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A naturalistic, 24-week, open-label, add-on study of vortioxetine in bipolar depression

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Summary

Aim. The efficacy of vortioxetine in major depressive disorder has been evaluated in many studies. However, there is a lack of studies assessing vortioxetine in bipolar depression.

Material and method. In 60 patients with bipolar depression, vortioxetine 10-20 mg daily was added to current mood stabilizing medication during 24-week, naturalistic, open-label study. The most frequent mood stabilizers were lamotrigine, quetiapine, olanzapine, and valproates. The therapeutic efficacy was evaluated by the *Clinical Global Impression – Improvement* (CGI-I) and *Clinical Global Impression – Severity* (CGI-S) scales. Patients were classified as responding to vortioxetine when they achieved 1 or 2 points on the CGI-I scale at any stage of observation. The criterion of remission was defined as score 1 on the CGI-S.

Results. 73% of all patients (44/60) responded to vortioxetine and 52% (31/60) achieved clinical remission of depressive symptoms (in mean 8.97±4.05 weeks). There were no significant associations between vortioxetine response/remission rates and: (1) the dose, (2) BD type, (3) clinical stage, (4) presence of rapid cycling, (5) history of psychotic symptoms, analyzed depressive symptoms, and (6) concomitantly used mood stabilizer. 4 patients (6.7%) stopped treatment due to adverse effects (nausea), and 7 patients (11.7%) discontinued treatment due to the phase switch. 14 patients (23%) experienced a loss of vortioxetine effectiveness after the initial response or remission.

Conclusions. The results indicate relatively high rates of response and remission during 24-week treatment in depressed bipolar patients receiving vortioxetine concomitantly with a mood stabilizer. This may indicate that vortioxetine added to a mood stabilizer may constitute an efficient and well tolerated therapeutic option in bipolar depression.

Key words: antidepressant drugs, vortioxetine, bipolar depression

Introduction

Vortioxetine is a novel multimodal antidepressant drug approved by the Food and Drug Administration in 2013. Besides its high-affinity for serotonin transporter (SERT) and inhibition thereof, vortioxetine presents multimodal action including antagonism of 5-HT_3, 5-HT_7 and 5-HT_{1D}, partial agonism of 5-HT_{1B} and agonism of 5-HT_{1A} receptors [1, 2]. Short – and long-term clinical trials have shown its efficacy in the treatment of moderate to severe major depressive disorder, in doses of 5-20 mg/day [3]. Vortioxetine treatment was associated with not only a significant decrease of depressive and anxiety symptoms, but also beneficial effects in reversing cognitive impairments related to depression and improvement in functional recovery domains such as family functioning, partner relationships, social, and emotional functioning [3]. Very low indices of drug discontinuation due to the side effects in open-label extension studies have been shown [4].

While there has been a substantial number of studies evaluating the effect of vortioxetine in major depressive disorder, there is a lack of research assessing the efficacy of vortioxetine in bipolar disorder. Antidepressant drug use in bipolar disorder (BD) remains controversial [5]. Many authors suggest that these substances may be ineffective and potentially harmful in bipolar depression, increasing suicidal risk, precipitating a manic/hypomanic episode, and inducing rapid cycling. Clinical studies, reviews and meta-analyses regarding this issue repeatedly reach contradictory conclusions [5]. Some studies and analyses indicate that cautious short-term treatment with antidepressants combined with mood stabilizing treatment may be useful for bipolar depression without concurrent agitation or hypomanic symptoms [6–9]. Data from randomized controlled trials suggest second-generation antipsychotics as first-line treatment for acute bipolar depression, such as quetiapine [10], lurasidone [11-13], olanzapine (alone or combined with fluoxetine) [14] and cariprazine [15]. Other therapeutic options involve lithium (alone or in combination [16, 17]), lamotrigine (as adjunctive treatment [18]) and electroconvulsive therapy [19]. However, due to the high prevalence of treatment-resistance in bipolar depression, there is a need for evaluating the effects of novel treatment strategies, also including antidepressant drugs with novel mechanisms of action.

In this study, we have evaluated the efficacy of vortioxetine combined with mood stabilizers during a 24-week, naturalistic, open-label study in a group of 60 patients with bipolar depression. We have performed longitudinal observation of treatment response, tolerability, and side effects, as well as their associations with clinical parameters.

Material and method

This was a naturalistic, 24-week, open-label study of vortioxetine treatment in BD patients in a current major depressive episode. In every case, vortioxetine was combined with the current mood stabilizers. At the time of the study, all participants were receiving mood stabilizing drugs of first-generation (lithium, valproates, carbamazepine) and/or second-generation (olanzapine, quetiapine, aripiprazole, lamotrigine) [20] – as mono – or polytherapy. The most frequent mood stabilizing drugs were lamotrigine – 36 patients (60%), quetiapine – 19 patients (32%), olanzapine – 15 patients (25%), valproates – 13 patients (22%) and aripiprazole – 9 patients (15%). One patient received lithium and one – carbamazepine.

Inclusion criteria: DSM-5 criteria of bipolar disorder, with a current major depressive episode; minimum score of 4 points in the *Clinical Global Impression – Severity* scale (CGI-S).

Exclusion criteria: depressive syndromes secondary to somatic diseases or their pharmacological treatment; manic, hypomanic or mixed symptoms; pregnancy or breastfeeding in women; serious, acute and chronic somatic or neurological diseases.

The study was approved by the Jagiellonian University Bioethics Committee, approval No. 122.6120.159.2015. All participants signed written informed consent.

Clinical evaluation

Patients were evaluated with the use of the *Clinical Global Impression – Improvement* (CGI-I) and *Clinical Global Impression – Severity* (CGI-S) scales [21]. The assessment was performed in seven time points of observation in the following weeks: 0, 4, 8, 12, 16, 20 and 24. Patients were classified as responding to vortioxetine treatment when they achieved 1 or 2 points on the CGI-I scale ("Very much improved" or "Much improved") at any point of the observation [22, 23]. The criterion of remission was not fulfilling the diagnosis of a depressive episode according to DSM-5 and a score of 1 on the CGI-S scale [22, 23]. Loss of effectiveness was defined as the increase in CGI-I points after an initial response to treatment during the time of observation. During consecutive points of observation, the following data were assessed: occurrence of side effects, phase switch or new psychopathological symptoms. Phase switch was defined as the fulfillment of DSM-5 criteria of hypomania/mania or mixed episode during vortioxetine treatment.

Patients were categorized into the early stage of BD when they fulfilled Kapczinski's criteria of Stage 1 (full symptomatic remission after previous episodes) or Stage 2 (rapid changes in illness phases; in-between episodic symptoms of coexisting psychiatric disorders – alcohol or other substance dependence or misuse, anxiety disorders, personality disorders – leading to impaired functioning; possible neurocognitive

impairment recorded in neuropsychological tests not affecting the clinical picture or the patient's functioning) [24, 25]. Patients were categorized into the late stage of BD when they fulfilled Kapczinski's criteria of Stage 3 (subsyndromal affective symptoms between episodes, shortening of periods of euthymia, increased number of acute phases, manifest neurocognitive impairment, and impairment of family and professional life) or Stage 4 (intensified symptoms and progressive deterioration of the patient) [24, 25].

Data analysis

The relationship between repeated CGI-I measures, vortioxetine dose (10 mg, 20 mg) and the duration of treatment in weeks (0, 4, 8, 12, 16, 20, 24) were analyzed with the use of two-way ANOVA with two factors: dose and time (repeated measure). Differences between time points were investigated using the post-hoc comparisons with the Bonferroni test. Calculations were done in R software, with the use of "lme" and "emmeans" functions, taken from "nlme" and "emmeans" packages (R CoreTeam, 2019 [26]). Missing data was carried out with the use of the Last-Observation-Carried-Forward (LOCF) method.

We have evaluated associations between vortioxetine response, remission, discontinuation (due to: adverse effects, phase switch, phase switch to mania, phase switch to mixed episode, phase switches in the group of patients responding to the vortioxetine treatment, and also due to lack of effectiveness and loss of effectiveness in the group of patients with response to the treatment) and clinical variables. The following variables were selected: sex, BD type, stage of the disease, lack of response to previous antidepressant drug treatments in the current episode, response to vortioxetine, remission after vortioxetine treatment, presence of rapid cycling, presence of selected symptoms of depression (anhedonia, anergia, cognitive dysfunctions, insomnia, irritability, anxiety, somatizations, current psychotic symptoms, suicidal thoughts), alcohol dependence/abuse, personality disorders, discontinuation due to adverse effects (including – nausea and dizziness), discontinuation due to phase switch (mania or mixed episode), discontinuation due to loss of effectiveness, discontinuation due to lack of effectiveness, history of psychotic symptoms, current treatment with quetiapine, lamotrigine, carbamazepine, aripiprazole, valproic acid or lithium. Data were analyzed with the series of Pearson's χ^2 tests with Yates' continuity correction.

Additionally, we have compared the mean number of previous unsuccessful antidepressant treatments in the current episode between groups with and without response to vortioxetine treatment (44 vs. 14 patients) and with and without remission after vortioxetine treatment (31 vs. 29 patients). Due to abnormal data distribution, the Wilcoxon rank-sum test with continuity correction has been used.

Results

Sixty BD outpatients with a current major depressive episode (23 BD I, 37 BD II) were recruited to a 24-week, naturalistic, open-label study of vortioxetine treatment. Patients' mean age was 45.27 ± 14.05 (range: 24-77). They were 26 males and 34 females. Their mean illness duration was 15.63 ± 10.53 years. The mean age of disease onset was 29.33 ± 9.61 years. The mean duration of vortioxetine treatment was 14.63 ± 9.49 (range: 3-24) weeks. The clinical description of the studied group is presented in Table 1.

Table 1. **Clinical characteristics of patients studied**

Bipolar I disorder (no. of patients (%))	23 (38%)
Bipolar II disorder (no. of patients (%))	37 (62%)
Positive history of psychotic episode (no. of patients (%))	17 (28%)
Early stage (no. of patients (%))	38 (63.3%)
Late stage (no. of patients (%))	22 (36.7%)
Rapid cycling (no. of patients (%))	14 (23.3%)
Comorbid personality disorders (no. of patients (%))	20 (33.3%)
Cognitive dysfunction complaints (no. of patients (%))	36 (60%)
Comorbid alcohol dependency or abuse (no. of patients (%))	8 (13.3%)
No. of comorbid somatic diseases	0.65 ± 0.97
No. of patients with at least one somatic disease (%)	23 (38.3%)
No. of mood stabilizers in current treatment	1.8 ± 0.73
No. of previous unsuccessful antidepressant drug treatments in current depressive episode	1.13 ± 1.19
No. of patients with previous unsuccessful antidepressant treatment in current depressive episode (%)	36 (60%)
Vortioxetine dosage (mg)	11.42 ± 3.46
No. of patients with vortioxetine dosage above 10 mg (%)	8 (13%)

Summary of the main outcomes is presented in Table 2. During the 24 weeks of observation, 44 out of 60 patients (73%) responded to vortioxetine treatment achieving score 1 or 2 on CGI-I. Mean time to response was 3.88 ± 1.71 weeks. Thirty-five patients responded in the 4th week of observation from treatment initiation, 8 patients responded in the 8th week, and one patient in the 12th week; 31 out of 60 patients (52%) achieved clinical remission during the study duration. Mean time to remission was 8.97 ± 4.05 weeks. Four patients had remission in 4th week, 15 patients in 8th week, 7 in 12th week, 2 in 16th week, 2 in 20th week and 1 in 24th week.

The clinical response measured with CGI was significantly associated with treatment duration ($\chi^2 = 179.22$, $df = 6$, $p < 0.0001$). Patients receiving 10 mg of vortioxetine showed a decrease of CGI-S mean score from 5.39 (95% CI, 4.93 to 5.84) at week 0 to 3.29 (95% CI, 2.84 to 3.74) at week 24. Patients treated with 20 mg of vortioxetine presented a decrease of mean CGI-S score from 6.25 (95% CI, 5.11 to 7.39) at week 0 to 2.37 (95% CI, 1.23 to 3.51) at week 24.

Table 2. **Rates of vortioxetine responses, remissions and adverse effects**

Response rates during vortioxetine treatment (no. of patients (%))	44 (73.3%)
Remission rates during vortioxetine treatment (no. of patients (%))	31 (52%)
Mean time to response (weeks)	3.88 ± 1.71
Mean time to remission (weeks)	8.97 ± 4.05
Adverse effects (no. of patients (%))	7 (11.7%)
Nausea (no. of patients (%))	6 (10%)
Dizziness (no. of patients (%))	1 (1.7%)
Discontinuation of vortioxetine due to adverse effects (no. of patients (%))	4 (6.7%)
Discontinuation of vortioxetine due to phase switch (no. of patients (%))	7 (11.7%)
Phase switch to hypomania/mania (no. of patients (%))	4 (6.7%)
Phase switch to mixed episode (no. of patients (%))	3 (5%)
Discontinuation due to lack of effectiveness (no. of patients (%))	17 (28.3%)
Mean no. of weeks to phase switch	21 ± 19
Loss of effectiveness of vortioxetine treatment (no. of patients (%))	14 (23% of all patients, 32% of responders)
Time to loss of effectiveness of vortioxetine treatment (no. of weeks)	8.85 ± 4.81

Changes in mean CGI scores obtained in the course of the study are shown in Figure 1. Two-way repeated measures ANOVA revealed significant differences in CGI scores between successive weeks of observation ($F(6, 342) = 43.50$, $p < 0.0001$). Moreover, it showed no significant effect of vortioxetine dose (10 mg vs. 20 mg) on CGI scores in any of the observation points ($F(1, 57) = 0.29$, $p = 0.59$). Post-hoc comparisons showed significant differences in CGI measures between initiation of treatment (week number 0) and every other point of observation, regardless of the dose used.

Thirty-seven patients (62%) remained in the study until 12 weeks, and 20 patients (33%) – until 24 weeks. Seventeen patients (28%) discontinued treatment due to the lack of effectiveness; 7 patients (11.7%) discontinued treatment due to the phase switch, of them 4 patients switched to manic or hypomanic episodes and 3 to mixed episodes. The number of weeks to phase switch was 21 ± 19 (min: 6 weeks, max: 52 weeks). Four patients (6.7%) stopped treatment due to adverse effects, 6 patients (10%) reported the presence of nausea and 1 patient (1.7%) reported dizziness associated with

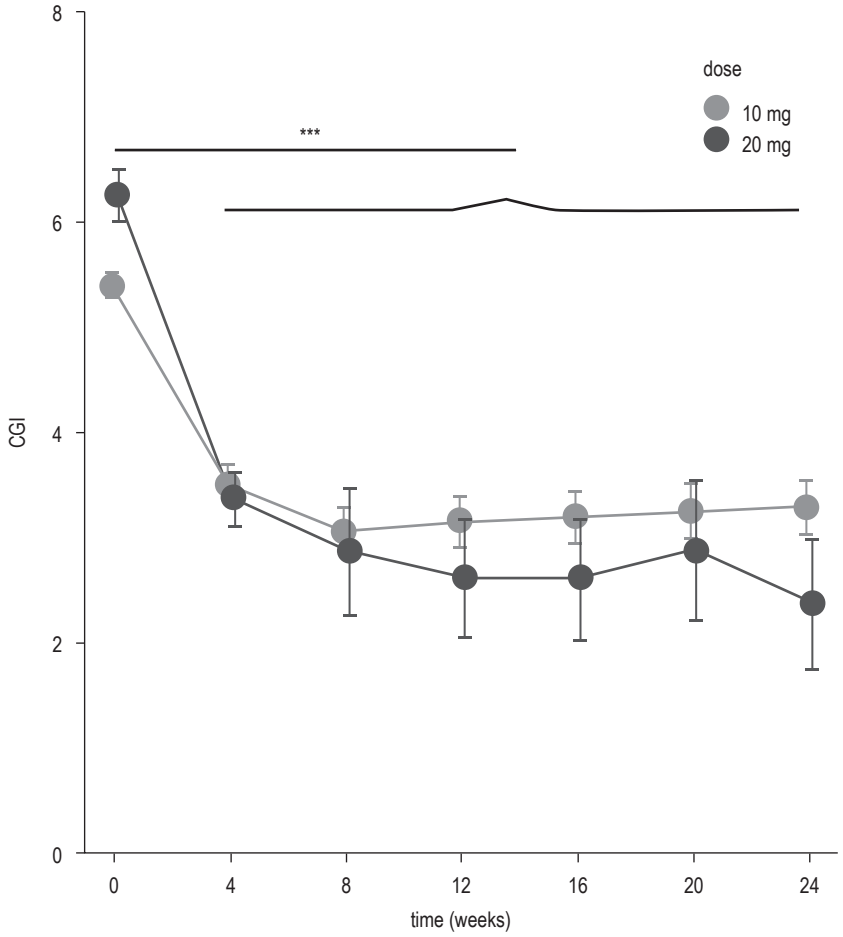

Figure 1. **Changes in mean Clinical Global Impression – Improvement scale scores over the course of the 24-week observation of vortioxetine treatment with the doses of 10 mg and 20 mg daily**

There were no statistically significant differences between the vortioxetine doses during the analyzed weeks. There were statistically significant differences between CGI-I scores during week 0 and every other week of observation. Post-hoc tests with Bonferroni correction $p < 0.001$ (***).

the treatment. In turn, 14 patients (23%) experienced a loss of vortioxetine treatment effectiveness, which occurred after 8.8 ± 4.8 weeks.

A series of Pearson's χ^2 tests resulted in the following significant associations: the number of individuals nonresponding to previous antidepressant drug treatment in the current depressive episode was significantly higher in the group of patients that did not achieve remission during vortioxetine treatment (22/29), compared with the

group of patients who did achieve remission due to vortioxetine treatment (14/31) ($\chi^2 = 4.67$, $df = 1$, $p = 0.03$). There was no significant difference between the mean number of unsuccessful antidepressant drug attempts in the current episode between vortioxetine responders (mean: 1.09 ± 1.12) and non-responders (mean: 1.25 ± 1.39, $W = 365$, $p = 0.83$). However, there was a significantly higher mean number of unsuccessful antidepressant drug attempts in persons without remission (mean: 1.5 5± 1.29) in comparison to persons with remission (mean: 0.74 ± 0.93, $W = 615.5$, $p = 0.01$). The rapid cycling patients represented a larger proportion in the group of participants discontinuing vortioxetine due to loss of effectiveness, initially responding to the vortioxetine than in the group of participants continuing treatment (7/14 in the group of discontinuing patients, 7/46 in the group of continuing patients, $\chi^2 = 5.44$, $df = 1$, $p = 0.02$).

Apart from the abovementioned relationships, there were no other statistically significant associations between vortioxetine response, remission, or discontinuation (due to any cause, including phase switch) and the following clinical variables: sex, BD type, stage of the disease, no response to previous antidepressant drug treatments in the current episode, rapid cycling, selected symptoms of depression (anhedonia, anergia, cognitive dysfunctions, insomnia, irritability, anxiety, somatizations, current psychotic symptoms, suicidal thoughts), alcohol dependence/abuse, personality disorders and history of psychotic symptoms.

As to the mood stabilizers used, there were no differences in response and remission rates between 36 patients using lamotrigine and the remaining 24 patients, as well as between 19 patients on quetiapine, 15 patients on olanzapine, and 13 patients on valproates vs. the remaining ones.

Discussion

In this study, we evaluated the efficacy of vortioxetine combined with mood stabilizers, in a group of patients with bipolar depression. During the 24-week naturalistic, open-label observation, we have observed that 44 out of 60 patients (73%) responded and 31 patients (52%) achieved clinical remission of a depressive episode. Our results have demonstrated a significant improvement using the CGI measures between initiation of vortioxetine treatment and every other time point of observation. There were no significant associations between vortioxetine response/remission rates and the vortioxetine dose, BD type (I, II or rapid-cycling), BD clinical stage (early vs. late), history of psychotic symptoms, analyzed symptoms of depression (anhedonia, anergia, cognitive dysfunction complaints, insomnia, irritability, anxiety, somatizations, suicidal thoughts) and concomitantly used mood stabilizer (quetiapine, lamotrigine, carbamazepine, aripiprazole, valproic acid or lithium).

To date, there have been only four published reports of vortioxetine use in BD. Those were case reports indicating a phase switch during vortioxetine treatment. Pirdoğan Aydın et al. [27] reported a case of a 58-year-old woman with a history of SSRI and venlafaxine treatment of recurrent depressive disorder who developed a hypomanic switch after ten days of 10 mg vortioxetine therapy. Sobreira et al. [28] described a case of a 41-year-old male with at least two previous depressive episodes and undiagnosed BD who developed a manic switch, seven days after addition of 10 mg/day of vortioxetine to 50 mg/day of trazodone. Maud [29] described a case of a BD patient with a mixed/manic switch within a week of increasing the dose of vortioxetine from 2.5 mg to 5 mg daily. D'Andrea et al. [30] presented a case of an 82-year-old male patient with recurrent major depressive disorder who developed mania within two weeks of switching sertraline to vortioxetine, that was titrated up to 10 mg/day in one week. De Carlo et al. [31] described a naturalistic open observation assessing the efficacy and tolerance of vortioxetine in patients with major depressive disorder, including both these with unipolar and bipolar depression. They analyzed the data of the whole sample offering no data regarding BD patients specifically, therefore providing little information about the efficacy and tolerance of vortioxetine in BD. In an extensive analysis of randomized and placebo-controlled trials and open-label extension studies, Baldwin et al. [4] reported that 1 out of 3,018 vortioxetine-treated patients had hypomania, while none of them had mania. A recent meta-analysis showed no data on the risk of a hypomanic/manic switch induced by vortioxetine in major depressive disorder patients [32, 33].

In our study, 7 (11.7%) out of 60 BD patients developed a phase switch which enforced discontinuation of vortioxetine treatment. Four patients switched to the hypomanic/manic episodes and three patients to the mixed episodes. Each of the mentioned patients was treated with at least one mood stabilizer (2 patients were treated with quetiapine, 4 with lamotrigine, 3 with olanzapine, 3 with valproic acid, 1 with carbamazepine, 1 with lithium and 1 with aripiprazole). The incidence rate of phase switch during our observations was similar to the ones previously reported in open studies where an SSRI was added to current mood stabilizer treatment, e.g., 3 out of 20 patients (15%) for add-on escitalopram [34], or 1 out of 10 patients (10%) for citalopram [35]. In the case of SNRI, venlafaxine had been shown to induce phase switch in 18 out of 86 patients (20.9%) during a 10-week trial and in 15 out of 31 patients (48.4%) in a year-long trial [36]. Bupropion had been shown to induce phase switch in 11 out of 66 (16.7%) and 7 out of 24 (29.2%) patients in a one year trial [36]. While caution is needed when antidepressants are used in BD patients, meta-analysis results indicate that SSRIs and other second-generation antidepressants are not significantly different than placebo in terms of short-term treatment-emergent affective switches [37].

None of the analyzed variables in our study, including BD type, history of rapid cycling, history of psychotic symptoms, and clinical stage of BD, were significantly associated with the occurrence of phase switch. While the reported cases indicated an affective switch within a period of 10 days [27-29] from vortioxetine treatment initiation, the mean number of weeks to phase switch in our study was 21 (min: 6 weeks, max: 52 weeks). However, it should be noted that due to the design of our study it is impossible to evaluate whether the observed phase switches occurred due to the natural course of the disease or the effect of the therapy [38]. Analysis of retrospective data between 1920 and 1959 found, in patients with a previous history of mania/hypomania, a rate of 29% for spontaneous switching from depression to hypomania [39]. Due to the uncertain estimate of which patients are likely to switch spontaneously, it is difficult to assess the degree to which antidepressants influence that risk [38].

The most common side effect reported in our study was nausea (n = 6, 10% of patients) which led to vortioxetine discontinuation in the case of 4 patients (6.7%). Our results corroborate the evaluation of vortioxetine in major depressive disorder patients. Baldwin et al. [4] indicated that nausea was the most common treatment-emergent adverse effect (20.9-31.2% of individuals) leading to the withdrawal of this drug in 0.8-27% of patients with unipolar depression.

We have observed a higher number of individuals nonresponding to previous antidepressant drugs in the current episode in the group of BD patients who did not achieve remission during vortioxetine treatment. Also, we have shown a higher number of previous unsuccessful courses of antidepressant treatments used in current depressive episodes in the group of patients with no remission in comparison to the patients achieving remission. There are no studies in BD evaluating the efficacy of switching one antidepressant drug to another, due to the lack of remission. Because of the relatively small number of participants in our study we were unable to evaluate the relationship between remission after vortioxetine treatment and the lack of efficacy of specific antidepressants in the past. We were also unable to evaluate whether vortioxetine efficacy is associated with the type of currently used mood stabilizer.

Fourteen patients (23%) lost the effectiveness of vortioxetine treatment after an initial response. The analysis revealed higher rates of patients with rapid cycling within this group. While only one patient with rapid cycling presented a manic episode during vortioxetine treatment, the loss of effectiveness cannot be solely explained by the occurrence of an affective switch in this group.

There are only few studies using staging models to evaluate treatment response in BD patients [40]. We have implemented Kapczinski's criteria to divide patients into the early and late stages in order to evaluate the association between BD progression and vortioxetine efficacy and tolerability [24]. We have shown that treatment response was independent of the clinical staging of BD.

We are aware of several limitations of our study: (a) the relatively small number of subjects; (b) the heterogeneity of BD patients group, consisting of BD I and BD II, and rapid cycling; (c) the fact that BD patients were treated simultaneously with different combinations of mood stabilizers; (d) the variations of vortioxetine dosage between patients; (e) the lack of rating scales specifically measuring depressive symptoms; (f) the naturalistic open-label model without placebo control and randomization.

Despite these limitations, our study presents the first – to our knowledge – observation of the treatment outcomes of vortioxetine combined with mood stabilizers in a group of patients with bipolar depression. We have shown relatively high rates of response (73%), with 52% of patients achieving clinical remission of depressive episodes and 11.7% of patients developing phase switch. Our results indicate that vortioxetine combined with a mood stabilizer may be a therapeutic option in bipolar depression and also supports the need for future double-blind placebo-controlled clinical trials aiming to evaluate vortioxetine efficacy and tolerability in BD patients.

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