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Original Article

The effects of duloxetine combined with olanzapine on climacteric depression and the neuroendocrine system

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Abstract: Objective: To explore the efficacy of duloxetine combined with olanzapine on climacteric depression and the combination's effects on the neuroendocrine system. Methods: A total of 166 patients with climacteric depression were assigned to a control group and an observation group (each n=83) according to the odd and even numbers of their visits. The control group was treated with duloxetine, and the observation group was treated with duloxetine combined with olanzapine, and both groups were treated for 8 consecutive weeks. In addition, we compared the two groups in terms of their: clinical efficacy, adverse reactions, anxiety, depression, cognitive function, sex hormone (follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (E_2)) levels, and central neurotransmitter (5-hydroxytryptamine (5-HT), and norepinephrine (NE)) levels before and after treatment. Results: The total effective rate in the observation group (95.18%) was higher than it was in the control group (83.13%) (P<0.05), but there was no significant difference in the incidence of adverse reactions between the two groups (P>0.05). After 8 weeks of treatment, both groups got significantly lower Hamilton anxiety scale (HAMA) scores and Hamilton depression rating scale (HAMD) scores, and significantly higher Montreal cognitive assessment (MoCA) scores, and the changes in the scores in the observation group were more significant (all P<0.05). Furthermore, the proportion of patients with a HAMA score <14 points and a HAMD score <17 points in the observation group was significantly larger than it was in the control group (P<0.01), and after 8 weeks of treatment, both groups showed significantly lower serum FSH and LH levels and significantly higher E_2, 5-HT, and NE levels (all P<0.05), and the changes in the observation group were more significant (all P<0.05). Conclusion: Duloxetine combined with olanzapine can powerfully relieve the anxiety, depression, and other clinical symptoms of patients with climacteric depression, and the combination can also improve their neuroendocrine systems and cognitive function with a high degree of safety.

Keywords: Duloxetine, olanzapine, climacteric depression, efficacy, neuroendocrine system, cognitive function

Introduction

Climacteric depression is a systemic psychological disease that occurs during menopause and is caused by a combination of various factors. The condition is characterized by paranoia, insomnia, dreaminess, tiredness, weakness, depression, mental slowness, anxiety, and reticence. Climacteric depression can even induce suicidal behavior under severe situations, which significantly compromises the physical and mental health and the quality of life of menopausal women [1, 2]. Its pathogenesis is complex. Most scholars believe that climacteric depression is related to the decline of neuroendocrine function and brain neurotransmitters [3]. Some studies have shown that premenstrual syndrome, depression history, menarche age, the number of babies born, and the stimulation of major events are strongly linked to climacteric depression [4]. The ovarian function and estrogen levels of menopausal women decline significantly, which brings about weaker negative feedback regulation effect on the pituitary secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), resulting in abnormal increases of patients' LH and FSH levels and further giving rise to vegetative nerve functional disturbance and triggering a series of neuropsychiatric symptoms [5, 6].

Climacteric depression is usually treated with drugs, including fluoxetine, duloxetine, paroxetine, citalopram, sertraline, and fluvoxamine, and it is also treated with Chinese patent medi-

cine such as Wuling capsules and Zhibai Dihuang pills. One study revealed that antidepressants combined with atypical neuroleptics can alleviate many of the clinical symptoms in climacteric depression patients [7]. Duloxetine is a new selective 5-hydroxytryptamine (5-HT) and norepinephrine (NE) reuptake inhibitor, and it's also a commonly used antidepressant, and it exerts an antidepressant effect mainly by inhibiting 5-HT and NE reuptake and increasing the levels of 5-HT and NE in the synaptic space [8]. However, the effect of duloxetine on inhibiting the dopamine (DA) reuptake is relatively weak, so duloxetine used alone does not perform well in relieving the symptoms of depression such as insomnia, dreaminess, and fatigue [9]. Olanzapine is a 5-HT/DA antagonist, which has an antidepressant effect by blocking central 5-HT_{2A} and 5-HT_{2C} receptors and which can also alleviate depression symptoms by selectively blocking the mesolimbic DA pathway and reducing the abnormal discharge of mesolimbic DA neurons in the mesolimbic system [10, 11]. However, there are no studies on the effects of duloxetine and olanzapine on the neuroendocrine system. In this study, we inferred that the antidepressant duloxetine combined with the atypical neuroleptic olanzapine can effectively treat climacteric depression and alleviate patients neuroendocrine system disorders, so we carried out the following experiments.

Materials and methods

General data

A total of 166 patients with climacteric depression treated at Jining Psychiatric Hospital from May 2016 to October 2019 were enrolled, all of whom met the diagnostic criteria of depression in the 10th Revision of *International Classification of Diseases* (ICD-10) [12]. The patients were assigned to a control group and an observation group (each n=83) according to the odd and even numbers of their visits.

The inclusion criteria: Perimenopausal or menopausal women meeting the above diagnostic criteria, patients with a Hamilton anxiety scale (HAMA) score ≥14 points, patients with a Hamilton depression rating scale (HAMD) score ≥17 points, and those who voluntarily signed an informed consent form after understanding the purpose of the study. The exclusion criteria: Patients suffering from other mental diseases or tumors, patients with psychotropic drug dependence, patients with an allergic constitution or allergic to the drugs used in this study, patients with a suicidal or violent tendency, and those with severe comorbid organic lesions in the heart, liver, or kidney. This study was approved by the Ethics Committee of Jining Psychiatric Hospital.

Methods

The patients in the control group were treated with duloxetine alone. Each patient orally took duloxetine hydrochloride enteric-coated tablets (20 mg, SPH Zhongxi Pharmaceutical Co., Ltd., Shanghai, China) 1 time/d and 20 mg/time for 14 consecutive days, and, after the 14 days, the dosage was gradually increased to 60 mg/time and 1 time/d according to the patient's condition within 2 weeks. The patients in the observation group were treated with duloxetine combined with olanzapine. Each patient orally took duloxetine hydrochloride enteric-coated tablets at the dosage and frequency matching those in the control group, and they also orally took olanzapine tablets (5 mg, Hanson Pharmaceutical Group Co., Ltd., Jiangsu, China) 1 time/d and 2.5 mg/time for 14 consecutive days, and, after the 14 days, the dosage of the olanzapine tablets was gradually increased to 5 mg/time and 1 time/d according to the patient's condition. The following outcome measures of the patients in the two groups were evaluated after they were treated for one course (8 weeks).

Outcome measures and efficacy evaluation standard

The clinical efficacy in the two groups was compared based on the HAMD reductive ratio. HAMD is the abbreviation of Hamilton depression rating scale, the most commonly used clinical scale for evaluating patients' degree of depression. The clinical efficacy is evaluated by calculating the reduction rate. Treatment with a HAMD reductive ratio equal to 75% or more was considered recuperative; treatment with a HAMD reductive ratio between 50% and 74.9% was considered markedly effective; treatment with a HAMD reductive ratio between 25% and 49.9% was considered

Table 1. Comparison of the general baseline data ($\bar{x}$ ± sd)

Group	Control group (n=83)	Observation group (n=83)	t	P
Age (years)	51.7±2.8	50.9±3.2	1.714	0.088
Course of disease (years)	2.2±1.1	1.9±1.0	1.839	0.068
BMI (kg/m^2)	22.56±2.68	23.17±3.16	1.341	0.182
E_2 (pg/mL)	20.55±5.38	21.67±6.43	1.217	0.225
HAMA score	17.68±2.31	17.54±2.27	0.394	0.694
HAMD score	20.04±3.22	19.75±3.84	0.527	0.599

Note: BMI: body mass index; E_2: estradiol; HAMA: Hamilton anxiety scale; HAMD: Hamilton depression rating scale.

effective, and treatment with a HAMD reductive ratio less than 25% was considered ineffective. The effective rate = the number of patients with (recuperative + markedly effective + effective treatment)/the total number of patients × 100%.

HAMA and HAMD were adopted to evaluate patients' anxiety and depression. HAMA is the abbreviation of Hamilton anxiety scale, which was compiled by Hamilton in 1959 and is the most commonly used clinical scale for assessing patient anxiety. It is listed as an important diagnostic tool for anxiety disorders in *Chinese Classification of Mental Disorders* Version 3 (CCMD-3). A HAMA score equal to 14 points or more indicates that the patient has anxiety, and a higher score indicates more serious anxiety. HAMD is the abbreviation of Hamilton depression rating scale compiled by Hamilton in 1960, and also the most commonly used clinical scale for evaluating patients' degree of depression. A HAMD score equal to 17 points or more indicates that the patient is depressed, and a higher score indicates more serious depression. Scoring based on the scales was carried out by trained full-time neurologists.

The levels of the neuroendocrine system-related indexes before and after the treatment were compared between the two groups. Fasting venous blood (5 mL) was sampled from each patient and centrifuged at 3000 r/min for 8-10 min after self-coagulation to take the serum for later analysis. The sex hormone levels, including FSH, LH, estradiol (E_2), and central neurotransmitters including 5-HT and NE in the serum were determined using an enzyme-linked immuno-sorbent assay (ELISA) with corresponding kits from the Rapidbio company in the United States the numbers of the kits were EY3809, EY0214, EY2405, EY9808, and EY3046, respectively.

The Montreal cognitive assessment (MoCA) was adopted to evaluate the patients' cognitive function. MoCA was developed by the Canadian Nasreddine and others, and its final version was determined in 2004, and it is a commonly-used and recognized assessment tool for the rapid screening of cognitive dysfunction. The scale consists of 30 points and a score lower than 26 points indicates that the patient suffers from cognitive impairment A lower MoCA score indicates more serious cognitive impairment. Scoring based on the scale was carried out by trained full-time neurologists.

The adverse reactions in the two groups were compared.

Statistical analysis

SPSS 20.0 was used for the statistical analysis of the data , and the enumeration data were expressed as the number of cases/percentage (n/%), and analyzed using χ^2 tests. In addition to the total incidences, all other indexes of adverse reactions were also analyzed using χ^2 tests. The quantitative data were expressed as the mean ± standard deviation ($\bar{x}$ ± sd), and compared between groups using independent sample T tests. Additionally, the comparisons of quantitative data before and after treatment were carried out using paired t tests. $P<0.05$ indicates a significant difference.

Results

Comparison of the general baseline data between the two groups

There were no significant differences between the two groups in the general baseline data, including body mass index (BMI), basic E_2 level, and the HAMA and HAMD scores (all $P>0.05$), so the two groups were comparable. See **Table 1**.

Table 2. Comparison of the clinical efficacy (n, %)

Group	Control group (n=83)	Observation group (n=83)	χ^2	P
Cured	10 (12.05)	21 (25.30)		
Markedly effectively	32 (38.55)	38 (45.78)		
Effectively	27 (32.53)	20 (24.10)		
No effectively	14 (16.87)	4 (4.82)		
Total effective rate	69 (83.13)	79 (95.18)	6.231	0.013

Table 3. Comparison of the anxiety and depression before and after treatment ($\bar{x}$ ± sd)

Group	Control group (n=83)	Observation group (n=83)	t	P
HAMA score				
Before treatment	17.68±2.31	17.54±2.27	0.394	0.694
After treatment	16.24±3.22**	13.02±2.84***	6.833	<0.001
HAMD score				
Before treatment	20.04±3.22	19.75±3.84	0.527	0.599
After treatment	18.68±2.95**	15.55±3.26***	6.486	<0.001

Note: HAMA: Hamilton anxiety scale; HAMD: Hamilton depression rating scale. Compared with the same group before treatment, **P<0.01, ***P<0.001.

Table 4. Comparison of the sex hormone levels before and after treatment ($\bar{x}$ ± sd)

Group	Control group (n=83)	Observation group (n=83)	t	P
FSH (IU/L)				
Before treatment	47.29±7.53	48.10±8.30	0.658	0.511
After treatment	45.09±5.30*	42.40±6.82***	2.837	0.005
LH (IU/L)				
Before treatment	21.20±3.34	22.05±4.20	1.443	0.151
After treatment	19.95±2.84*	18.64±2.60***	3.1	0.002
E_2 (pg/mL)				
Before treatment	20.55±5.38	21.67±6.43	1.217	0.225
After treatment	24.68±6.44***	28.14±8.32***	2.996	0.003

Note: FSH: follicle-stimulating hormone; LH: luteinizing hormone; E_2: estradiol. Compared with the same group before treatment, *P<0.05, ***P<0.001.

Comparison of the clinical efficacy between the two groups

After 8 weeks of treatment, the control group showed a total effective rate of 83.13%, with 10 patients cured, 32 patients treated markedly effectively, 27 patients treated effectively, and 14 patients treated ineffectively, while the observation group showed a total effective rate of 95.18%, with 21 patients cured, 38 patients treated markedly effectively, 20 patients treated effectively, and 4 patients treated ineffectively, so the total effective rate in the observation group was significantly higher than it was in the control group (P<0.05). See **Table 2**.

Comparison of the anxiety and depression in the two groups before and after the treatment

After 8 weeks of treatment, both groups got significantly lower HAMA and HAMD scores, and the changes in the scores in the observation group were more significant (P<0.001). See **Table 3**.

After the treatment, in the control group, there were 38 patients with a HAMA score less than 14 points and 41 patients with a HAMD score less than 17 points, but in the observation group, there were 56 patients with a HAMA score less than 14 points and 58 patients with a HAMD score less than 17 points, so the proportion of patients with a HAMA score <14 and a HAMD score <17 in the observation group was significantly larger than it was in the control group (χ^2=7.947, P=0.005; χ^2=7.233, P=0.007).

Comparison of the sex hormone levels in the two groups before and after the treatment

After 8 weeks of treatment, both groups showed significantly lower serum FSH and LH levels, and a significantly higher E_2 level (<0.05), and the changes in the observation group were more significant (P<0.01). See **Table 4**.

Comparison of the levels of central neurotransmitters in the two groups before and after the treatment

After 8 weeks of treatment, both groups showed significantly higher serum 5-HT and NE levels (P<0.001), and the changes in the observation group were more significant (P<0.05). See **Table 5**.

Table 5. Comparison of the central neurotransmitter levels before and after treatment ($\bar{x}$ ± sd) ng/mL

Group	Control group (n=83)	Observation group (n=83)	t	P
5-HT				
Before treatment	132.48±39.50	140.20±41.08	1.234	0.219
After treatment	197.59±35.40***	210.73±37.90***	2.308	0.022
NE				
Before treatment	102.20±16.59	105.35±15.40	1.268	0.207
After treatment	155.48±15.60***	187.09±19.79***	11.428	<0.001

Note: 5-HT: 5-hydroxytryptamine; NE: norepinephrine. Compared with the same group before treatment, ***P<0.001.

Table 6. Comparison of the cognitive function before and after treatment ($\bar{x}$ ± sd)

Group	Control group (n=83)	Observation group (n=83)	t	P
MoCA score				
Before treatment	25.10±1.05	24.78±1.33	1.72	0.087
After treatment	25.75±2.11*	26.59±2.28***	2.463	0.015

Note: MoCA: Montreal cognitive assessment. C. Compared with the same group before treatment, *P<0.05, ***P<0.001.

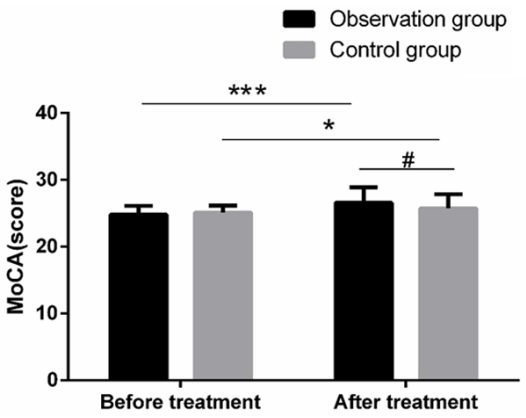

Figure 1. Comparison of the cognitive function before and after treatment. MoCA: Montreal cognitive assessment. C. Compared with the observation group before and after treatment, #P<0.05; Compared with the observation and control group before treatment, ***P<0.001; Compared with the observation and control group after treatment, *P<0.05.

Comparison of the cognitive function in the two groups before and after the treatment

After 8 weeks of treatment, both groups got significantly higher MoCA scores (*P*<0.05), and the observation group's MoCA score was significantly higher than the control group's score (*P*<0.05). See **Table 6** and **Figure 1**.

Comparison of the adverse reactions in the two groups

During treatment, the control group showed a total incidence of adverse reactions of 14.46%, with dizziness and nausea in 2 patients, dry mouth in 5 patients, drowsiness in 3 patients, and blurred vision in 2 patients, while the observation group showed a total incidence of adverse reactions of 18.07%, with dizziness and nausea in 4 patients, dry mouth in 3 patients, drowsiness in 5 patients, and blurred vision in 3 patients, so there was no significant difference in the total incidence of adverse reactions between the two groups (*P*>0.05, **Table 7**).

Discussion

For patients with climacteric depression, their central neurotransmitters 5-HT and NE levels decrease abnormally and give rise to adaptive changes in receptor function, which in turn leads to neuroimmune abnormalities and negative feedback regulation dysfunction of the hypothalamic-pituitary-adrenal axis [13]. Although antidepressant therapy can increase the levels of one or more central monoamine neurotransmitters in the central nervous system, it has a limited effect on relieving the clinical symptoms of climacteric depression when used alone.

Wang et al. studied 100 patients with climacteric depression, and they treated their control group with duloxetine and their observation group with duloxetine combined with olanzapine, finding that the total effective rate in the observation group was significantly higher than it was in the control group (96% *vs.* 72%), and the alleviation of anxiety and depression in the observation group was more significant than it was in the control group [14]. This find-

Table 7. Comparison of the adverse reactions (n, %)

Group	Control group (n=83)	Observation group (n=83)	χ^2	P
Dizziness and nausea	2(2.41)	4(4.82)	0.173	0.678
Dry mouth	5(6.02)	3(3.61)	0.131	0.717
Drowsiness	3(3.61)	5(6.02)	0.131	0.717
Blurred vision	2(2.41)	3(3.61)	0	1
Total incidence	12(14.46)	15(18.07)	0.398	0.528

ing indicates that duloxetine combined with olanzapine is more effective than duloxetine alone in treating climacteric depression, and it is consistent with the results of our study. In our study, the observation group treated with duloxetine combined with olanzapine for 8 consecutive weeks got significantly lower HAMA and HAMD scores than the control group, and the proportion of patients with a HAMA score <14 points and a HAMD score <17 points in the observation group was significantly larger than it was in the control group. In addition, the total effective rate in the observation group was as high as 95.18%, and there was no significant difference between the two groups in terms of adverse reactions. These results imply again that duloxetine combined with olanzapine is more effective than duloxetine alone in treating climacteric depression, and the combination brings about no serious adverse reactions and provides a high degree of safety.

"Central monoamine neuron conduction defect" is a hypothesis for depression. Most depression patients show a significant increase in the levels of 5-HT and NE in the synaptic space after antidepressant treatment [15], which indirectly confirms the rationality of this hypothesis. The deficiency of the central neurotransmitters 5-HT and NE in depression patients can change the function of patients' neuroendocrine systems, further lowering the levels of the central neurotransmitters and giving rise to neuroimmune abnormalities and negative feedback regulation dysfunction of the hypothalamic-pituitary-adrenal axis. If it is not intervened with quickly and reasonably, it will intensify the decline of the central neurotransmitter 5-HT and NE levels and aggravate the depression, increasing the patients' suffering and negatively affecting their prognosis [16]. In menopausal women, the consistent decrease of the serum estrogen levels, the negative feedback regulation dysfunction of the hypothalamic-pituitary-adrenal axis, and endocrine system dysfunction give rise to abnormal changes in the levels and activities of neurotransmitters including 5-HT and NE, which is one of the causes of neuropsychiatric symptoms and autonomic dysfunction symptoms in depression patients [17]. In this study, it was found that the observation group treated with duloxetine combined with olanzapine for 8 consecutive weeks showed significantly higher serum E_2, 5-HT, and NE levels and significantly lower serum FSH and LH levels than the control group, indicating that duloxetine combined with olanzapine is more effective at alleviating the neuroendocrine system dysfunction of the patients with climacteric depression. The results are consistent with those of the study by Englisch et al. [18], and it may be related to the inhibition of duloxetine and olanzapine on the central 5-HT receptors.

Some patients with depression may also have mild to moderate cognitive dysfunction, which is manifested by memory loss, visual space function, executive function, and information processing speed and may have a certain influence on complex psychological activities [19, 20]. Estrogen can affect the growth of nerve growth factors and neurons and the formation of synapsis and can promote the synthesis of central neurotransmitters and intensify the effect of monoamine neuronal receptors in the brain, thus affecting brain function [21]. A decline in the estrogen level and hypothalamic secretion dysfunction are also the main causes of cognitive dysfunction in menopausal women. In this study, the observation group treated with duloxetine combined with olanzapine for 8 consecutive weeks got a significantly higher MoCA score than the control group, suggesting that duloxetine combined with olanzapine can strongly improve the cognitive function of patients with climacteric depression. However, in this study, we did not analyze the changes in hormone levels, the central neurotransmitter levels, or the HAMA, HAMD, and MoCA scores within each week during the treatment, and we will dynamically observe and analyze the improvement effect of the joint use of the two drugs on

patients with climacteric depression in more detail in a future study.

To sum up, duloxetine combined with olanzapine can effectively relieve anxiety, depression, and other clinical symptoms of patients with climacteric depression and can also improve the neuroendocrine system and cognitive function with a high degree of safety, and its clinical efficacy is higher than that of duloxetine alone.

Disclosure of conflict of interest

None.

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