
HAMA (Week 4)	11.24±1.02	13.95±1.05
MADRS (Week 4)	16.98±0.78	18.84±0.79
YMRS (Week 4)	5.62±0.62	3.32±0.63*

Data are expressed as mean±standard error of the mean (SEM) or number (percentage) of patients. * P<0.05. BMI: body mass index; HAMD-24: Hamilton Rating Scale for Depression (24-items); HAMA: Hamilton Anxiety Rating Scale; MADRS: Montgomery-Aberg Depression Rating Scale; YMRS: Young Mania Rating Scale.

3.6 Treatment-emergent mania

TEM was defined as the changed YMRS total score of ⩾16. Three patients were recorded and diagnosed in the first four weeks. In the second stage, no TEM occurred in the VAL groups; however, three patients (10.3%, 3/29) switched to mania in the VOR group, despite a significantly higher baseline YMRS in the VAL group than that in the VOR group (5.77±0.73 vs. 3.31±0.48, P<0.05). We extended the clinical follow-up period by an additional four weeks. Finally, no new incidents of TEM occurred in any group at the end of Week 16.

4 Discussion

The present study is the first to evaluate the efficacy and safety of VOR as an adjunctive therapeutic agent combined with LUR for bipolar II depression. In the first two weeks of the second stage, the depression symptom was significantly improved in the VOR group compared to the VAL group; however,

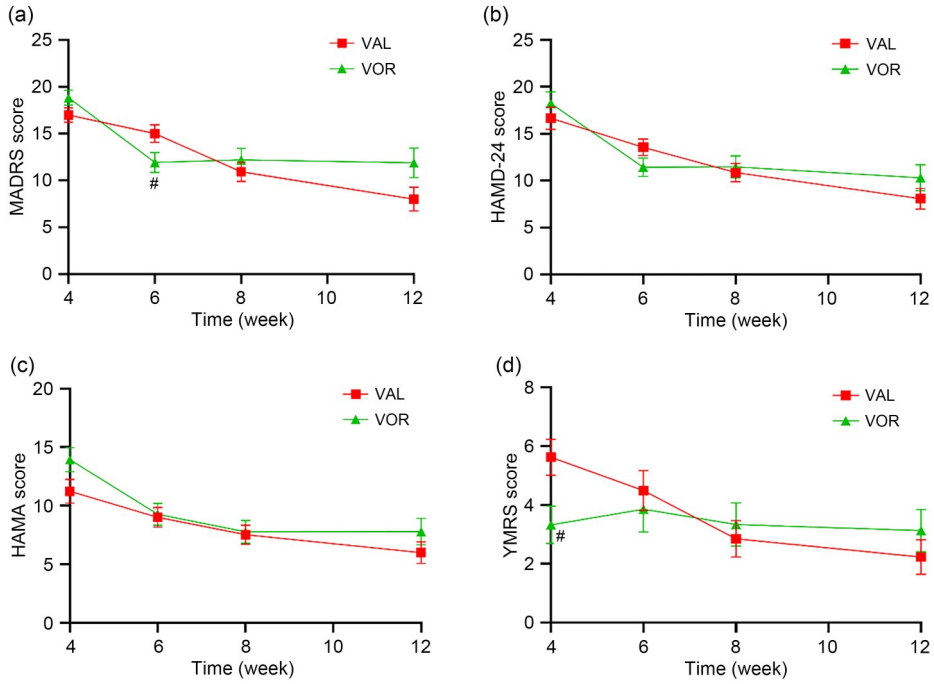

Fig. 4 Changes in the MADRS (a), HAMD-24 (b), HAMA (c), and YMRS (d) scores of the VAL and VOR groups in phase 2 treatment. VAL: lurasidone plus valproate group; VOR: lurasidone plus vortioxetine group. Data are expressed as mean±standard error of the mean (SEM). # *P*<0.05, VOR vs. VAL. MADRS: Montgomery-Asberg Depression Rating Scale; HAMD-24: Hamilton Rating Scale for Depression (24-items); HAMA: Hamilton Anxiety Rating Scale; YMRS: Young Mania Rating Scale.

Table 4 Adverse events

Event	VAL (*n*=31)	VOR (*n*=29)	*P*
At least one event	29 (93.5%)	22 (75.9%)	>0.05
Nausea/vomiting	13 (41.9%)	15 (51.7%)	>0.05
Headache	2 (6.5%)	1 (3.4%)	>0.05
Akathisia	4 (12.9%)	2 (6.9%)	>0.05
Somnolence[a]	10 (32.3%)	7 (24.1%)	>0.05
Parkinsonism[b]	3 (9.6%)	2 (6.9%)	>0.05
Weight gain	6 (19.4%)	3 (10.3%)	>0.05

Data are expressed as number (percentage) of patients. [a] Somnolence: hypersomnia, sedation, and somnolence. [b] Parkinsonism: cogwheel rigidity, drooling, parkinsonism, psychomotor retardation, and tremor.

the superiority of VOR was not sustained in the following six weeks. The results showed that the VOR combination has a potential for treating depressive mood. Considering the cyclic characteristics of BDs, expert consensus recommends avoiding or limiting antidepressant prescriptions (ADs) in BDs, and guidelines commonly suggest using ADs only during severe depressive episodes with poor responses to mood stabilizers and/or antipsychotics (Cheniaux and Nardi, 2019). However, a review article highlighted that approximately one-third of patients with BD between acute episodes took ADs under pressure to manage their depressive phase, with inconsistent results for efficacy (Dell'Osso et al., 2021). Notably, some studies and analyses indicated that cautious short-term treatment with antidepressants combined with mood-stabilizing treatments may reduce depressive episodes in BDs, especially BD-II, without increasing the risk of new manic/hypomanic episodes (Tondo et al., 2013; Liu et al., 2017; Pacchiarotti and Verdolini, 2021; Terao, 2021). Nonetheless, there is still insufficient evidence on the efficacy and switching risk of VOR in treating patients with bipolar II depression. Our study demonstrated that combined VOR decreased depressive symptoms more rapidly than combined VAL in the first two weeks, which is an advantage that might be important for BD patients with suicidal ideation or attempts.

Furthermore, only one 24-week, open-label, add-on VOR study in bipolar depression has demonstrated that 73.3% of all patients (44/60) responded to VOR and 51.7% (31/60) achieved clinical remission of depressive symptoms, indicating that VOR added to a mood stabilizer may constitute an efficient therapeutic option for bipolar depression (Siwek et al., 2022). Our study

also demonstrated that the efficacy of an 8-week add-on VOR therapy was similar to the proven efficacy of LUR combined with VAL therapy (Loebel et al., 2014b; Calabrese et al., 2017), which was recommended as the first-line treatment for bipolar depression in the 2018 CANMAT and ISBD guidelines (Yatham et al., 2018). Therefore, LUR combined with VOR may be an alternative treatment option for patients with bipolar depression. However, the efficacy of this drug combination should be validated on an independent large-size cohort.

Notably, several studies have reported phase switching in the bipolar depression induced by VOR (Sobreira et al., 2017; D'Andrea et al., 2019). In one such study, seven (11.7%) of 60 patients with BD developed a treatment-emergent affective switch (Siwek et al., 2022). Our study reported a similar proportion of patients (10.3%, 3/29) who switched to the manic state in the VOR group, which had a higher rate than the VAL group. The switching rate was consistent with previous open studies on selective serotonin reuptake inhibitors (SSRIs) added to current mood stabilizer treatments (switching rate 7%–16% for SSRIs) (Leverich et al., 2006; Sidor and Macqueen, 2011). However, the difference in the switching rates between the two groups was not statistically significant. Our results suggested that LUR combined with VOR did not increase the risk of switching in patients with bipolar II depression. Furthermore, we analyzed three patients who developed treatment-emergent hypomania. Their HAMA and YMRS scores at baseline were 16 and 8, 15 and 2, and 25 and 5, respectively. To our knowledge, patients with YMRS scores≥4, or comorbid with anxiety-related disorders, may experience agitation, restlessness, and distractibility, overlapping symptoms of mixed depression in BD. These symptoms may indicate mixed features of depressive episodes; therefore, antidepressants should be used cautiously.

The most typical TEAEs were nausea both in the VOR group (15/29, 51.7%) and the VAL group (13/31, 41.9%). Given that more than 95% of 5-HT in the body is localized in the gastrointestinal (GI) tract, VOR may affect the 5-HT system localized therein, leading to nausea and vomiting. Furthermore, the incidence rate of nausea in the VOR group in our study was higher than that in previous reports (20.9%–31.2%) (Baldwin et al., 2016). This difference may be attributed to the fact that for the combination of LUR, the most frequent adverse event was nausea (incidence rate of 10.4%–17.4%) (Loebel et al., 2014a). Somnolence ranked second, which was followed by weight gain in both groups. However, the proportion of patients who discontinued treatment owing to an adverse event was similar, with <15% in each treatment group. These results indicated that despite a slightly increased incidence of adverse events during combination treatment with VOR, this did not lead to an increased withdrawal rate due to adverse events. Skin-related adverse events, such as pruritus, have been frequently reported in previous research (Li et al., 2023). However, acute severe skin reactions associated with VOR have only been reported in four cases.

Our study is the first to evaluate the monotherapy efficacy of LUR in treating bipolar II depression, as defined by the DSM-5. Notably, 37 (37%, 37/100) patients responded to monotherapy with LUR with reduced MADRS total score within the first four weeks. Several studies have shown that LUR is effective in treating bipolar I depression patients (Loebel et al., 2014a; Kato et al., 2020), and in these studies, 38.5%–53.0% of patients receiving 20–120 mg/d of LUR achieved ≥50% improvement on the MADRS at the endpoint (six weeks). These results are consistent with a previous study that focused on patients with depressive episodes in bipolar II and other specified bipolar and related disorders (bipolar II/OSBDs) receiving a mean dose LUR of (31.0±15.0) mg/d, with a remission rate of 38.1% at Week 12 (Takaesu et al., 2022). These data indicate that less than 40% patients with bipolar depression fail to respond to LUR monotherapy, which calls for combination with antidepressant or mood stabilizers to satisfy actual clinical needs.

Our results showed no significant difference in LUR doses between the response and no-response groups, although the no-response group received a slightly higher dose at the end of the fourth week. We investigated whether serum LUR concentrations were correlated with clinical efficacy, but did not find significant differences in LUR concentration between the response and no-response groups. At the same time, there was no correlation between LUR concentration and the MADRS reduction rate (r=0.117, P=0.303). These negative findings indicate that the effectiveness of LUR treatment may not be directly linked to drug concentration. In previous monotherapy studies, an 20–60 mg/d dose of LUR significantly exceeded the benefits of 80–120 mg/d in reducing depressive symptoms in patients with bipolar I depression. However,

increasing the dose of LUR did not seem to improve its clinical efficacy in patients with bipolar depression. This phenomenon can be potentially attributed to various biological and psychological factors. Besides the 5-HT1A and 5-HT7 receptor mechanism of LUR (Roberts et al., 2016), the patient's personality and psychological stress both affect the outcome of clinical intervention.

For the reasons above, a 20 mg/d dose of LUR was sufficiently therapeutic for 32.3% of patients with bipolar depression. As the dose is increased to an average of 40 mg, the D2 receptor blockade becomes sufficiently high to mediate the antipsychotic effect (63%–67% for 40 mg, 77%–84% for 60 mg) (Meltzer et al., 2011; Wong et al., 2013). The high D2 receptor occupancy effect in patients treated with higher doses may be associated with depressogenic effects (Ali et al., 2020). In addition, moderate affinity for 5-HT1A receptors may be vital in bipolar depression (Ishibashi et al., 2010; Fountoulakis et al., 2012), and a significant association between functional 5-hydroxytryptamine receptor 1A polymorphisms and treatment response to LUR has been verified in patients with acute psychotic schizophrenia (Yoshikawa et al., 2020). Therefore, the differences in the efficacy of LUR treatment among patients may be associated with their receptor expression profiles. Moreover, other factors, such as variations in the expression of LUR target receptors and psychosocial influences, may also affect the efficacy of this drug, especially in adolescent patients. These results highlight the need for well-designed clinical studies to further explore the impact of the pharmacological properties of the receptor on the efficacy of LUR in patients with bipolar depression.

Our study has several limitations. Firstly, because of the single-arm design of 4-week LUR monotherapy trial, only external historical data could be compared to evaluate the safety and effectiveness of the drug during the first stage. Therefore, the results should be interpreted cautiously. Secondly, the age of participants was younger in comparison with similar clinical trials, which is the limitation of single-center studies. Therefore, replication with a larger sample including more middle-aged and older patients from more centers is required. Thirdly, the trial completion rate was relatively moderate, and the significant dropout rate in the VOR group might have violated the missing-at-random assumption of the generalized linear mixed model and increased the Type II error in a potentially significant comparison.

5 Conclusions

Evidence-based therapies are urgently required for treating patients with bipolar II depression. LUR monotherapy appears to be effective in treating these patients and its combination with VOR can benefit those with insufficient response to LUR. In future studies, a clinical trial with a larger sample size is required.

Data availability statement

All datasets analyzed in this study are available from the corresponding author upon request.

Acknowledgments

This work was partially supported by the Construction Fund of Key Medical Disciplines of Hangzhou (No. OO2020491), the National Key Research and Development Program of China (No. 2023YFC2506200), the Zhejiang Provincial Key Research and Development Program (No. 2021C03107), the Research Project of Jinan Microecological Biomedicine Shandong Laboratory (No. JNL-2023001B), the Leading Talent of Scientific and Technological Innovation–"Ten Thousand Talents Program" of Zhejiang Province (No. 2021R52016), the Innovation Team for Precision Diagnosis and Treatment of Major Brain Diseases (No. 2020R01001), and the Chinese Medical Education Association (No. 2022KTZ004). Sponsors had no role in the design, analysis, interpretation, or publication of the study.

Authors contribution

Shaohua HU and Jian XIE conceived and designed the experiments. Chunxiao DAI, Yaoyang FU, Yinbo LI, and Chengcheng ZHOU performed the clinical study. Qingwei ZHAO, Meihua LIN, Xuanwei LI, Xiao LI, and Keke HUANG performed the therapeutic drug monitoring. Chunxiao DAI and Yaoyang FU analyzed the data and wrote the paper. All authors have read and approved the final manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Chunxiao DAI, Yaoyang FU, Xuanwei LI, Meihua LIN, Yinbo LI, Xiao LI, Keke HUANG, Chengcheng ZHOU, Jian XIE, Qingwei ZHAO, and Shaohua HU declare that they have no conflict of interest.

This study was approved by the Clinical Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine, China (Approval No. IIT20210111C-R1), and registered on the ClinicalTrials.gov (Clinicaltrials.gov identifier:

NCT05481957). Informed consent was obtained from all patients and their families.

References

Ali Z, Tegin C, El-Mallakh RS, 2020. Evaluating lurasidone as a treatment option for bipolar disorder. *Expert Opin Pharmacother*, 21(3):253-260. https://doi.org/10.1080/14656566.2019.1695777

Baldwin DS, Chrones L, Florea I, et al., 2016. The safety and tolerability of vortioxetine: analysis of data from randomized placebo-controlled trials and open-label extension studies. *J Psychopharmacol*, 30(3):242-252. https://doi.org/10.1177/0269881116628440

Bang-Andersen B, Ruhland T, Jørgensen M, et al., 2011. 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(9): 3206-3221. https://doi.org/10.1021/jm101459g

Berhan A, Barker A, 2014. Vortioxetine in the treatment of adult patients with major depressive disorder: a meta-analysis of randomized double-blind controlled trials. *BMC Psychiatry*, 14:276. https://doi.org/10.1186/s12888-014-0276-x

Calabrese JR, Pikalov A, Streicher C, et al., 2017. Lurasidone in combination with lithium or valproate for the maintenance treatment of bipolar I disorder. *Eur Neuropsychopharmacol*, 27(9):865-876. https://doi.org/10.1016/j.euroneuro.2017.06.013

Calabrese JR, Durgam S, Satlin A, et al., 2021. Efficacy and safety of lumateperone for major depressive episodes associated with bipolar I or bipolar II disorder: a phase 3 randomized placebo-controlled trial. *Am J Psychiatry*, 178(12):1098-1106. https://doi.org/10.1176/appi.ajp.2021.20091339

Cheniaux E, Nardi AE, 2019. Evaluating the efficacy and safety of antidepressants in patients with bipolar disorder. *Expert Opin Drug Saf*, 18(10):893-913. https://doi.org/10.1080/14740338.2019.1651291

Cipriani A, Furukawa TA, Salanti G, et al., 2018. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet*, 391(10128):1357-1366. https://doi.org/10.1016/S0140-6736(17)32802-7

Clemente AS, Diniz BS, Nicolato R, et al., 2015. Bipolar disorder prevalence: a systematic review and meta-analysis of the literature. *Braz J Psychiatry*, 37(2):155-161. https://doi.org/10.1590/1516-4446-2012-1693

Crump C, Sundquist K, Winkleby MA, et al., 2013. Comorbidities and mortality in bipolar disorder: a Swedish national cohort study. *JAMA Psychiatry*, 70(9):931-939. https://doi.org/10.1001/jamapsychiatry.2013.1394

D'Andrea G, de Ronchi D, Giaccotto L, et al., 2019. Vortioxetine treatment-emergent mania in the elderly: a case report. *Australas Psychiatry*, 27(4):413. https://doi.org/10.1177/1039856219839471

de Diego-Adelino J, Crespo JM, Mora F, et al., 2022. Vortioxetine in major depressive disorder: from mechanisms of action to clinical studies. An updated review. *Expert Opin Drug Saf*, 21(5):673-690. https://doi.org/10.1080/14740338.2022.2019705

DelBello MP, Goldman R, Phillips D, et al., 2017. Efficacy and safety of lurasidone in children and adolescents with bipolar I depression: a double-blind, placebo-controlled study. *J Am Acad Child Adolesc Psychiatry*, 56(12):1015-1025. https://doi.org/10.1016/j.jaac.2017.10.006

Dell'Osso B, Arici C, Cafaro R, et al., 2021. Antidepressants in bipolar disorder: analysis of correlates overall, and in BD-I and BD-II subsamples. *J Affect Disord*, 292:352-358. https://doi.org/10.1016/j.jad.2021.05.043

Dome P, Rihmer Z, Gonda X, 2019. Suicide risk in bipolar disorder: a brief review. *Medicina (Kaunas)*, 55(8):403. https://doi.org/10.3390/medicina55080403

Forte A, Baldessarini RJ, Tondo L, et al., 2015. Long-term morbidity in bipolar-I, bipolar-II, and unipolar major depressive disorders. *J Affect Disord*, 178:71-78. https://doi.org/10.1016/j.jad.2015.02.011

Fountoulakis KN, Kelsoe JR, Akiskal H, 2012. Receptor targets for antidepressant therapy in bipolar disorder: an overview. *J Affect Disord*, 138(3):222-238. https://doi.org/10.1016/j.jad.2011.04.043

Fountoulakis KN, Tohen M, Zarate CA, 2024. Pharmacodynamic properties of lumateperone and its efficacy in acute bipolar depression: a mechanistic hypothesis based on data. *Eur Neuropsychopharmacol*, 81:1-9. https://doi.org/10.1016/j.euroneuro.2024.01.002

Goldberg JF, Perlis RH, Bowden CL, et al., 2009. Manic symptoms during depressive episodes in 1,380 patients with bipolar disorder: findings from the STEP-BD. *Am J Psychiatry*, 166(2):173-181. https://doi.org/10.1176/appi.ajp.2008.08050746

Grande I, Berk M, Birmaher B, et al., 2016. Bipolar disorder. *Lancet*, 387(10027):1561-1572. https://doi.org/10.1016/S0140-6736(15)00241-X

Greenberg WM, Citrome L, 2017. Pharmacokinetics and pharmacodynamics of lurasidone hydrochloride, a second-generation antipsychotic: a systematic review of the published literature. *Clin Pharmacokinet*, 56(5):493-503. https://doi.org/10.1007/s40262-016-0465-5

Ishibashi T, Horisawa T, Tokuda K, et al., 2010. Pharmacological profile of lurasidone, a novel antipsychotic agent with potent 5-hydroxytryptamine 7 (5-HT_7) and 5-HT_{1A} receptor activity. *J Pharmacol Exp Ther*, 334(1):171-181. https://doi.org/10.1124/jpet.110.167346

Kaltenboeck A, Winkler D, Kasper S, 2016. Bipolar and related disorders in DSM-5 and ICD-10. *CNS Spectr*, 21(4): 318-323. https://doi.org/10.1017/S1092852916000079

Kato T, Ishigooka J, Miyajima M, et al., 2020. Double-blind, placebo-controlled study of lurasidone monotherapy for the treatment of bipolar I depression. *Psychiatry Clin Neurosci*, 74(12):635-644. https://doi.org/10.1111/pcn.13137

Ketter TA, Sarma K, Silva R, et al., 2016. Lurasidone in the long-term treatment of patients with bipolar disorder: a 24-week open-label extension study. *Depress Anxiety*, 33(5):424-434. https://doi.org/10.1002/da.22479

Leverich GS, Altshuler LL, Frye MA, et al., 2006. Risk of switch in mood polarity to hypomania or mania in patients with bipolar depression during acute and continuation trials of venlafaxine, sertraline, and bupropion as adjuncts to mood stabilizers. *Am J Psychiatry*, 163(2):232-239. https://doi.org/10.1176/appi.ajp.163.2.232

Li ZJ, Liu SH, Wu QX, et al., 2023. Effectiveness and safety of vortioxetine for the treatment of major depressive disorder in the real world: a systematic review and meta-analysis. *Int J Neuropsychopharmacol*, 26(6):373-384. https://doi.org/10.1093/ijnp/pyad018

Liu BS, Zhang Y, Fang H, et al., 2017. Efficacy and safety of long-term antidepressant treatment for bipolar disorders—a meta-analysis of randomized controlled trials. *J Affect Disord*, 223:41-48. https://doi.org/10.1016/j.jad.2017.07.023

Loebel A, Cucchiaro J, Silva R, et al., 2014a. Lurasidone monotherapy in the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *Am J Psychiatry*, 171(2):160-168. https://doi.org/10.1176/appi.ajp.2013.13070984

Loebel A, Cucchiaro J, Silva R, et al., 2014b. Lurasidone as adjunctive therapy with lithium or valproate for the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *Am J Psychiatry*, 171(2):169-177. https://doi.org/10.1176/appi.ajp.2013.13070985

McGirr A, Vöhringer PA, Ghaemi SN, et al., 2016. Safety and efficacy of adjunctive second-generation antidepressant therapy with a mood stabiliser or an atypical antipsychotic in acute bipolar depression: a systematic review and meta-analysis of randomised placebo-controlled trials. *Lancet Psychiatry*, 3(12):1138-1146. https://doi.org/10.1016/S2215-0366(16)30264-4

McIntyre RS, Calabrese JR, 2019. Bipolar depression: the clinical characteristics and unmet needs of a complex disorder. *Curr Med Res Opin*, 35(11):1993-2005. https://doi.org/10.1080/03007995.2019.1636017

McIntyre RS, Cha DS, Kim RD, et al., 2013. A review of FDA-approved treatment options in bipolar depression. *CNS Spectr*, 18(Suppl 1):4-20. https://doi.org/10.1017/S1092852913000746

McIntyre RS, Suppes T, Earley W, et al., 2020. Cariprazine efficacy in bipolar I depression with and without concurrent manic symptoms: post hoc analysis of 3 randomized, placebo-controlled studies. *CNS Spectr*, 25(4):502-510. https://doi.org/10.1017/S1092852919001287

Meltzer HY, Cucchiaro J, Silva R, et al., 2011. Lurasidone in the treatment of schizophrenia: a randomized, double-blind, placebo- and olanzapine-controlled study. *Am J Psychiatry*, 168(9):957-967. https://doi.org/10.1176/appi.ajp.2011.10060907

Mitchell PB, Goodwin GM, Johnson GF, et al., 2008. Diagnostic guidelines for bipolar depression: a probabilistic approach. *Bipolar Disord*, 10(1Pt 2):144-152. https://doi.org/10.1111/j.1399-5618.2007.00559.x

Montgomery SA, Asberg M, 1979. A new depression scale designed to be sensitive to change. *Br J Psychiatry*, 134(4):382-389. https://doi.org/10.1192/bjp.134.4.382

Mørk A, Pehrson A, Brennum LT, et al., 2012. Pharmacological effects of Lu AA21004: a novel multimodal compound for the treatment of major depressive disorder. *J Pharmacol Exp Ther*, 340(3):666-675. https://doi.org/10.1124/jpet.111.189068

Pacchiarotti I, Verdolini N, 2021. Antidepressants in bipolar II depression: yes and no. *Eur Neuropsychopharmacol*, 47:48-50. https://doi.org/10.1016/j.euroneuro.2021.04.009

Pae CU, Wang SM, Han CS, et al., 2015. Vortioxetine: a meta-analysis of 12 short-term, randomized, placebo-controlled clinical trials for the treatment of major depressive disorder. *J Psychiatry Neurosci*, 40(3):174-186. https://doi.org/10.1503/jpn.140120

Post RM, 2016. Treatment of bipolar depression: evolving recommendations. *Psychiatr Clin North Am*, 39(1):11-33. https://doi.org/10.1016/j.psc.2015.09.001

Roberts RJ, Lohano KK, El-Mallakh RS, 2016. Antipsychotics as antidepressants. *Asia Pac Psychiatry*, 8(3):179-188. https://doi.org/10.1111/appy.12186

Sheehan DV, Lecrubier Y, Sheehan KH, et al., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*, 59(Suppl 20):22-33.

Sidor MM, Macqueen GM, 2011. Antidepressants for the acute treatment of bipolar depression: a systematic review and meta-analysis. *J Clin Psychiatry*, 72(2):156-167. https://doi.org/10.4088/JCP.09r05385gre

Siwek M, Chrobak AA, Soltys Z, et al., 2022. A naturalistic, 24-week, open-label, add-on study of vortioxetine in bipolar depression. *Psychiatr Pol*, 56(3):509-522. https://doi.org/10.12740/PP/OnlineFirst/132962

Sobreira G, Oliveira J, Brissos S, 2017. Vortioxetine-induced manic mood switch in patient with previously unknown bipolar disorder. *Braz J Psychiatry*, 39(1):86. https://doi.org/10.1590/1516-4446-2016-2113

Suttajit S, Srisurapanont M, Maneeton N, et al., 2014. Quetiapine for acute bipolar depression: a systematic review and meta-analysis. *Drug Des Devel Ther*, 8:827-838. https://doi.org/10.2147/DDDT.S63779

Takaesu Y, Takeshima M, Watanabe K, 2022. Effectiveness and tolerability of lurasidone for bipolar types I and II and other specified bipolar depression: a 12-week observational study. *J Clin Psychopharmacol*, 42(5):485-488. https://doi.org/10.1097/JCP.0000000000001590

Terao T, 2021. Neglected but not negligible aspects of antidepressants and their availability in bipolar depression. *Brain Behav*, 11(8):e2308. https://doi.org/10.1002/brb3.2308

Tondo L, Baldessarini RJ, Vázquez G, et al., 2013. Clinical responses to antidepressants among 1036 acutely depressed patients with bipolar or unipolar major affective disorders. *Acta Psychiatr Scand*, 127(5):355-364. https://doi.org/10.1111/acps.12023

Wong DF, Kuwabara H, Brašić JR, et al., 2013. Determination of dopamine D_2 receptor occupancy by lurasidone using positron emission tomography in healthy male subjects. *Psychopharmacology (Berl)*, 229(2):245-252. https://doi.org/10.1007/s00213-013-3103-z

Yalin N, Young AH, 2020. Pharmacological treatment of bipolar depression: what are the current and emerging options? *Neuropsychiatr Dis Treat*, 16:1459-1472. https://doi.org/10.2147/NDT.S245166

Yatham LN, Kennedy SH, Parikh SV, et al., 2018. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord*, 20(2):97-170. https://doi.org/10.1111/bdi.12609

Yoshikawa A, Li J, Meltzer HY, 2020. A functional HTR1A polymorphism, rs6295, predicts short-term response to lurasidone: confirmation with meta-analysis of other antipsychotic drugs. *Pharmacogenomics J*, 20(2):260-270. https://doi.org/10.1038/s41397-019-0101-5

Young RC, Biggs JT, Ziegler VE, et al., 1978. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*, 133:429-435. https://doi.org/10.1192/bjp.133.5.429