Randomized Controlled Trial

Efficacy of acupuncture at ghost points combined with fluoxetine in treating depression: A randomized study

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Institutional review board statement: The study was reviewed and approved by the Shanghai TCM-Integrated Hospital, Shanghai University of Traditional Chinese Medicine Institutional Review Board.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflicts-of-interest statement: Yi Wang, Yu-Wei Huang, Ai-Jia Zhang, Jing-Hua Xu, Wen Wang, Zhi-Hai Hu, Department of Acupuncture and Moxibustion, Shanghai TCM-Integrated Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai 200082, China

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Abstract

BACKGROUND
Depression affects more than 350 million people worldwide. In China, 4.2% (54 million people) of the total population suffers from depression. Psychotherapy has been shown to change cognition, improve personality, and enhance the ability to cope with difficulties and setbacks. While pharmacotherapy can reduce symptoms, it is also associated with adverse reactions and relapse after drug withdrawal. Therefore, there has been an increasing emphasis placed on the use of non-pharmacological therapies for depression. The hypothesis of this study was that acupuncture at ghost points combined with fluoxetine would be more effective than fluoxetine alone for the treatment of depression.

AIM
To investigate the efficacy of acupuncture at ghost points combined with fluoxetine for the treatment of patients with depression.
Acupuncture combined with fluoxetine in depression treatment

There is no conflict of interest.

Data sharing statement: No additional data are available.

Supported by Shanghai Science and Technology Commission TCM Guidance Project, No. 19401935500; Shanghai University of Traditional Chinese Medicine Budget Scientific Research Project, No. 2020LK079; and Medical Innovation Research Special General Project of Shanghai Science and Technology Commission, No. 21YJ1923500.

Country/Territory of origin: China

Specialty type: Clinical Neurology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report’s scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

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Received: November 16, 2021
Peer-review started: November 16, 2021
First decision: December 9, 2021
Revised: December 11, 2021
Accepted: December 25, 2021
Article in press: December 25, 2021
Published online: January 21, 2022
P-Reviewer: Abe K, Patel VC
S-Editor: Wang JL

Methods
This randomized controlled trial included patients with mild to moderate depression (n = 160). Patients received either acupuncture at ghost points combined with fluoxetine (n = 80) or fluoxetine alone (control group, n = 80). Needles were retained in place for 30 min, 5 times a week; three treatment cycles were administered. The Mann-Whitney U test was used to compare functional magnet resonance imaging parameters, Hamilton depression rating scale (HAMD) scores, and self-rating depression scale (SDS) scores between the acupuncture group and control group.

Results
There were no significant differences in HAMD or SDS scores between the acupuncture group and control group, before or after 4 wk of treatment. The acupuncture group exhibited significantly lower HAMD and SDS scores than the control group after 8 wk of treatment (P < 0.05). The acupuncture group had significantly lower fractional Amplitude of Low Frequency Fluctuations values for the left anterior wedge leaf, left posterior cingulate gyrus, left middle occipital gyrus, and left inferior occipital gyrus after 8 wk. The acupuncture group also had significantly higher values for the right inferior frontal gyrus, right insula, and right hippocampus (P < 0.05). After 8 wk of treatment, the effective rates of the acupuncture and control groups were 51.25% and 36.25%, respectively (P < 0.05).

Conclusion
The study results suggest that acupuncture at ghost points combined with fluoxetine is more effective than fluoxetine alone for the treatment of patients with mild to moderate depression.

Key Words: Traditional Chinese medicine; Acupuncture; Ghost point; Fluoxetine; Depression; Resting state magnetic resonance

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Core Tip: Acupuncture is an effective auxiliary method for the treatment of clinical depression. In this study, the authors found that the combined use of acupuncture at ghost points and fluoxetine may be more effective than fluoxetine alone for the treatment of patients with mild to moderate depression.

Introduction
Depression affects approximately 4.4% of the global population and is characterized by persistent mood depression, physical symptoms, intellectual disability, cognitive impairment, and decreased activity. It not only has adverse effects on physical and mental health, but also increases social and economic burden[1]. While selective serotonin reuptake inhibitors, tricyclic antidepressants, and other Western medicine treatments have satisfactory clinical effectiveness, they also have significant side effects, such as dependency and withdrawal reactions[2].

Acupuncture is an effective auxiliary method for the treatment of clinical depression. It mainly stimulates the nerve-related signaling pathway by adjusting neurotransmitter redistribution via the integration of the central nervous system, thus facilitating brain function through self-regulation of the human body. Nevertheless, its effect on prognosis remains to be further analyzed. While the results of a previous study have suggested that acupuncture can promote the onset of selective 5-hydroxytryptamine reuptake inhibitors and reduce adverse reactions[3], the related
mechanistic interactions are currently unclear. Therefore, this study explored the effect of acupuncture at ghost points combined with fluoxetine on clinical indicators of depression and resting-state functional magnetic resonance imaging (fMRI) parameters in patients with mild to moderate depression.

**MATERIALS AND METHODS**

**Patient recruitment and inclusion criteria**
A total of 160 patients diagnosed with mild to moderate depression between January 2019 and December 2021 were recruited. Patients were included if they (1) met the diagnostic criteria for depression, according to the fifth edition of the American Handbook on Diagnosis and Statistics of Mental Disorders[4,5]; (2) had a score between 17 and 24 points on the 17-item Hamilton depression rating scale (HAMD); and (3) were between 19 and 75 years of age. The exclusion criteria were as follows: history of brain tumor or cerebrovascular disease; cardiac or pulmonary dysfunction; infectious diseases; dementia or Alzheimer’s disease; other mental disorders; history of craniocebral trauma or surgery; and other serious diseases. The study protocol was approved by the appropriate medical ethics committee, and all patients provided written informed consent prior to examination and treatment.

**Treatment methods**
Patients were randomly allocated to receive either (1) acupuncture at ghost points combined with fluoxetine (acupuncture group, n = 80); or (2) fluoxetine alone (control group, n = 80). The following acupoints were selected: governor vessel, Dazhui, spine, and Mingmen, combined with 13 ghost points on the star (flat thorn), people, less business, Yinbai, Laogong, and Shenmai (Table 1). Procedures were conducted in accordance with the national acupoint positioning standard for the selection of acupoints, acupoint positioning, and acupuncture depth, the “acupoint name and positioning” standard (GB/T12346-2006).

The Dazhui (GV14) acupoint is located in the spinal region (in the subspinous depression of the seventh cervical spine and on the posterior median line). The Jizhong (GV6) acupoint is located in the subspinal depression of the 11th thoracic spine and is on the posterior median line. The Mingmen (GV4) acupoint is located in the subspinous depression of the second lumbar spine and on the posterior midline. The Shaozhang (LU11) acupoint is located approximately 2.5 mm above the metacarpophalangeal joint of the finger, the radial side of the distal segment of the thumb and the medial side of the nail root. The Yinbai (SP1) acupoint is 2.5 mm posterior to the distal segment of the most medial toe, at the toenail corner.

The Laogong (PC8) acupoint is in the metacarpal region. It is oriented horizontally to the proximal third of the metacarpophalangeal joint, while the second and third metacarpal bones are inclined towards the third metacarpal bone. The Shenmai (BL62) acupoint is in the ankle region, below the tip of the lateral malleolus and in the depression between the lower edge of the lateral malleolus and the calcaneus.

Each patient assumed a sitting position and routine local skin disinfection was performed. A 40-mm disposable stainless-steel needle with a diameter of 0.25 mm (Huatu brand) was first applied at the Du meridian points via the flat needling method. Patients then assumed a supine position and direct needling (with the retaining needle applied for 30 min) was performed at ghost acupoints via the Shangxingping acupuncture method. All acupuncture operators previously underwent uniform training and all operative procedures were standardized. Needles were retained in place for 30 min, 5 times a week (10 times as an observation course); a total of three treatment cycles were administered.

Fluoxetine capsules (20 mg/d for adult and elderly patients) were administered orally in accordance with the psychiatrist’s instructions. If necessary, the dose was re-evaluated and adjusted within the first 3–4 wk of treatment as higher doses increase the risk of adverse reactions. Some patients did not experience any obvious effects with a standard 20 mg dose; in such cases, doses were gradually increased to a maximum of 60 mg.

Resting-state fMRI scans were performed after routine scans to confirm the absence of organic brain lesions. A conventional structural image scan was performed using the T1 weighted image merge sequence. The scanning parameters were as follows: repetition time = 2300 ms; echo time = 2.2 ms; field-of-view = 256 mm × 256 mm; voxel = 1 mm × 1 mm × 1 mm; matrix = 256 × 256; number of layers = 192; number of excitations = 1; and a scanning time of approximately 5 min. The scanning parameters
Table 1 Comparison of general information of the two groups of patients, n (%)

| Factors               | Acupuncture group (n = 80) | Fluoxetine group (n = 80) | $t$/$\chi^2$ | $P$ value |
|-----------------------|-----------------------------|---------------------------|--------------|-----------|
| Age (yr)              | 47.96 ± 6.5                 | 46.3 ± 7.2                | 1.475        | 0.142     |
| Years of education (yr) | 7.9 ± 2.2                   | 8.1 ± 2.4                | -0.549       | 0.583     |
| HAMD score (points)   | 20.13 ± 2.20                | 19.75 ± 2.38             | 1.049        | 0.296     |
| SDS score (points)    | 61.84 ± 4.55                | 60.63 ± 4.92             | 1.615        | 0.108     |
| Gender                |                             |                           |              |           |
| Male                  | 22 (27.50)                  | 28 (35.00)                | 1.477        | 0.224     |
| Female                | 58 (72.50)                  | 52 (65.00)                | 1.047        | 0.306     |
| Smoking               |                             |                           |              |           |
| Yes                   | 12 (15.00)                  | 18 (22.50)                | 1.653        | 0.199     |
| No                    | 68 (85.00)                  | 62 (77.50)                | 1.283        | 0.257     |
| Drinking              |                             |                           |              |           |
| Yes                   | 16 (20.00)                  | 10 (12.50)                | 2.209        | 0.137     |
| No                    | 64 (80.00)                  | 70 (87.50)                | 1.200        | 0.273     |
| Hypertension          |                             |                           |              |           |
| Yes                   | 35 (43.75)                  | 28 (35.00)                | 1.047        | 0.306     |
| No                    | 45 (56.25)                  | 52 (65.00)                | 1.283        | 0.257     |
| Diabetes              |                             |                           |              |           |
| Yes                   | 17 (21.25)                  | 23 (28.75)                | 2.209        | 0.137     |
| No                    | 63 (78.75)                  | 57 (71.25)                | 1.200        | 0.273     |
| Hyperlipidemia        |                             |                           |              |           |
| Yes                   | 15 (18.75)                  | 23 (28.75)                |              |           |
| No                    | 65 (81.25)                  | 57 (71.25)                |              |           |

HAMD: Hamilton depression rating scale.

for functional imaging using the echo planner imaging sequence were as follows: repetition time = 2000 ms; echo time = 30 ms; field-of-view = 220 mm; slice thickness = 3.5 mm; layer spacing = 0.6 mm; voxel = 3.44 mm × 3.44 mm × 3.44 mm; fractional anisotropy = 90; matrix = 64 × 64; number of layers = 33 (using layer-by-layer scanning); number of excitations = 1; time points = 240; and a scanning time of approximately 8 min. Pre- and post-treatment evaluations of fMRI parameters were performed and comparisons were made between the groups.

Clinical parameters and detection methods

Clinical parameters comprised the HAMD, self-rating depression scale (SDS), and traditional Chinese medicine (TCM) syndrome score. The HAMD consists of 17 test items[6]. Higher scores reflect more severe depression. The absence of depression is indicated by a score < 7. A total score in the range of 7–17 suggests that a patient may have depression, while a score between 17 and 24 confirms the diagnosis of depression. A total score > 24 indicates severe depression.

The SDS contains 20 items[7]. Norm data from the Chinese population defines mild, moderate, and severe depression by scores of 53, 53–62, and 63–72 points, respectively. The TCM syndrome score is based on the “Criteria for Diagnosis and Efficacy of TCM Symptoms”[8], which includes the three main syndromes of impatience and irritability, chest tightness, and rib distension. The secondary syndromes comprise headache, red eyes, bitter mouth, noise, constipation, and short yellow urine. Scores reflecting the severity of the main syndromes range from 0–6, while those for the secondary syndromes range from 0–3. Higher scores reflect greater syndrome severity.

The HAMD reduction rate ([before treatment - after treatment]/before treatment × 100%) was used to evaluate the treatment efficacy[9]. Reduction rates of ≥ 90,
70%–89%, and ≤ 69% indicated that the treatments were markedly effective, effective, and ineffective, respectively.

**Statistical analysis**

The distributions of the HAMD scores, SDS scores, and fMRI parameters were tested for normality. Following confirmation of approximate normal distributions (expressed as “mean ± SD”), the *t*-test was used for comparisons between the two groups. Enumeration data were expressed as *n* (%). The *χ*² test was used to compare nominal variables such as sex, combined diseases, and the presence of adverse reactions. The groups were compared in terms of ordinal variables using the Mann–Whitney *U* test to evaluate differences in clinical efficacy. The Statistical Package for Social Science version 21.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. The level of statistical significance was set at α = 0.05.

**RESULTS**

There were no significant differences in HAMD or SDS scores between the acupuncture and control groups, before or after 4 wk of treatment. After 8 wk of treatment, the acupuncture group exhibited significantly lower HAMD and SDS scores than the control group (*P* < 0.05). Within-group comparisons showed that HAMD and SDS scores in both groups were significantly lower after 4 and 8 wk compared to those recorded before treatment (*P* < 0.05) (Table 2).

Comparisons between the groups before and after 4 wk of treatment did not yield significant differences in fractional amplitude of low frequency fluctuations (fALFF) values of the left posterior cingulate gyrus, left posterior cingulate gyrus, left anterior wedge leaf, left middle occipital gyrus, left inferior occipital gyrus, right inferior frontal gyrus, right cerebral island, or right hippocampus. After 8 wk of treatment, the fALFF values of the left posterior cingulate gyrus, left anterior wedge leaf, left middle occipital gyrus, and left inferior occipital gyrus were significantly lower in the acupuncture group than in the control group (*P* < 0.05). The fALFF values of the right inferior frontal gyrus, right insula, and right hippocampus in the acupuncture group were significantly higher than those in the control group (*P* < 0.05) (Table 3). TCM syndrome scores before treatment were not significantly different between the groups (Table 4). Plasma adrenocorticotropic hormone (ACTH), cortisol, and corticotropin-releasing hormone levels were not significantly different between the acupuncture and control groups. After 8 wk of treatment, the plasma ACTH and cortisol levels in the acupuncture group were significantly lower than those in the control group (*P* < 0.05) (Table 5). Within-group comparisons showed that the plasma ACTH, cortisol, and corticotropin-releasing hormone levels in the two groups were lower than those before treatment (*P* < 0.05). After 8 wk of treatment, 51.25% of the acupuncture group showed improvement, the effective rate was 41.25%, and the ineffective rate was 7.50%. The effective rate of the control group was 36.25%, the effective rate was 50.00%, and the ineffective rate was 13.75% (Table 6). The clinical effectiveness of the acupuncture group was significantly higher than that of the control group (*P* < 0.05) (Table 7).

**DISCUSSION**

The pathophysiology of depression is currently unclear, despite prior investigations of the intestinal flora hypothesis and the role of neurotransmitters, neurotrophic factors, and neuroendocrine-immune interactions[10]. Pharmacotherapy is the primary treatment modality for depression. Selective serotonin reuptake inhibitors and tricyclic antidepressants act on neurotransmitters, cytokines, and their receptors, thereby modifying complex inflammatory pathways. Although such drugs are highly effective in reducing symptoms, they are also associated with adverse reactions and relapse after drug withdrawal.[11].

TCM theory postulates that the underlying basis of depression is a poor mood due to Qi stagnation, which leads to dysfunction of the viscera. Thus, acupuncture treatment for patients with depression often uses acupoints associated with soothing of the liver and depression relief, as well as tranquilization of the heart and mind. These acupoints include Baihui, Yintang, and other governor vessels. The selection of acupoints in patients with mild to moderate depression in the present study was based on the unique theory of Shen’s acupuncture treatment for depression syndrome, which
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Table 2 Comparison of Hamilton depression rating scale scores and self-rating depression scale scores between the two groups (mean ± SD, scores)

| Group            | n  | HAMD score (points)                              | SDS score (points)   |
|------------------|----|--------------------------------------------------|----------------------|
|                  |    | Before treatment                                 | 4 wk of treatment    | 8 wk of treatment |
|                  |    | 20.13 ± 2.20                                     | 16.60 ± 2.85         | 13.64 ± 2.75a    |
| Acupuncture group| 80 | 19.75 ± 2.38                                     | 17.21 ± 2.91a        | 15.20 ± 2.48a    |
| Fluoxetine group | 80 | 19.75 ± 2.38                                     | 17.21 ± 2.91a        | 15.20 ± 2.48a    |
|                  |    | 61.84 ± 4.55                                     | 56.92 ± 5.10a        | 51.14 ± 6.12a    |
|                  |    | 57.88 ± 5.53                                     | 54.63 ± 5.58a        | 54.63 ± 5.58a    |
| t value          |    | 1.049                                            | -1.340               | -3.768            |
| P value          |    | 0.296                                            | 0.182                | 0.000             |

*P < 0.05 vs this group before treatment.
HAMD: Hamilton depression rating scale; SDS: Self-rating depression scale.

Table 3 Comparison of fractional amplitude of low frequency fluctuations values between the two groups of patients (mean ± SD)

| Acupuncture group-fluoxetine group (fALFF difference) | MNI coordinates (mm) | Voxel | t value |
|--------------------------------------------------------|----------------------|-------|---------|
| Before treatment                                       | X   | Y   | Z   |       |
| Cingulate back                                         | -3  | -11 | 13  | -0.431|
| Left precuneus                                         | -4  | -8  | -4  | 1.102 |
| Middle occipital gyrus                                 | -9  | 6   | 8   | 1.339 |
| Left suboccipital back                                 | -14 | -21 | 9   | 1.482 |
| Lower forehead of right frame                          | 14  | 12  | -2  | 1.773 |
| Right insula                                           | 15  | 18  | -5  | 1.295 |
| Right hippocampus                                      | 11  | -1  | 13  | 1.374 |
| Post treatment                                         |      |     |     | |
| Cingulate back                                         | 14  | 18  | -11 | 2.23  |
| Left precuneus                                         | 5   | 13  | 6   | 1.748 |
| Middle occipital gyrus                                 | 12  | 38  | 8   | 2.548 |
| Left suboccipital back                                 | 7   | 14  | 11  | 3.251 |
| Lower forehead of right frame                          | -18 | -16 | 9   | 3.926 |
| Right insula                                           | -17 | -13 | 14  | 1.554 |
| Right hippocampus                                      | -13 | 12  | -11 | 0.983 |

fALFF: Fractional amplitude of low frequency fluctuations.

Involves “regulating yang and eliminating pathogenic factors”[12]. After 4 and 8 wk of treatment, the HAMD and SDS scores in both the acupuncture and control groups were significantly lower than those before treatment.

Patients in the acupuncture group had significantly lower HAMD and SDS scores than patients in the control group. This suggests that the long-term clinical effect of acupuncture at ghost points combined with fluoxetine is better than fluoxetine alone for the treatment of mild to moderate depression. The decrease in scores between weeks 4 and 8 was not as notable as that observed from baseline to week 4. This could be attributed to the fact that the scores for each scale have a lower limit; indeed, both HAMD and SDS scores had entered a relatively stable range after 8 wk of treatment, even approaching values observed in patients without depression.

The assessment of the neurophysiology and neuroanatomy of affective disorders with fMRI can be used to facilitate the diagnosis of depression. Some studies have suggested that fALFF and regional homogeneity values can be used as indicators for
Table 4 Comparison of traditional Chinese medicine syndrome scores between the two groups of patients (mean ± SD, scores)

| Group           | n  | TCM syndrome points | t value | P value |
|-----------------|----|---------------------|---------|---------|
|                 |    | Before treatment    | Post treatment |
| Acupuncture     | 80 | 21.73 ± 4.20        | 7.96 ± 1.55 | 27.511 | 0.000 |
| Fluoxetine      | 80 | 20.68 ± 4.47        | 10.20 ± 2.39 | 18.493 | 0.000 |
| t value         |    | 1.531               | -7.033 |
| P value         |    | 0.128               | 0.000 |

TCM: Traditional Chinese medicine.

Table 5 Comparison of plasma adrenocorticotropic hormone, Cor and corticotropin-releasing hormone levels before and after treatment in the two groups

| Group           | n  | ACTH (ng/L)         | Cor (ng/L)        | CRH (ng/L)       |
|-----------------|----|---------------------|-------------------|------------------|
|                 |    | Before treatment    | 8 wk of treatment | Before treatment | 8 wk of treatment |
| Acupuncture     | 80 | 38.74 ± 7.20        | 28.64 ± 5.51      | 122.64 ± 14.81  | 98.13 ± 11.77   |
| Fluoxetine      | 80 | 40.01 ± 8.14        | 31.47 ± 7.08      | 120.28 ± 16.57  | 105.25 ± 13.60  |
| t value         |    | -1.045              | -2.821            | 0.950            | -3.541           |
| P value         |    | 0.297               | 0.005             | 0.344            | 0.001            |

αP < 0.05 vs this group before treatment.
ACTH: Adrenocorticotropic hormone; CRH: Corticotropin-releasing hormone.

Table 6 Comparison of clinical efficacy between the two groups of patients, n (%)

| Group           | n  | Markedly effective | Efficient | Invalid |
|-----------------|----|--------------------|-----------|---------|
| Acupuncture     | 80 | 41 (51.25)         | 33 (41.25) | 6 (7.50) |
| Fluoxetine      | 80 | 29 (36.25)         | 40 (50.00) | 11 (13.75) |
| Z               |    | -2.041             |           |         |
| P value         |    | 0.041              |           |         |

Table 7 Comparison of the incidence of adverse reactions between the two groups of patients, n (%)

| Group           | n  | Insomnia | Nausea | Irritable | Anxiety | Tremor | Complication rate |
|-----------------|----|----------|--------|-----------|---------|--------|-------------------|
| Acupuncture     | 80 | 1        | 1      | 0         | 2       | 0      | 4 (5.00)         |
| Fluoxetine      | 80 | 4        | 2      | 2         | 4       | 1      | 13 (16.25)       |
| χ²              |    |          |        |           |         |        | 5.331            |
| P value         |    |          |        |           |         |        | 0.021            |

the early diagnosis and monitoring of depression[13]. After 8 wk of treatment in the present study, the fALFF values of the left posterior cingulate gyrus, left precuneus, left middle occipital gyrus, and left inferior occipital gyrus were significantly lower in the acupuncture group than in the control group. In contrast, the fALFF values of the right inferior frontal gyrus, right insula, and right hippocampus in the acupuncture group were higher than those in the control group[14,15]. These results suggest that the combined use of acupuncture at ghost points and fluoxetine has a greater effect on the regulation of neurological function compared to fluoxetine alone when used in patients with mild to moderate depression[16]. Acupuncture combined with fluoxetine
may play an antidepressant role by reducing the fALFF values of patients in the frontal lobe, middle frontal gyrus, parietal lobe, anterior central gyrus, precuneus, and parietal lobule, which are higher than those of healthy people. The combined use of acupuncture and fluoxetine affects a wider range of brain regions than fluoxetine alone, thus indicating that each treatment may regulate brain function via different mechanisms. Acupuncture may have a more significant regulatory role in a greater number of brain regions compared to pharmacotherapy[17,18].

Previous studies have reported significantly lower TCM syndrome scores in an acupuncture group compared to a fluoxetine group after 8 wk of treatment; a greater clinical efficacy was achieved with acupuncture treatment[19,20]. In addition, the incidence of adverse reactions in the acupuncture group (5.71%) was significantly lower than that in the fluoxetine group (25.71%). This suggested that acupuncture at ghost points combined with fluoxetine had a greater clinical efficacy than fluoxetine alone in patients with mild to moderate depression. The results of the present study provide additional evidence for the efficacy of acupuncture in the treatment of depression. Acupuncture exerts its effects via multiple targets and mechanisms; these comprise the regulation of neurotransmitters and receptors, nerve plasticity, the neuroendocrine-immune network, and the brain-gut axis. This study demonstrated that the combined use of acupuncture and pharmacotherapy may provide synergistic benefits in patients with mild to moderate depression. Additional studies are warranted to further investigate the efficacy of different acupuncture and drug combinations.

CONCLUSION

The combined use of acupuncture at ghost points and fluoxetine may be more effective than fluoxetine alone for the treatment of patients with mild to moderate depression. At the same time, it has a better effect on improving the TCM syndrome of patients and regulating the neurological function of brain functional areas.

ARTICLE HIGHLIGHTS

Research background
Depression affects more than 350 million people worldwide. In China, 4.2% (54 million people) of the total population suffers from depression.

Research motivation
This study provided data reference for the treatment of depression.

Research objectives
This study explored the effect of acupuncture at ghost points combined with fluoxetine on clinical indicators of depression and resting-state functional magnetic resonance imaging (fMRI) parameters in patients with mild to moderate depression.

Research methods
They were divided into acupuncture group (acupuncture at ghost points combined with fluoxetine) and fluoxetine group (fluoxetine alone) with 80 cases in each group.

Research results
The acupuncture group was better than the fluoxetine group.

Research conclusions
Acupuncture at ghost points combined with fluoxetine is more effective than fluoxetine.

Research perspectives
The combined use of acupuncture at ghost points and fluoxetine may be more effective than fluoxetine alone for the treatment of patients with mild to moderate depression.
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