Original Article
Effect of vortioxetine on patients with depression and brain-derived neurotrophic factor

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Abstract: Objective: This study aimed to investigate the clinical effect of vortioxetine on patients with depression. Methods: A total of 85 patients diagnosed with depression in our hospital from January 2018 to January 2019 were divided into control group (CG, n=42) and observation group (OG, n=43) using the random number table. The CG group was given duloxetine and the OG group was given vortioxetine. The interventions used in two groups were the same. After 2 months of continuous treatment, their brain-derived neurotrophic factor (BDNF) levels, social function, quality of sleep, depression improvement, and executive function were analyzed. Results: (1) BDNF levels in OG were higher than those in CG after 1 and 2 months of treatment (P<0.05). (2) After 2 months of treatment, OG had lower scores in terms of social life, work and family responsibilities than those in CG (P<0.05). (3) The improvement rate of OG was 83.72% and that of CG was 88.10% (P>0.05). (4) At the end of 2 months of treatment, and 1 month and 3 months after treatment, PSQI scores in OG were lower than those in CG (P<0.05). (5) At 3 months after treatment, the correct responses (CR) and categories completed (CC) in OG were better than those in CG (P<0.05) whilst random errors (RE) and perseverative errors (PE) were decreased as compared with CG (P<0.05). The response administered (RA) was not significantly different from CG (P>0.05). (6) The incidence of adverse reactions was 16.28% in OG and 35.71% in CG, respectively (P<0.05). Conclusion: Vortioxetine used in patients with depression could increase BDNF levels, improve depression and restore cognitive and executive function to normal. The higher recovery rate promises its application.

Keywords: Vortioxetine, depression, curative effect, brain-derived neurotrophic factor

Introduction
Depression is the most common mental disease. The clinical manifestations include cognitive disorder, lack of motivation, apparent and persistent depressed mood [1]. Due to the rapid development of the society and internet, the sense of privacy is gradually impaired, and the life stress on contemporary people is also increasing, which leads to the occurrence of depression. The rising incidence and the trend of younger age are involved in all ages [2].

Among all depression categories, mild and moderate depressions account for a greater proportion. These are the earlier stages of major depression and can develop into major depression if not effectively treated, which will seriously impact the patients' life, work and study by further declining cognitive and social functions, make them disconnected from society and even tend to self-mutilation and suicide, threatening living quality and life [3, 4]. Currently, antidepressants combined with continuous psychological interventions are usually used in the clinical treatments for patients diagnosed with depression. Duloxetine hydrochloride is the serotonin and norepinephrine reuptake inhibitor (SNRIS) acting on 5-hydroxytryptamine (5-HT) and noradrenaline (NE) to show antidepressant effect by inhibiting the reuptake, leaving the drugs in synaptic cleft with a higher concentration [5, 6]. Vortioxetine is a sort of potent reuptake inhibitor acting on 5-HT and highly compatible with 5-HT transporters although with poor affinity to NE or dopamine transporters [7].

Duloxetine has been widely recognized for its effectiveness in depression treatment. In contrast, there have been few clinical studies of the new antidepressant vortioxetine. In this paper,
85 patients with depression were enrolled to investigate the application of vortioxetine in the treatment of depression, so as to provide more scientific evidences for clinic application.

Materials and methods

Materials

A total of 85 patients with depression admitted to our hospital from January 2018 to January 2019 were divided into control group (CG, n=42) and observation group (OG, n=43) using the random number table. (1) Inclusion criteria: patient who meets the diagnostic criteria for depression [1]; who got a score of 7 or above using Hamilton Depression Scale-24 (HAMD-24) [8]; males or females who aged over 18 years; who was conscious and cooperated with the investigation and evaluation; who had voluntarily signed the informed consent. This study was approved by the ethics committee. (2) Exclusion criteria: patient who had hearing or visual disorder; who had serious diseases with vital organs involved; who had received psychotropic drug therapy within 60 days prior to this study; who had a history of electroconvulsive therapy prior to this study; who showed a serious suicidal tendency; who had a history of drug abuse; or who was in pregnancy or lactation.

Methods

Patients in OG were given vortioxetine: vortioxetine hydrobromide (Specification: 10 mg × 14 tablets, Approval No.: SFDA H20170383, Manufacturer: H.Lundbeck A/S), 10 mg/d for 2 months. The dosage was adjusted on the basis of individual responses and reduced to 5 mg/d as depressive symptoms improved. Once the patients got some relief, treatment was continued for more than 6 months to consolidate the effects.

Patients in CG were given duloxetine: duloxetine hydrochloride (Specification: 20 mg × 24 tablets, Approval No.: SFDA H20130056, Manufacturer: Jiangsu Nhwa Pharmaceutical Co., Ltd.) initially 20 mg twice a day and gradually increased to 30 mg × 3 times/d for 2 months if the depression was improved. Once the patients got some relief, treatment was continued for more than 6 months to consolidate the effects.

During the treatment, in case of the patients in either group suffered from obvious sleep disturbance, 0.5-1.0 mg lorazepam tablets were given before bedtime every night (Specification: 1 mg/tablet, Approval No.: SFDA H200-60105, Manufacturer: Shandong Xinyi Pharmaceutical Co., Ltd.).

Observed indicators

Brain derived neurotrophic factor (BDNF) Level: 5 ml of fasting venous blood was collected in the morning before, 1 month after, and 2 months after the treatment and placed still in water bath at a constant temperature for 1 hour followed by centrifugation for 5 minutes at 3000 rpm to separate the blood corpuscles and serum. A 1.5 ml centrifuge tube was used to collect the supernatant which was then stored at -20°C. The serum BDNF was determined by enzyme-linked immunosorbent assay (ELISA) within 2 hours according to the instructions.

Social function: After 2 months of treatment, a 3-month follow-up was performed for all patients. Before treatment and 3 months after treatment, Sheehan disability scale (SDS) [9], which covers three modules, i.e. social life, work and family responsibilities, with each scoring 0-10, was used to evaluate the social function of patients. The higher scores indicate the greater impacts and the worse function.

Depression improvement: Before treatment and after 2 months of treatment, HAMD-24 was used for depression evaluation including despair factor, body weight factor, anxiety/somatization factor, retardation factor, day and night variation factor, cognitive disorder factor, and sleep disorder factor. A final score of 24 points or above is considered severe depression, that of 17-23 points is moderate and 7-16 points mild. Less than 7 points means no depression. As for comparison of scores before and after treatment, a reduction of more than 90% indicates complete improvement in depression, a decrease of 50-90% means partial improvement whilst a decrease of less than 50% suggests unimproved. Depression improvement = completely improvement + partial improvement.

Quality of sleep: A 3-month follow-up was performed for all patients after 2 months of treat-
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Pittsburgh sleep quality index (PSQI) [10] was applied to determine patients' sleep quality before treatment, at the end of 2 months of treatment, and 1 and 3 months after the treatment, respectively. The scale consists of 19 self-evaluation and 5 peer-evaluation items, each of which scored 0-21. The higher scores indicate the worse sleeping quality.

Execution function: These were evaluated by Wisconsin Card Sorting Test (WCST) [11] covering correct responses (CR), categories completed (CC), random errors (RE), perseverative errors (PE) and response administered (RA) before and after 2 months of treatment.

Adverse reactions: Drug-related adverse reactions were recorded using treatment emergent symptom scale (TESS) [12] after treatment.

Statistical analysis

Statistical analysis was performed using SPSS22.0. Measurement data were expressed as mean ± standard deviation (mean ± SD) where inter-group and intra-group comparisons were based on independent-sample t test. Enumeration data were expressed as n (%) and inter-group and intra-group comparisons were based on X² test, in addition to multipoint comparisons within group using ANVOA. P<0.05 indicated statistically significant differences.

Results

Comparison of general information in both groups

There were no significant differences between the two groups in terms of gender distribution, average age, HAMD-24 scores at admission, and average period after diagnosis (P>0.05) (Table 1).

Comparison of BDNF levels in both groups

Before treatment, BDNF levels were recorded as 1.15±0.86 ng/L in OG and 1.10±0.79 ng/L in CG. After 1 month and 2 months of treatment, BDNF levels were 1.73±0.92 ng/L in OG and 1.37±0.83 ng/L in CG. After 2 months of treatment, BDNF levels were 2.29±1.02 ng/L in OG and 1.81±0.97 ng/L in CG. Before treatment, both groups showed little differences in BDNF (P>0.05), which were increased after 1 month and 2 months of treatment, and the differences compared with those before treatment were significant (P<0.05). BDNF levels were higher in OG after 1 month and 2 months of treatment (P<0.05) (Figure 1).

Table 1. Comparison of general information in both groups (X±sd)/[n (%)]

<table>
<thead>
<tr>
<th>Items</th>
<th>OG (n=43)</th>
<th>CG (n=42)</th>
<th>t/X²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>20 (46.51)</td>
<td>19 (45.24)</td>
<td>0.014</td>
<td>0.906</td>
</tr>
<tr>
<td>Female</td>
<td>23 (53.49)</td>
<td>23 (54.76)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>37.85±14.16</td>
<td>38.92±15.02</td>
<td>0.338</td>
<td>0.736</td>
</tr>
<tr>
<td>HAMD-24 scores at admission (points)</td>
<td>14.63±3.28</td>
<td>15.49±3.50</td>
<td>1.169</td>
<td>0.246</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.26±2.18</td>
<td>23.51±2.41</td>
<td>0.441</td>
<td>0.661</td>
</tr>
<tr>
<td>Period of depression after diagnosis (months)</td>
<td>10.52±4.19</td>
<td>11.23±4.34</td>
<td>0.767</td>
<td>0.445</td>
</tr>
</tbody>
</table>

Figure 1. Comparison of BDNF levels in both groups. Before the treatment, the two groups showed little differences in BDNF (P>0.05). After 1 month and 2 months of treatment, BDNF levels in OG were significantly higher than those in CG (P<0.05). & refers to P<0.05 in inter-group comparisons.
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Comparison of social function in both groups

There were no significant differences in social life, work, and family responsibilities indicators in OG before treatment (P>0.05). After 2 months of treatment, OG and CG showed intra-group statistical differences in social life, work, and family responsibilities before and after treatment (P<0.05). After 2 months of treatment, scores in OG were lower than those in CG (P<0.05) (Table 2; Figure 2).

Comparison of depression improvement in both groups

After 2 months of treatment, the numbers of cases completely improved were 16 (37.21%) in OG and 15 (35.71%) in CG, the numbers of cases partially improved were 20 (46.51%) in OG and 22 (52.38%) in CG, and the cases unimproved were 7 (16.28%) in OG and 5 (11.90%) in CG. The depression improvement rate of OG was 83.72% and that of CG was 88.10%, with no statistically significant difference (P>0.05) (Figure 3).

Comparison of sleep quality in both groups

Before treatment, PSQI scores were 14.23±2.26 in OG and 14.50±2.34 in CG; After 2 months of treatment, PSQI scores were 9.89±1.75 in OG and 12.24±2.01 in CG; At 1 month after treatment, PSQI scores were 7.29±1.34 in OG and 8.97±1.58 in CG; At 3 months after treatment, PSQI scores were 5.02±0.87 in OG and 6.31±1.06 in CG. Before treatment, there was no significant difference between OG and CG in PSQI scores (P>0.05). After 2 months of treatment as well as at 1 month and 3 months after treatment, the PSQI scores in the two groups were decreased (P<0.05), leading to statistical differences in intra-group comparisons (P<0.05). The PSQI scores of OG after 2 months of treatment as well as at 1 month and 3 months after treatment were lower than those of CG (P<0.05) (Figure 4).

Comparison of executive function in both groups

No statistical difference was found before treatment in terms of CR, CC, RE and PE and RA (P>0.05). At 3 months after treatment, CR and CC increased (P<0.05) whilst RE and PE decreased (P<0.05) in both groups, but there was little difference in RA (P>0.05). Regarding intergroup comparison, OG showed higher CR and CC (P<0.05) and lower RE and PE (P<0.05) compared with CG. There was little difference in RA (P>0.05) (Table 3).

Comparison of adverse reactions in both groups

OG had 7 cases of adverse reactions, with the incidence of adverse reactions of 16.28%. CG

Table 2. Changes in social function before and after treatment in both groups (X ± sd, points)

<table>
<thead>
<tr>
<th>Groups</th>
<th>Temporal point</th>
<th>Social life</th>
<th>Work</th>
<th>Familial responsibilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>OG (n=43)</td>
<td>Before treatment</td>
<td>7.21±1.16</td>
<td>7.06±1.23</td>
<td>7.52±1.50</td>
</tr>
<tr>
<td></td>
<td>At the end of 2 months of treatment</td>
<td>4.86±0.82</td>
<td>4.53±0.90</td>
<td>4.37±0.87</td>
</tr>
<tr>
<td>CG (n=42)</td>
<td>Before treatment</td>
<td>7.25±1.20</td>
<td>7.13±1.27</td>
<td>7.57±1.56</td>
</tr>
<tr>
<td></td>
<td>At the end of 2 months of treatment</td>
<td>5.72±0.95</td>
<td>6.21±0.97</td>
<td>6.30±1.14</td>
</tr>
<tr>
<td>t</td>
<td></td>
<td>4.471</td>
<td>8.280</td>
<td>8.787</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Note: t, & p refer to comparative statistics between the two groups after 2 months of treatment.

Figure 2. Comparison of social function in both groups. After 2 months of treatment, OG showed lower scores in social life, work, and family responsibilities than CG (P<0.05). # refers to P<0.05 in intergroup comparisons.
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had 15 cases of adverse reactions, with the incidence of adverse reactions of 35.71%. The incidence of adverse reactions in OG was significantly lower than that in CG, and the difference was statistically significant ($P<0.05$) (Table 4).

Discussion

The new antidepressant vortioxetine has been clinically applied for its acting on not only 5-HT transporter but also various 5-HT receptors [13]. It is capable of directly binding to these receptors and antagonistic to 5-HT1D, 5-HT7, and 5-HT3. It is believed that the mechanisms of action of vortioxetine in the treatment of depression belong to regulation of receptor activity and inhibition of transporters [14]. In animal experiments, vortioxetine, when used in rat model of depression, elevated the levels of 5-HT, dopamine, NE, acetylcholine and histamine in the areas of brain including ventral hippocampus and prefrontal cortical cells that are related to depressive episode by interaction with different receptors mentioned above. Besides, it regulates the function of glutamatergic and γ-GABA neurons to exert antidepressant effects [15, 16].

Patients with depression may have cognitive impairments with respect to disorders in executive function, memory, learning ability, and attention [17]. WCST can effectively assess the executive function of the prefrontal lobe. Chiu et al [18] found that executive function comes from the interaction of prefrontal cortex and subcortical brain regions. In this paper, CR and CC increased whilst RE and PE decreased after 2 months of treatment in OG and were higher than those in CG ($P<0.05$), suggesting that with the application of vortioxetine patients’ understanding of WCST tasks, visual attention required for categorization as well as auditory attention to feedbacks were improved, thereby changing the patients’ behaviors, making their cognition more flexible and their executive function more complete.

Mårtensson et al [19] indicated that although there was little difference in the recovery rates between duloxetine and vortioxetine in the treatment of depression, vortioxetine was
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Table 3. Changes in executive function before and after treatment in both groups (\(\bar{x} \pm \text{sd}\))

<table>
<thead>
<tr>
<th>Groups</th>
<th>Temporal point</th>
<th>CR</th>
<th>CC</th>
<th>RE</th>
<th>PE</th>
<th>RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>OG (n=43)</td>
<td>Before treatment</td>
<td>60.05±12.38</td>
<td>3.42±1.09</td>
<td>12.75±3.38</td>
<td>32.26±15.27</td>
<td>107.58±13.27</td>
</tr>
<tr>
<td></td>
<td>3 months after treatment</td>
<td>74.19±10.43</td>
<td>5.89±1.53</td>
<td>7.50±1.75</td>
<td>15.78±7.37</td>
<td>112.52±15.49</td>
</tr>
<tr>
<td>CG (n=42)</td>
<td>Before treatment</td>
<td>61.37±11.81</td>
<td>3.29±1.02</td>
<td>13.02±3.29</td>
<td>33.35±14.25</td>
<td>110.85±14.39</td>
</tr>
<tr>
<td></td>
<td>3 months after treatment</td>
<td>67.45±8.91</td>
<td>4.51±1.37</td>
<td>10.15±1.53</td>
<td>22.45±10.46</td>
<td>105.78±17.95</td>
</tr>
<tr>
<td>t</td>
<td>3.200</td>
<td>4.377</td>
<td>7.426</td>
<td>3.405</td>
<td>1.855</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.002</td>
<td>0.000</td>
<td>0.000</td>
<td>0.001</td>
<td>0.067</td>
<td></td>
</tr>
</tbody>
</table>

Note: t, & p refer to comparative statistics between the two groups after 2 months of treatment.

Table 4. Comparison of drug related adverse reactions in both groups [n (%)]

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>OG (n=43)</th>
<th>CG (n=42)</th>
<th>(X^2)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight gain</td>
<td>1 (2.33)</td>
<td>3 (7.14)</td>
<td>1.100</td>
<td>0.294</td>
</tr>
<tr>
<td>Insomnia</td>
<td>0 (0.00)</td>
<td>1 (2.38)</td>
<td>1.036</td>
<td>0.309</td>
</tr>
<tr>
<td>Sleepiness</td>
<td>1 (2.33)</td>
<td>2 (4.76)</td>
<td>0.370</td>
<td>0.543</td>
</tr>
<tr>
<td>Constipation</td>
<td>0 (0.00)</td>
<td>1 (2.38)</td>
<td>1.036</td>
<td>0.309</td>
</tr>
<tr>
<td>Weak</td>
<td>2 (4.65)</td>
<td>3 (7.14)</td>
<td>0.238</td>
<td>0.624</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>1 (2.33)</td>
<td>2 (4.76)</td>
<td>0.370</td>
<td>0.543</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (4.65)</td>
<td>3 (7.14)</td>
<td>0.238</td>
<td>0.624</td>
</tr>
<tr>
<td>Total incidence</td>
<td>7 (16.28)</td>
<td>15 (35.71)</td>
<td>4.184</td>
<td>0.041</td>
</tr>
</tbody>
</table>

Social life, work, and family responsibilities scores in OG after 2 months of treatment were lower than those in CG (\(P<0.05\)). PSQI scores in OG after 2 months of treatment, at 1 month after treatment as well as 3 months after treatment were lower than those in CG (\(P<0.05\)). These results revealed the relation with the complex pharmacological effects of vortioxetine that blocks 5-HT reuptake (similar to SSRIs), and binds to G-protein related receptors to activate 5-HT1A receptors fully and 5-HT1B receptors partially while antagonizing 5-HT1D & 5-HT7 receptors. It also antagonizes 5-HT3 receptors through the combination with ion channel associated receptors [23]. These mechanisms effectively fight against depression and improve patients’ cognitive function, thereby improving social function [24]. These also reduce adverse effects associated with inhibition of 5-HT reuptake.

In conclusion, vortioxetine is worthy of promotion in the treatment of depression by elevating the level of brain-derived neurotrophic factor, relieving depression, improving patients’ social function and sleep quality and reducing adverse reactions to ensure therapeutic safety. However, the study sample size in this paper is relatively small, the follow-up period was inadequate, and analysis of the results was not comprehensive enough, which inevitably made the results biased. Future researches will use a larger sample size and cover all sorts of aspects to collect more scientific and representative conclusions, thus providing more evidence for the treatment of depression.
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Disclosure of conflict of interest

None.

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