

Original Article

Study on the efficacy and mechanism of paroxetine hydrochloride combined with repetitive transcranial magnetic stimulation in the treatment of post-stroke depression

Weili Liu¹, Weiyang Ding²

¹Department of Neurology, The Fifth Medical Center, Chinese PLA General Hospital, Beijing, China; ²Department of Psychological Rehabilitation, The 967th Hospital of The Joint Logistics Support Force of The Chinese People's Liberation Army, Dalian, Liaoning Province, China

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Abstract: Objective: To explore the efficacy and mechanism of paroxetine hydrochloride combined with repetitive transcranial magnetic stimulation (rTMS) in the treatment of post-stroke depression (PSD). Methods: Totally 74 patients with PSD were randomly divided into paroxetine hydrochloride (PX) group and paroxetine hydrochloride combined with rTMS (PT) group, with 37 cases in each group. The differences in clinical efficacy, serum nerve peptide Y (NPY), corticotropin releasing factor (CRF), brain derived neurotrophic factor (BDNF), depression condition, expression of monoamine neurotransmitter, quality of life and secondary effects were compared between the PX and PT groups. Results: The effective rate of PT group was statistically different from that of PX group ($P=0.027$). After treatment, the Hamilton Depression Scale (HAMD) score of the PT group was significantly lower than that of the PX group ($P<0.001$), and the 36-Item Short-Form Health Survey (SF-36) score was significantly higher than that of the PX group (both $P<0.001$). After treatment, the expression of dopamine (DA), 5-hydroxytryptamine (5-HT) and norepinephrine (NE) in both groups increased ($P<0.05$). The expression of epinephrine (E) decreased compared with that before treatment ($P<0.05$). The expression of DA, 5-HT and NE in the PT group were higher than those in the PX group, and the expression of E was lower than that in the PX group ($P<0.05$ or $P<0.001$). Before treatment, there was no statistical significance in NPY, CRF and BDNF between PX and PT groups ($P>0.05$). After treatment, the expression of NPY and BDNF in both groups increased compared with those before treatment ($P<0.001$); the expression of CRF decreased compared with that before treatment ($P<0.001$); the expressions of NPY, CRF and BDNF in the PT group were higher than those in the PX group ($P<0.001$). There was no significant difference in the proportion of secondary effects between PT and PX groups ($P=0.649$). Conclusion: The therapeutic effect of paroxetine hydrochloride combined with rTMS on patients with PSD is better than paroxetine alone. It can significantly increase the neurotransmitter level of patients, improve quality of life, thereby improving the mental health. The safety of combination therapy is better.

Keywords: Repetitive transcranial magnetic stimulation, paroxetine hydrochloride, quality of life, secondary effects, post-stroke depression

Introduction

PSD is one of the most common complications in patients with stroke, which seriously slows the speed of recovery [1]. According to foreign statistics, the incidence of PSD is as high as about 60%. However, in China, especially in large cities and grade 3 and first-class hospitals, the diagnosis rate of PSD is only about 20-30%. The main reason is that when the patient develops obvious abnormal symptoms

such as depression and crying, their family and friends consider these symptoms as normal reactions after illness and will focus on the treatment of stroke. They think that the emotional change will gradually improve after positive treatment and rehabilitation, and rarely think it an independent disease which needs to be treated [2, 3].

The main clinical manifestations in patients with PSD are similar to those in depression

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Table 1. General information ($\bar{x} \pm sd$)

| Factors | PX group (n=37) | PT group (n=37) | t | P |
|---------------------------|--------------------|--------------------|-------|-------|
| Gender (n) | | | 0.286 | 0.592 |
| Male | 16 | 23 | | |
| Female | 21 | 14 | | |
| Location of stroke (n) | | | 0.048 | 0.826 |
| Basal ganglia | 10 | 11 | | |
| Cerebellum | 8 | 9 | | |
| Parietal lobe | 9 | 7 | | |
| Others | 10 | 10 | | |
| Dysfunction (n) | | | 0.023 | 0.879 |
| With | 21 | 22 | | |
| Without | 16 | 15 | | |
| Complications (n) | | | | |
| Diabetes mellitus | 7 | 9 | 0.250 | 0.617 |
| Hypertension | 5 | 8 | 0.692 | 0.405 |
| Others | 25 | 20 | 0.556 | 0.455 |
| Age (year) | 55.20±6.20 | 56.20±5.30 | 1.062 | 0.290 |
| Course of disease (month) | 3.56±0.18 | 3.34±0.09 | 0.854 | 0.394 |
| BMI (kg/m ²) | 24.34±1.21 | 25.03±2.16 | 1.695 | 0.094 |

Note: PX: paroxetine hydrochloride; PT: paroxetine hydrochloride combined with repetitive transcranial magnetic stimulation; BMI: body mass index.

patients, with significant changes in their emotions and personality [4]. Studies have shown that PSD is mainly caused by neurotransmitters and emotional network damage due to nerve damage, rather than the psychological response of the disease [5]. Some patients can't get out of the doldrums or even develop major depression, even though their functional recovery is getting better and better. Therefore, early identification, diagnosis and timely treatment for patients with PSD are the key to the rapid recovery of their stroke [6].

rTMS is a common clinical magnetic signal therapy, which mainly stimulates the brain nerves to achieve the purpose of treatment. rTMS is mainly applied in psychosis, neurological diseases and rehabilitation therapy [7]. PX is a new selective serotonin reuptake inhibitor (SSRI) antidepressant, which is one of the commonly used drugs in clinical treatment of depression [8]. However, there are few clinical studies on the treatment of PSD with the combination of the two therapies. Hence, this study explored the efficacy and mechanism of paroxetine hydrochloride combined with repetitive transcranial magnetic stimulation in the treatment of PSD by analyzing the differences in

clinical efficacy, serum NPY, CRF, BDNF, depression, expression of monoamine neurotransmitter, quality of life and secondary effects of patients in the PX and PT groups.

Materials and methods

General information

Total 74 patients with PSD treated The Fifth Medical Center, Chinese PLA General Hospital from March 2018 to December 2019 were randomly divided into the PX group and PT group, with 37 cases in each group. This study was approved by the Ethics Committee of The Fifth Medical Center, Chinese PLA General Hospital. There was no significant difference in general information between the two groups ($P > 0.05$). See **Table 1**.

Inclusion and exclusion criteria

Inclusion criteria: The selected patients were all diagnosed with PSD according to the third edition of the Chinese Diagnostic Criteria for Mental Disorders (CCMD-3) [9]; patients were with complete information and able to cooperate with treatment; patients were informed of the study and agree to the experiment; no treatment has been taken in the past one month; patients were less than 80 years old.

Exclusion criteria: Patients with contraindications in this study such as contraindicating to experimental drugs, incomplete information, family history and medical history of mental disorders, extremely major depression, severe movement disorder and confusion were excluded from the study.

Treatment

PX group: Patients in this group were treated with paroxetine hydrochloride (Hubei Jiuzhou Kangda Biotechnology Co., Ltd., batch number: H20031106) alone, orally, once daily and at a dosage of 20 mg for each time.

PT group: Patients in this group were treated with rTMS on the basis of paroxetine hydrochloride.

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ride. YRDCCY-1 magnetic stimulator (Yiruide Medical Equipment Company, Wuhan) was applied. The left prefrontal cortex was treated by the magnetic stimulator with stimulation time of 2 seconds for each time, interval time of 28 seconds, movement threshold of 80% and frequency of 10 Hz. The coil was kept parallel to the skull. The treatment was lasting 20 minutes each time and was conducted once daily and 5 times each week. In the course of treatment, patients with sudden depression-related episodes such as major depressive episode should be given appropriate interventions. If the symptoms are mild, relative drugs should be used for treatment. If the situation is very serious, the trial should be stopped for systematic treatment. Patients in both groups were treated continuously for 2 months.

Outcome measures

Primary indicators: depression condition, clinical efficacy, monoamine neurotransmitters, serum-related indicators. Secondary indicators: quality of life, secondary effects.

Depression condition

Patients' depression was detected by HAMD one day before treatment and seven days after treatment. The higher the score, the more serious the depression.

Clinical efficacy

Seven days after treatment, self-rating depression scale (SDS) was used to evaluate the treatment effect. Cured: SDS score decreased by more than 75%; markedly effective: SDS score decreased by 50-74%; effective: SDS score decreased by 25-49%; invalid: SDS score decreased by less than 25%. Effective rate = (cured number + markedly effective number + effective number)/total number of patients * 100%.

Quality of life

Seven days after treatment, the SF-36 rating scale was used for evaluation of the quality of life, with a total score of 100 points. The higher the score, the better the quality of life.

Serum-related indicators

Totally 5 mL of fasting venous blood was extracted in the morning one day before treatment and seven days after treatment, and cen-

trifuged routinely. Serum NPY and CRF were measured by radioimmunoassay, and serum BDNF was measured by enzyme-linked immunosorbent assay. NPY, CRF and BDNF kits were purchased from Beijing Aviva Biotechnology Co., LTD.

Monoamine neurotransmitters

The collection method of serum was the same as above. One day before treatment and seven days after treatment, the expressions of monoamine neurotransmitters including DA, 5-HT, NE and E, etc. were detected by enzyme-linked immunosorbent assay. DA, 5-HT, NE and other kits were purchased from Shanghai Shuangying Biotechnology Co., Ltd.

Secondary effects

During the treatment, secondary effects such as headache, nausea and vomiting were observed and analyzed.

Statistical analysis

All data were analyzed by SPSS 23.0 statistical software. The differences in depression condition, clinical efficacy, quality of life, serum-related indicators, monoamine neurotransmitter and secondary effects were analyzed between PX and PT groups. The measurement data were expressed as mean \pm standard deviation ($\bar{x} \pm sd$). Independent-samples T test was applied for the comparison among groups. Paired-samples T test was used for comparison before and after treatment within groups. The count data were expressed as percentage n (%), chi-square test (χ^2) was used for comparison within groups. $P < 0.05$ was considered statistically significant.

Results

Comparison of clinical efficacy

After treatment, a total of 17 patients in the PX group and 25 patients in the PT group showed better clinical efficacy. The effective rate of PT group was statistically different from that of PX group ($\chi^2=4.889$, $P=0.027$). See **Table 2**.

Analysis of depression in both groups

The results showed that before treatment, the HAMD scale scores of patients in the PX group

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

| Index | PX group | PT group | t | P |
|--------------------|------------|------------|-------|-------|
| Gender (n) | 37 | 37 | | |
| Get well | 17 (45.95) | 25 (67.57) | 9.003 | 0.029 |
| Markedly effective | 7 (18.92) | 8 (21.62) | | |
| Effective | 5 (13.51) | 3 (8.11) | | |
| Invalid | 8 (21.62) | 1 (2.70) | | |
| Efficient rate (%) | 78.38 | 97.30 | 4.889 | 0.027 |

Note: PX: paroxetine hydrochloride; PT: paroxetine hydrochloride combined with repetitive transcranial magnetic stimulation.

Table 3. Comparison of HAMD scale scores ($\bar{x} \pm sd$)

| Index | PX group | PT group | t | P |
|------------------|------------|------------|--------|--------|
| Gender (n) | 37 | 37 | | |
| Before treatment | 27.26±6.21 | 28.01±6.47 | 0.719 | 0.473 |
| After treatment | 23.16±3.41 | 14.25±2.11 | 19.110 | <0.001 |
| t | 4.978 | 17.39 | | |
| P | <0.001 | <0.001 | | |

Note: PX: paroxetine hydrochloride; PT: paroxetine hydrochloride combined with repetitive transcranial magnetic stimulation; HAMD: Hamilton Depression Scale.

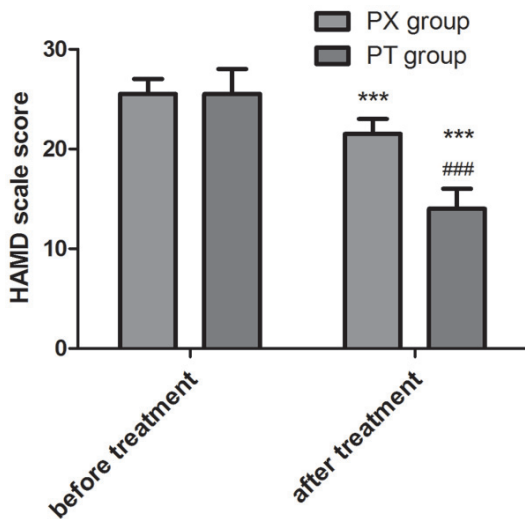


Figure 1. Comparison of HAMD scale scores. PX for paroxetine hydrochloride; PT for paroxetine hydrochloride combined with repetitive transcranial magnetic stimulation; HAMD for Hamilton Depression Scale. Compared with the same group before treatment, *** $P < 0.001$; compared with PX group after treatment, ### $P < 0.001$.

and PT group were 27.26 ± 6.21 and 28.01 ± 6.47 , respectively, and there was no significant difference in scale scores ($P > 0.05$). After treatment, there was a significant downward trend in HAMD scale scores in both groups, and the

HAMD scale score in the PT group was significantly lower than that in the PX group (both $P < 0.001$). See **Table 3** and **Figure 1**.

Comparison of quality of life scores

The quality of life scores was compared between PX and PT groups 7 days after treatment, and the results showed that the average score of quality of life in the PT group was higher than that in the PX group ($P < 0.05$). See **Table 4**.

Comparison of serum-related indicators

Before treatment, there was no significant difference in NPY, CRF and BDNF levels between PX and PT groups ($P > 0.05$). After treatment, the expressions of NPY and BDNF in both groups have increased compared with those before treatment ($P < 0.001$), while the expression of CRF has decreased ($P < 0.001$). The expressions of NPY, CRF and BDNF in the PT group were better

than those in the PX group ($P < 0.001$). See **Table 5** and **Figure 2**.

Comparison of expression of monoamine neurotransmitters

It can be seen from the table that there was a small difference in the expressions of DA and other indicators between PX and PT groups before treatment ($P > 0.05$). After treatment, the expression of DA, 5-HT and NE in both groups increased (all $P < 0.05$), the expression of E decreased compared with that before treatment ($P < 0.05$), and the expression of monoamine neurotransmitters in the PT group was better ($P < 0.05$ or $P < 0.001$). See **Table 6**.

Comparison of secondary effects

The results showed that 6 patients in the PX group developed related secondary effects, accounting for 16.22%, and 7 patients in the PT group developed secondary effects, accounting for 18.92%. The incidence of secondary effects in the PT group was slightly higher than that in the PX group, but there was no significant difference ($P > 0.05$). See **Table 7**.

Discussion

Previous studies have shown that the pathogenesis of PSD is the reduction of the function

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Table 4. Comparison of SF-36 scores ($\bar{x} \pm sd$)

| Index | PX group (n=37) | PT group (n=37) | t | P |
|------------------------|-----------------|-----------------|--------|--------|
| Physiological function | 76.34±5.37 | 89.33±6.47 | 11.350 | <0.001 |
| Physical pain | 78.24±6.26 | 89.65±7.57 | 8.536 | <0.001 |
| Energy | 74.64±7.76 | 83.76±8.94 | 7.523 | <0.001 |
| Social function | 71.63±5.36 | 80.83±7.28 | 7.478 | <0.001 |
| Emotional title | 79.27±7.65 | 87.18±7.64 | 5.376 | <0.001 |
| Mental health | 70.63±5.23 | 87.37±7.27 | 13.740 | <0.001 |
| General health | 69.54±7.34 | 87.38±7.26 | 12.700 | <0.001 |
| Daily activities | 77.64±5.27 | 86.73±6.84 | 7.736 | <0.001 |

Note: PX: paroxetine hydrochloride; PT: paroxetine hydrochloride combined with repetitive transcranial magnetic stimulation; SF-36: 36-Item Short-Form Health Survey.

Table 5. Comparison of serum NPY, CRF and BDNF levels ($\bar{x} \pm sd$)

| Index | NPY (ng/L) | CRF (μ g/L) | BDNF (μ g/L) |
|------------------|-----------------|------------------|-------------------|
| Before treatment | | | |
| PX group (n=37) | 127.25±14.05 | 65.17±10.32 | 5.37±0.48 |
| PT group (n=37) | 128.34±15.64 | 64.54±11.59 | 5.46±0.37 |
| t | 0.315 | 0.246 | 0.903 |
| P | 0.753 | 0.805 | 0.369 |
| After treatment | | | |
| PX group (n=37) | 143.24±19.64*** | 54.16±9.47*** | 8.34±1.03*** |
| PT group (n=37) | 176.84±20.34*** | 45.16±7.25*** | 11.24±1.12*** |
| t | 7.228 | 4.590 | 11.590 |
| P | <0.001 | <0.001 | <0.001 |

Note: Compared with the same group before treatment, ***P<0.001. PX: paroxetine hydrochloride; PT: paroxetine hydrochloride combined with repetitive transcranial magnetic stimulation; NPY: nerve peptide Y; CRF: corticotropin releasing factor; BDNF: brain derived neurotrophic factor.

or secretion of monoamine neurotransmitters such as 5-hydroxytryptamine in the brain tissue, which in turn lead to a series of neurological disorders in patients [10]. Paroxetine hydrochloride has obvious advantages such as rapid efficacy, long duration of efficacy and low risk of adverse reactions [11]. Repetitive transcranial stimulation is a non-invasive regulation technique. After penetrating the patient's skull with different frequency of pulsed magnetic fields, it has an effect on brain function, and in turn improves the excessive low or high functional parts of brain tissue, regulates neurotransmitters such as dopamine, 5-HT, etc., so as to play a therapeutic role [12, 13]. The prefrontal cortex regulates individual cognition and emotions. The left dorsolateral prefrontal cortex is stimulated by high-frequency pulsed magnetic fields, which promotes the generation of posi-

tive emotions in the human body, thereby achieving the purpose of improving depression [14, 15].

This study showed that rTMS on the basis of paroxetine hydrochloride treatment could more effectively relieve depression and improve the expression of serum NPY, CRF, BDNF and other monoamine neurotransmitters. Studies have found that paroxetine hydrochloride could inhibit the binding of presynaptic neurons and 5-HT in patients with PSD, thereby reducing the expression of monoamine neurotransmitters such as 5-hydroxytryptamine in the synaptic space and resisting depression [16]. Rong's study has showed

that paroxetine hydrochloride combined with idebenone in the treatment of PSD could significantly improve the patient's depressive symptoms and increase the clinical treatment effect [17]. Zhao's study showed that although paroxetine hydrochloride achieved therapeutic effects by improving the concentration of monoamine neurotransmitters in patients' brain, it did not inhibit monoamine oxidase and had low affinity to some transmitters such as dopamine receptor and histamine H1 receptor. Therefore, the therapeutic effect of paroxetine hydrochloride alone was quite different, and it had poor efficacy in some patients [18]. Zhu's study showed that compared with paroxetine hydrochloride combined with early rehabilitation training, the clinical efficacy of paroxetine hydrochloride alone in the treatment of elderly patients with PSD was significantly lower than

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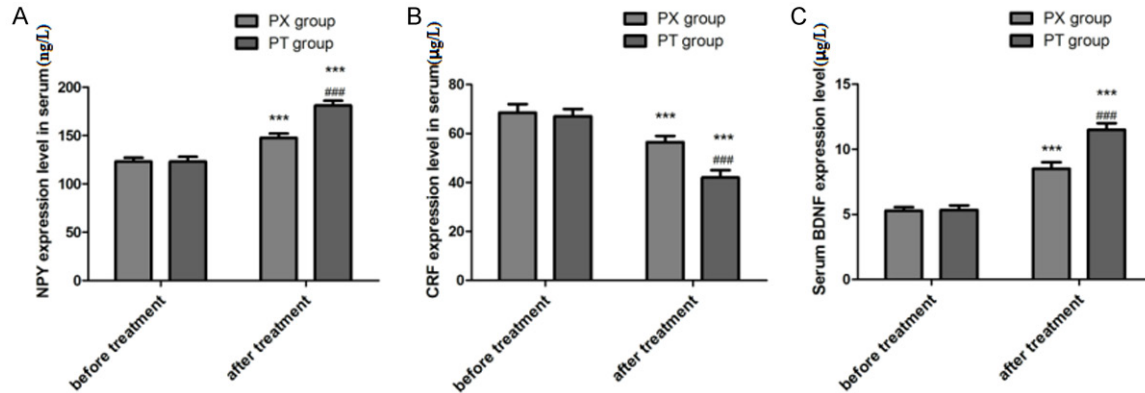


Figure 2. Comparison of serum NPY, CRF and BDNF levels. A: For the expression of serum NPY in both groups; B: For the expression of serum CRF in both groups; C: For the expression of serum BDNF in both groups. NPY for nerve peptide Y; CRF for corticotropin releasing factor; BDNF for brain derived neurotrophic factor; PX for paroxetine hydrochloride; PT for paroxetine hydrochloride combined with repetitive transcranial magnetic stimulation. Compared with the same group before treatment, ***P<0.001; compared with PX group after treatment, ###P<0.001.

Table 6. Comparison of expression of monoamine neurotransmitters between PX and PT groups ($\bar{x} \pm sd$)

| Index | DA (pg/mL) | 5-HT (pg/mL) | NE (ng/L) | E (ng/100 mg) |
|------------------|--------------|--------------|---------------|---------------|
| Before treatment | | | | |
| PX group (n=37) | 80.14±12.64 | 25.48±5.38 | 598.45±97.16 | 270.12±68.75 |
| PT group (n=37) | 81.34±13.19 | 26.28±6.84 | 594.22±98.35 | 268.48±68.59 |
| t | 0.399 | 0.559 | 0.185 | 0.102 |
| P | 0.690 | 0.577 | 0.853 | 0.918 |
| After treatment | | | | |
| PX group (n=37) | 90.48±16.34* | 31.48±7.34* | 601.48±97.26* | 235.13±64.68* |
| PT group (n=37) | 99.34±17.49* | 40.35±7.19* | 679.49±93.35* | 203.26±39.48* |
| t | 2.252 | 5.251 | 3.520 | 2.558 |
| P | 0.027 | <0.001 | <0.001 | 0.012 |

Note: Compared with the same group before treatment, *P<0.05. PX: paroxetine hydrochloride; PT: paroxetine hydrochloride combined with repetitive transcranial magnetic stimulation; DA: dopamine; 5-HT: 5-hydroxytryptamine; NE: norepinephrine; E: epinephrine.

Table 7. Comparison of secondary effects (n, %)

| Index | PX group | PT group | χ^2 | P |
|------------|-----------|-----------|----------|-------|
| Gender (n) | 37 | 37 | | |
| Headache | 2 (5.41) | 1 (2.70) | | |
| Nausea | 1 (2.70) | 2 (5.41) | | |
| Vomiting | 3 (8.11) | 4 (10.81) | | |
| Incidence | 6 (16.22) | 7 (18.92) | 0.207 | 0.649 |

Note: PX: paroxetine hydrochloride; PT: paroxetine hydrochloride combined with repetitive transcranial magnetic stimulation.

that in the combined group. Paroxetine hydrochloride combined with early rehabilitation training could significantly improve patients'

depressive symptoms and their quality of life. It deserved to be popularized clinically [19].

The main reason why repetitive transcranial magnetic stimulation has a good therapeutic effect on patients with PSD is that repetitive transcranial magnetic stimulation can significantly regulate the excitability of bilateral cerebral cortex in patients with PSD and increase the expression of neurotransmitter such as norepinephrine, 5-hydroxytryptamine and acetylcholine [20, 21]. Studies by Deng Jiafeng showed that the stimulation of anodic transcranial direct current on the left dorsolateral prefrontal cortex in patients with PSD could reduce or eliminate depression or anxiety and improve

daily quality of life [22]. Wang's study showed that the combined use of paroxetine hydrochloride and rTMS had a significant effect on patients with PSD, which could effectively improve serum BDNF and CRF, reduce HAMD scores and the degree of depression, as well as improve treatment effect without increasing adverse reactions, meanwhile it was safe [23]. Fang's study showed that rTMS combined with paroxetine was a better treatment for depression, which showed a tendency of rapider efficiency. rTMS might have a quicker improvement on anxiety and somatization symptoms [24]. In this study, paroxetine hydrochloride combined with rTMS was also used for the treatment of patients with PSD, but the research direction was different from the above studies. This study comprehensively analyzed the mechanism and therapeutic effect of combination therapy from the perspective of serum-related indicators and various monoamine neurotransmitters.

This study has certain deficiencies in the research process. Due to the cost and other issues, no comprehensive physical examination was conducted for all the experimental personnel, such as the screening of brain-related neurological diseases. The influence of other factors could not be excluded. Due to the lack of time, only one-year cases were selected for the trial, and the number of patients selected was insufficient, which might result in a certain deviation. The duration of trial would be better if extended to 3-5 years.

In summary, compared with paroxetine hydrochloride alone, paroxetine hydrochloride combined with rTMS had a better therapeutic effect on patients with PSD, which could significantly improve patients' depression score and had lower clinical secondary effects.

Disclosure of conflict of interest

None.

Address correspondence to: Weiyan Ding, Department of Psychological Rehabilitation, The 967th Hospital of The Joint Logistics Support Force of The Chinese People's Liberation Army, No. 24 Lining Street, Lvshunkou District, Dalian 116042, Liaoning Province, China. Tel: +86-13354087743; E-mail: dingweiyan80jy@163.com

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