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Original Article

The effects of vortioxetine on patients with depression and its effects on the brain-derived neurotrophic factor and norepinephrine levels

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Abstract: Objective: The purpose of this study was to investigate the effects of vortioxetine in patients with depression and to evaluate any changes in the brain-derived neurotrophic factor (BDNF) and norepinephrine (NE) levels. Method: A total of 89 patients with depression were recruited for the study and divided into a study group (the SG, n=44, routine medication + vortioxetine) and a control group (the CG, n=45, routine medication) according to the treatment options. The curative effects, the Hamilton Depression Scale (HAMD) scores before treatment and after 2, 4, and 8 weeks of treatment were evaluated. The Sheehan Disability Scale (SDS) was used to assess the social function at baseline, and after 2, 4, and 8 weeks of treatment. The BDNF and NE levels were compared before the treatment and after 8 weeks of treatment. Results: The curative effect in the SG was better than it was in the CG ($P<0.05$). Compared with the CG, the SG exhibited lower HAMD and SDS scores after 2, 4, and 8 weeks of treatment, and higher BDNF and NE levels after 8 weeks of treatment ($P<0.05$); There was a statistically significant difference in the incidence of adverse events between the two groups. Conclusion: The efficacy of vortioxetine for depression is supported by lower HAMD scores, a higher social function, improved serum BDNF and NE levels, and higher treatment safety.

Keywords: Vortioxetine, depression, curative effect, BDNF, NE

Introduction

With the acceleration of social change and the increase in workplace pressure, the number of patients with psychological disorders has been increasing yearly. Depression involves a long-term low mood and a loss of interest in activities and is one of the most common mood disorders [1, 2]. Patients with depression often feel inexplicably sad, down or miserable most of the time. The clinical manifestations are complex, and some patients feel inferior and worthless, leading to anorexia and suicide attempts. Some patients have severe anxiety, psychomotor agitation, and severe cases also experience hallucinations, delusions of victimization, or other psychological symptoms [3, 4]. The data show that depression has endangered public health. A 2017 survey showed that 322 million people suffered from depression worldwide. The International Research Center for Mental Disorders warned that the lifetime incidence of depression in individuals is about 8%-12% [5-7]. Depression is characterized by a high prevalence and a high recurrence rate, and it not only significantly affects the individual's work and family life, but also brings a huge burden to society and the individual's family. Therefore, early diagnosis and interventions are recommended clinically.

Vortioxetine is a prescription antipsychotic and antidepressant medication used to treat major depressive disorder in adults. It is a potent serotonin (5-HT) transporter (SERT) inhibitor. It has a strong affinity for 5-HT and reuptake inhibition on norepinephrine (NE). The 5-HT and NE concentrations in the synaptic cleft can be increased by inhibiting the reuptake of 5-HT and NE. It has been confirmed by many studies that vortioxetine is effective in the treatment of depression [8, 9].

Brain-derived neurotrophic factor (BDNF), discovered in 1982, is a pleiotropic neurotrophin. Some studies have pointed out that the impairment of neural plasticity and cell regeneration ability may be the pathological basis of depression. BDNF involves the emotional and behavioral activities regulated by the central nervous system. Therefore, it is speculated that a decrease in BDNF levels may be closely related to the occurrence and development of depression [10-12]. The role of NE in depression has also been explored by many studies. Some studies conclude that there is a clear correlation between the NE levels and anxiety in depression patients, and an association between the NE levels and suicidal behaviors has also been preliminarily found. Therefore, this index is often used in the monitoring and evaluation of depression [13].

Although there are plenty of studies on the effect of vortioxetine on depression, there are few studies focusing on evaluating its effects on the BDNF and NE levels in patients with depression. This study focuses on the BDNF and NE levels and provides evidence for the clinical promotion of vortioxetine.

Materials and methods

Baseline data

A total of 89 patients with depression admitted to our hospital from January 2019 to December 2019 were divided into the study group (SG, n=44) and the control group (CG, n=45) according to the choice of treatment methods.

Inclusion criteria: (1) patients clinically diagnosed with depression and who met the DSM-IV diagnostic criteria [14], (2) patients ≥18 years old, (3) patients who were conscious and complied with the intervention, (4) patients with Hamilton Depression Scale (HAMD) scores ≥18, and (5) patients whose clinical symptoms had lasted for over 4 weeks. All the patients signed an informed consent. This study was approved by the Ethics Committee of Guangdong Second Provincial General Hospital.

Exclusion criteria: (1) patients over 65 years old, (2) patients with a history of mild mania induced by drugs, (3) patients who had taken other antidepressants before the treatment, (4) patients who were alcohol or drug dependent, (5) patients with poor treatment adherence, (6) patients with malignant tumors, (7) patients with other diseases affecting the results of the study, (8) pregnant or lactating women, and (9) patients with severe liver or kidney dysfunction.

Treatment options

The patients in the CG were given olanzapine tablets (Ollanin, Jiangsu Haosen Pharmaceutical Group Co., Ltd., 10 mg per tablet, H20010799) in addition to routine psychological and physical therapies, 10 mg once daily for 8 weeks.

The patients in the SG were also prescribed vortioxetine (Xindayue, H. Lundbeck A/S, 10 mg per tablet, H20170383) in addition to the treatment administered in the CG, 10 mg once daily for 8 weeks.

Outcome measurement

Efficacy rate comparison: After 8 weeks of treatment, the efficacy rates of the two groups were evaluated using the Clinical Global Impression rating scale (CGI), a 7 point scale that requires the clinician to assess how much the patient's condition has improved or worsened relative to a baseline state at the beginning of the intervention. The subjects were divided into four categories: invalid, minimally improved, improved, and very much improved. Efficacy rate = (minimally improved + improved + very much improved)/total number of cases × 100% [15].

HAMD comparison: The HAMD scale was used to evaluate the severity of the depression before the treatment, and after 2, 4 and 8 weeks of treatment. The HAMD scale includes 17 items with Likert scales of 0 to 4. A total score of 7 or less indicates normal; a score of 7-17 indicates possible depression; a score of 18-24 suggests the existence of depression, and a score of 25 and above represents severe depression [16]. The assessment of the two groups was conducted by the same physician.

Sheehan disability scale (SDS) scores before and after treatment: The SDS scale was used

Table 1. Baseline data (mean ± SD)/[n (%)]

Data		SG (n=44)	CG (n=45)	t/X^2	*P*
Gender	Male	23	23	0.012	0.913
	Female	21	22		
Average age (year)		40.31±3.23	40.44±3.11	0.193	0.847
Average course (month)		10.28±3.21	10.31±3.09	0.045	0.964
Educational level	Illiterate	10	11	0.187	0.849
	Primary school	14	14		
	Junior high school	15	16		
	College	5	4		
Marital status	Married	40	40	0.1	0.752
	Single	4	5		
Month salary (RMB)	<1000	6	5	0.312	0.544
	1000-3000	27	29		
	>3000	11	11		

Table 2. Efficacy rates [n (%)]

Grouping	Cases	Very much improvement	improvement	Slightly improvement	ineffective	Efficacy rate
SG	44	20 (45.45)	20 (45.45)	3 (6.82)	1 (2.27)	43 (97.73)
CG	45	15 (33.33)	19 (42.22)	4 (8.89)	7 (15.56)	38 (84.44)
X^2	-	-	-	-	-	4.798
P	-	-	-	-	-	0.028

to assess social functions before treatment and after 2, 4, and 8 weeks of treatment. It involves aspects such as work, social life, and family life and is scored with Likert scales of 0-10. Higher scores indicate more serious social dysfunction [17].

The BDNF and NE levels before and after the treatment: Fasting blood samples were collected before the treatment and at the eighth week of treatment and were tested using an enzyme-linked immunosorbent assay (ELISA) to measure the BDNF and NE levels. The quantification was carried out strictly in accordance with the kit's instructions. Each indicator was measured three times and the average value was taken as the final result.

The incidence of adverse events during the treatment: The incidences of insomnia, drowsiness, liver and kidney dysfunction, gastrointestinal reactions, and other adverse events during the 8-week treatment period were compared.

Statistical analysis

SPSS 22.0 was used for the statistical analysis. The measurement data were expressed as the mean ± standard deviation (mean ± SD). The differences between groups were compared using Student's t tests. The count data were expressed as [n (%)] and tested using chi-square tests. $P<0.05$ was considered statistically significant [18].

Results

Baseline data

There were no statistically significant differences in terms of the baseline data such as the gender ratio, the average age, the average course of the disease, or marital status between the two groups ($P>0.05$) (**Table 1**).

Overall efficacy rate

In the SG, 20 cases were very much improved, 20 cases were improved, 3 cases were slightly improved, and 1 case was ineffective, for a total efficacy rate of 97.73%. In the CG, 15 cases were very much improved, 19 cases were improved, 4 cases were slightly improved, and 7 cases were ineffective, for a total efficacy rate of 84.44%. The difference in the efficacy rates was statistically significant ($P<0.05$) (**Table 2**).

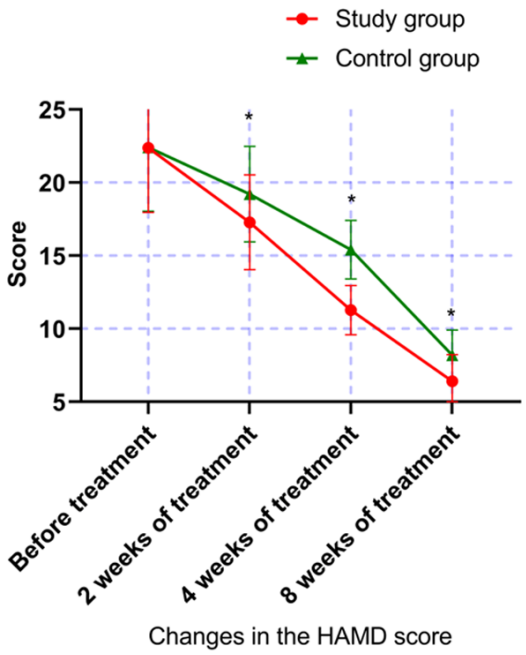

Figure 1. Changes in the HAMD scores before and after treatment. There was no statistically significant difference in the HAMD scores between the two groups before the treatment ($P>0.05$). At the 2nd, 4th, and 8th weeks of treatment, the HAMD scores in the SG were significantly lower than they were in the CG. *$P<0.05$.

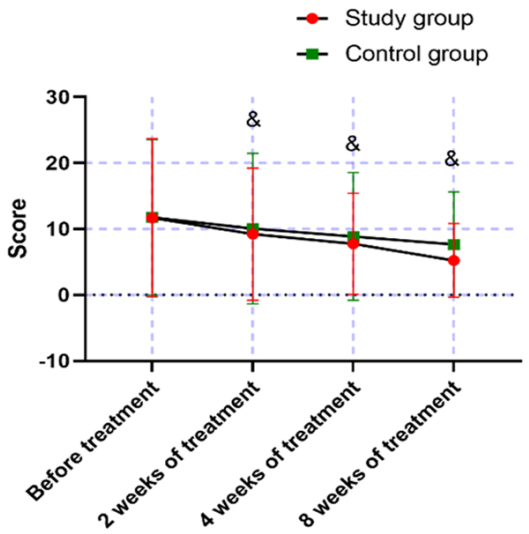

Figure 2. Changes in the SDS scores between the two groups. There was no statistically significant difference in the SDS scores between the two groups before the treatment ($P>0.05$). The SDS scores of the patients in the SG were significantly lower than they were in the SG after 2, 4, and 8 weeks of treatment. &$P<0.05$.

The HAMD scores before and after treatment

The HAMD scores in the two groups were not significantly different before the treatment ($P>0.05$). At the 8th week of treatment, the HAMD scores were improved in both groups ($P<0.05$), and the HAMD scores in the SG were significantly lower than they were in the CG ($P<0.05$) (**Figure 1**).

The SDS scores before and after the treatment

No significant difference was observed in the SDS scores between the two groups before the treatment ($P>0.05$). At the 2nd, 4th, and 8th weeks of treatment, the SDS scores of both groups showed a significant decrease compared to the pre-treatment scores ($P<0.05$), and the SG exhibited lower SDS scores than the CG after the treatment ($P<0.05$) (**Figure 2**).

The BDNF and NE levels before and after the treatment

No differences were observed in BDNF and NE levels between the two groups ($P>0.05$). After the treatment, the BDNF and NE levels were significantly increased in both groups ($P<0.05$), and the levels in the SG were higher than they were in the CG ($P<0.05$) (**Figure 3**).

The incidence of adverse events during the treatment

The incidence of adverse events in the SG was lower than it was in the CG ($P<0.05$) (**Table 3**).

Discussion

Depression is a common mental disorder, and the number of patients with depression has been increasing. Clinical practice has found that depression has a significant effect on patients' physical sensations, psychological activities, life and work, etc. A 10-year prospective survey showed that the lifetime risk of suicide among patients with depression is as high as 6% [19]. Data show that depression has become a global public health challenge. According to the World Health Organization estimates, the prevalence of depression is about 3% at the global level [20]. Another study pointed out that depression ranks second with regard to the burden of psychiatric disease in China [21]. Depression is characterized by a high prevalence and a high relapse

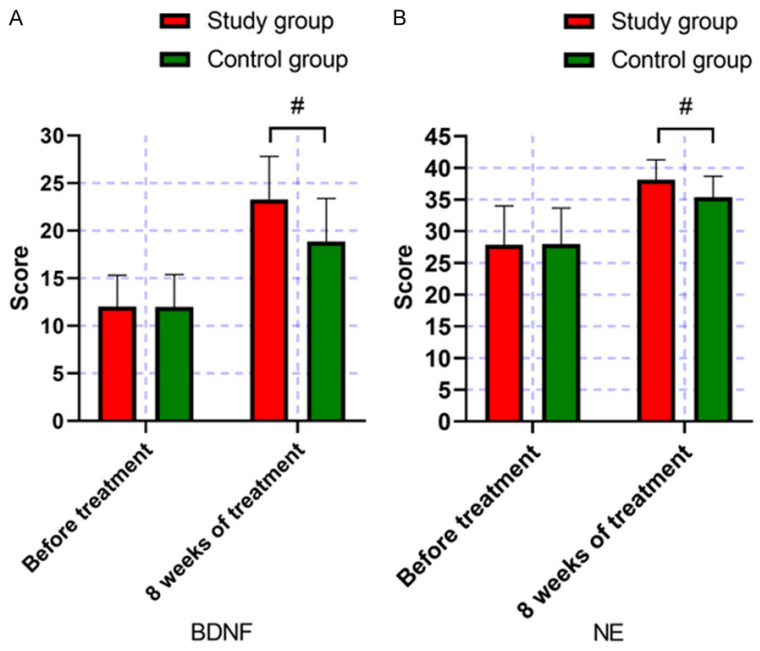

Figure 3. Changes in the BDNF and NE levels before and after the treatment. There was no statistically significant difference in the BDNF and NE scores between the two groups before the treatment ($P>0.05$). The BDNF (A) and NE (B) levels in the SG were significantly higher than they were in the CG after 8 weeks of treatment. #$P<0.05$.

rate. Affected individuals are generally characterized by clinical manifestations such as a low mood, decreased interest, sharp fluctuations in weight, excessive self-blame, and decreased thinking abilities, and the patients' career paths or quality of life are significantly impaired. Therefore, intervention and early treatment are recommended clinically to improve patient prognosis [22].

The pathogenesis of depression remains unclear and is influenced by biological, psychological and social factors. The current clinical goals for the treatment of depression are to relieve the symptoms, prevent recurrence, and minimize the disability and suicide rates. Existing treatments for depression include drug, psychological, and physical therapies [23]. Drug therapy is still the mainstream treatment method. Monoamine oxidase inhibitors, 5-HT & NE reuptake inhibitors, and melatonin receptor inhibitors are frequently prescribed to regulate the secretion of cytokines, proteins, and other substances to improve the clinical symptoms. Although good therapeutic effects can be achieved, adverse reactions caused by the long-term use of the drugs have prevented patients from complying with the treatment. In the early stage of drug therapies, serious adverse reactions can lead to interruptions in the treatment [24]. In addition, some studies have pointed out that a single drug often has a poor treatment effect on depression and brings significant adverse reactions, and that combination therapy would be more satisfactory.

Our results showed that the treatment efficiency of the SG was better than it was in the CG, suggesting that the addition of vortioxetine can effectively improve the treatment of patients with depression. Some scholars have shown that vortioxetine can enhance the treatment efficiency of routine therapies [25].

Some studies have indicated that vortioxetine acts by inhibiting the 5-HT transporter reuptake and regulating the 5-HT receptor for treating depression, and the effective rate can be as high as 84.48%, which is similar to the results of this study [26]. We believe that vortioxetine not only combines with the 5-HT transporter, but that it also combines with a variety of 5-HT receptors to exert a therapeutic effect. Animal studies have suggested that vortioxetine can antagonize the 5-HT7 receptor to exert anti-anxiety and anti-depressive properties. It can also continuously promote the release of 5-HT by stimulating the 5-HT1A receptors. Vortioxetine was found to have up to 6 pharmacological targets for 5-HT reuptake inhibitory receptors so the treatment effect with vortioxetine is significantly improved.

Impaired social functioning associated with depression is one of the typical clinical manifestations. Our comparison of the HAMD and SDS scores showed that the addition of vortioxetine effectively reduced the scores and improved the social functioning of patients with depression. At the same time, our comparison of the adverse reactions indicated that

Table 3. Adverse events [n (%)]

Grouping	Cases	insomnia	drowsiness	liver and kidney dysfunction	gastrointestinal reactions	Rate
SG	44	1 (2.27)	1 (2.27)	2 (4.55)	2 (4.55)	6 (13.64)
CG	45	4 (8.89)	4 (8.89)	3 (6.67)	3 (6.67)	14 (31.11)
X^2	-	-	-	-	-	3.899
P	-	-	-	-	-	0.048

vortioxetine is safe. The reason may be that it has many targets, so it avoids the possibility of excessive stimulation on one single receptor to induce adverse reactions.

Our results show that the application of vortioxetine significantly increased the BDNF and NE levels in patients with depression. Neurotrophic theory holds that damage to neuroplasticity and cell regeneration are a crucial pathological basis for inducing depression. Neurotrophic factors are also related to the development of depression. BDNF is the most abundant neurotrophic factor in the human body. One study found that BDNF is involved in the development of depression through 5-HT signaling [27]. After treatment, the patients' BDNF levels in the SG increased from (12.01±2.34) ng/ml to (23.28±3.21) ng/ml, which was better than the (18.87±3.19) ng/ml in the CG, indicating that vortioxetine improves the clinical symptoms of patients with depression by up-regulating the BDNF levels.

The underlying mechanism is related to vortioxetine's function of regulating neuronal activity and reducing brain cell apoptosis. There is a theory that low NE concentrations in the central nervous system can induce depression. A study has found that NE levels in depressed patients without suicidal behaviors were (56±20) ng/L, which is significantly lower than the (156±169) ng/L of patients with suicidal behaviors [28], suggesting that there is a correlation between the NE levels and the conditions of patients with depression. After the treatment, the NE levels of the SG were significantly higher than they were before treatment, as was the case in the CG, illustrating that the addition of vortioxetine significantly reversed the NE deficiency in the patients with depression, and this is also supported by the fact that the patients' HAMD scores were decreased.

In summary, vortioxetine can significantly and safely reduce the HAMD scores and improve the social functioning and serum BDNF and NE levels. The shortcomings of this study include the following: (1) the sample size included in the study was small; (2) the lack of a long-term follow-up. We will carry out a randomized double-blind study with a larger sample size and long-term follow-up to obtain more representative and accurate conclusions.

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Disclosure of conflict of interest

None.

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