Improvement in quality of life in depressed patients following verum acupuncture or electroacupuncture plus paroxetine: a randomized controlled study of 157 cases

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Abstract
Depressed patients with scores of 17 or more on the 17 items of the Hamilton Depression Rating Scale were treated with the antidepressant drug paroxetine. They also underwent verum acupuncture or electroacupuncture at Baihui (GV20) and Yintang (GV29). The World Health Organization Quality of Life Scale Brief Version showed a significant increase in the total scores of patients who underwent verum acupuncture and electroacupuncture for 6 weeks compared with those who were given paroxetine only; significantly increased physical domain and social relationship scores in verum acupuncture patients compared with paroxetine only; and significantly elevated psychological domain scores with electroacupuncture compared with paroxetine only. These results indicate that both verum acupuncture and electroacupuncture can improve quality of life in depressed patients undergoing paroxetine treatment.

Key Words
acupuncture; electroacupuncture; depression; paroxetine; World Health Organization Quality of Life Scale Brief Version; quality of life; Chinese medicine; neural regeneration

Research Highlights
(1) The World Health Organization Quality of Life Scale Brief Version was used to evaluate the quality of life of depressed patients undergoing acupuncture plus paroxetine treatment. Scores for physical function and social relationships were significantly elevated, as were those in the psychological domain in patients undergoing electroacupuncture.
(2) The four-factor domain was superior to the six-factor domain in evaluating quality of life in depressed patients treated with acupuncture plus antidepressant drugs.

Abbreviation
WHOQOL-BREF, World Health Organization Quality of Life Scale Brief Version
INTRODUCTION

Antidepressant drugs are commonly used to treat depression, effectively reducing the risk of recurrence\(^{1-7}\). However, about 50% of depressed patients have not been diagnosed, and some patients respond poorly to antidepressant drugs. Moreover, clinical studies show significant adverse effects of antidepressant drugs, and a new generation of antidepressant drugs remains under investigation\(^{8-11}\). Previous studies have demonstrated that the traditional Chinese medicine acupuncture, which has been extensively used to treat depression\(^{12-14}\), has significantly fewer adverse effects and greater safety than antidepressant drugs\(^{15-17}\). Verum acupuncture performed in 20 depressed patients ameliorated the condition to a certain degree, and 40% of patients said they had experienced the expected effects\(^{18}\). In a meta-analysis of 833 patients in nine studies\(^{14}\), the effects of verum acupuncture alone were similar to those of antidepressant drugs alone. However, use of acupuncture alone in the treatment of depression can also be unsatisfactory\(^{19}\). In a previous study acupuncture was used to treat 30 depressed patients who had responded poorly to antidepressant drugs; this treatment was safe and effective\(^{20}\). In addition, verum acupuncture or electroacupuncture in combination with fluoxetine had superior effects in treating depression compared with fluoxetine alone\(^{21-23}\). Thus, a combination of acupuncture and antidepressant drugs may be an option for the treatment of depression. However, there is no evidence to confirm its efficacy and reliability due to a limited number of relevant studies\(^{14}\). Chinese studies have shown paroxetine to have superior efficacy and safety over other antidepressant drugs\(^{24-25}\). Therefore, the present study combined acupuncture at Baihui (GV20) and Yintang (GV29)\(^{26}\) with paroxetine to treat depressed patients, and evaluated the improvement in quality of life using the World Health Organization Quality of Life Scale Brief Version (WHOQOL-BREF) published in 1998\(^{27-29}\).

RESULTS

Quantitative analysis of participants

One hundred and fifty-seven depressed patients were enrolled and randomly assigned to three treatment groups: drug control (paroxetine, \(n = 48\)), verum acupuncture (verum acupuncture + paroxetine, \(n = 53\)) and electroacupuncture (electroacupuncture + paroxetine, \(n = 56\)). The acupuncture points were Baihui and Yintang. Thirty patients withdrew from the study, leaving 127 cases (38 drug control, 45 verum acupuncture and 44 electroacupuncture) in the final analysis.

Baseline data analysis of participants

The number of female patients was greater than that of males. The patients were aged 20–40 years and the duration of their illness was less than 55 months. Before treatment, there were no statistically significant differences between groups in terms of gender, age and duration of illness \((P > 0.05; \text{Table 1})\).

### Table 1 Patients’ baseline data

| Item                  | Drug control group \((n = 38)\) | Verum acupuncture group \((n = 45)\) | Electroacupuncture group \((n = 44)\) | \(P\)   |
|-----------------------|---------------------------------|-------------------------------------|--------------------------------------|--------|
| Age (year)            | 36.0±11.2                       | 32.5±9.6                            | 32.9±9.3                             | 0.243  |
| Gender [M/F (\(n\)]   | 16/22                           | 17/28                               | 19/25                                | 0.862  |
| Duration of illness (month) | 19.7±24.2                     | 23.2±28.3                            | 21.2±29.9                            | 0.843  |

Measurement data were expressed as the mean ± SD. Comparison of age and duration of illness was conducted using one-way analysis of variance; differences in gender were compared using the chi-square test. M: Male; F: female.

Improvement of quality of life

On the WHOQOL-BREF (Table 2), compared with before treatment, only the scores for social relationships were elevated in the drug control group, but the scores for every quality of life item were significantly increased in the verum acupuncture and electroacupuncture groups after 6 weeks of treatment \((P < 0.05)\). The total scores for quality of life were significantly increased in all three groups \((P < 0.05)\). Compared with the drug control group after 6 weeks of treatment, psychological domain scores and scores for spirituality were significantly increased in the electroacupuncture group \((P < 0.05)\), and scores for level of independence and social relationships were significantly increased in the verum acupuncture group \((P < 0.05)\). The total scores for quality of life were significantly elevated in patients who underwent verum acupuncture or electroacupuncture compared with those who received paroxetine only \((P < 0.05)\). On the four-domain WHOQOL-BREF, physical domain scores were significantly higher in the verum acupuncture group compared with the drug control group after 6 weeks of treatment \((P < 0.05)\). Psychological domain scores were significantly higher in the electroacupuncture group compared with the drug control group.
The results of the present study show that the effects of control group ($P < 0.05$; Table 3).

Table 2 Scores on the six-domain World Health Organization Quality of Life Scale Brief Version administered before and after treatment

| Domain          | Drug control group ($n = 38$) | Verum acupuncture group ($n = 45$) | Electroacupuncture group ($n = 44$) | $F$ | $P$ |
|-----------------|-------------------------------|-----------------------------------|------------------------------------|-----|-----|
| Physical        |                               |                                   |                                    |     |     |
| Baseline        | 2.2±0.8                       | 1.8±0.7                           | 1.8±0.8                            | 3.675 | 0.028 |
| 6 weeks         | 2.5±0.7                       | 2.8±0.8                           | 2.8±0.8                            | 2.809 | 0.072 |
| $F$             | 3.484                         | 36.855                            | 35.073                             |     |     |
| $P$             | 0.070                         | 0.000                             | 0.000                              |     |     |
| Psychological   |                               |                                   |                                    |     |     |
| Baseline        | 2.4±0.9                       | 2.3±0.9                           | 2.1±0.9                            | 1.060 | 0.350 |
| 6 weeks         | 2.7±0.7                       | 3.0±0.6                           | 3.1±0.7**                         | 4.508 | 0.013 |
| $F$             | 3.669                         | 16.296                            | 51.815                             |     |     |
| $P$             | 0.063                         | 0.000                             | 0.000                              |     |     |
| Level of indepen-dence |              |                                   |                                    |     |     |
| Baseline        | 12.2±1.9                      | 12.3±2.1                          | 11.7±2.4                           | 0.719 | 0.489 |
| 6 weeks         | 12.4±1.6                      | 13.6±2.3*                         | 13.1±2.0                          | 3.611 | 0.030 |
| $F$             | 5.545                         | 12.761                            | 18.995                             |     |     |
| $P$             | 0.465                         | 0.001                             | 0.000                              |     |     |
| Social relationships |              |                                   |                                    |     |     |
| Baseline        | 11.9±2.6                      | 12.2±2.9                          | 11.1±2.5                           | 2.055 | 0.132 |
| 6 weeks         | 12.3±2.0                      | 14.0±2.1*                         | 12.8±1.9                          | 4.313 | 0.015 |
| $F$             | 10.574                        | 16.041                            | 15.079                             |     |     |
| $P$             | 0.002                         | 0.000                             | 0.000                              |     |     |
| Environment     |                               |                                   |                                    |     |     |
| Baseline        | 11.2±1.7                      | 10.8±1.9                          | 10.7±1.9                           | 0.599 | 0.551 |
| 6 weeks         | 11.7±1.4                      | 11.4±1.1                          | 11.6±1.4                          | 0.572 | 0.566 |
| $F$             | 3.787                         | 5.125                             | 5.672                              |     |     |
| $P$             | 0.059                         | 0.029                             | 0.022                              |     |     |
| Spirituality    |                               |                                   |                                    |     |     |
| Baseline        | 11.0±1.3                      | 10.8±2.1                          | 10.5±2.2                           | 0.685 | 0.506 |
| 6 weeks         | 10.7±1.4                      | 11.1±1.6                          | 11.7±1.5*                         | 4.983 | 0.008 |
| $F$             | 1.554                         | 1.294                             | 14.863                             |     |     |
| $P$             | 0.220                         | 0.261                             | 0.000                              |     |     |
| Total           | 50.8±5.9                      | 50.2±7.6                          | 47.9±7.0                           | 1.975 | 0.143 |
| 6 weeks         | 53.1±5.7                      | 55.8±6.5                          | 55.1±5.9                          | 2.147 | 0.121 |
| $F$             | 7.243                         | 22.740                            | 40.039                             |     |     |
| $P$             | 0.011                         | 0.000                             | 0.000                              |     |     |
| Increase in score | 2.4±5.4                      | 5.6±7.9*                          | 7.2±7.5*                           | 4.783 | 0.010 |

a $P < 0.05$, vs. drug control group; b $P < 0.05$, vs. electroacupuncture group. Higher scores represent better quality of life. Measurement data are expressed as mean ± SD.

Intergroup comparison was conducted using one-way analysis of variance; intragroup differences were compared using analysis of variance of repetitive measurements. Intergroup comparison of data with significant differences compared with baseline was conducted using covariance analysis.

DISCUSSION

In treatment of depression with Mianserin and acupuncture, the effects of acupuncture were not predominant and may have been only a placebo effect[29]. The results of the present study show that the effects of electroacupuncture + paroxetine were better than verum acupuncture + paroxetine, indicating differences in effect among different acupuncture methods. Experience and manipulation during needling may play a major role[30][31]. Our results also show that electroacupuncture + paroxetine was superior in improving patients’ psychological domain compared with verum acupuncture + paroxetine, and verum acupuncture + paroxetine had the greatest effect on improving the physical domain and social relationships. Wang et al[32] suggested that acupuncture may produce cheerful feelings in patients through the endopoid peptide system and thereby attenuate anxiety[32]. In the present study, the effects of electroacupuncture and verum acupuncture in combination with the antidepressant drug paroxetine differed, possibly due to the greater intensity of stimulation produced by electroacupuncture, which was more effective in eliminating negative emotions than verum acupuncture. However, excessive stimulation may cause discomfort. Verum acupuncture is relatively gentle, and can better control pain.

Table 3 Scores on the four-domain in World Health Organization Quality of Life Scale Brief Version administered before and after treatment

| Domain          | Drug control group ($n = 38$) | Verum acupuncture group ($n = 45$) | Electroacupuncture group ($n = 44$) | $F$ | $P$ |
|-----------------|-------------------------------|-----------------------------------|------------------------------------|-----|-----|
| Physical        |                               |                                   |                                    |     |     |
| Baseline        | 14.4±2.2                      | 14.1±2.3                          | 13.6±2.5                           | 1.217 | 0.300 |
| 6 weeks         | 14.9±2.1                      | 16.3±2.8*                         | 15.9±2.4                          | 3.586 | 0.031 |
| $F$             | 2.176                         | 28.754                            | 42.393                             |     |     |
| $P$             | 0.149                         | 0.000                             | 0.000                              |     |     |
| Psychological   |                               |                                   |                                    |     |     |
| Baseline        | 13.3±1.7                      | 13.0±2.5                          | 12.6±2.8                           | 1.031 | 0.360 |
| 6 weeks         | 13.3±1.9                      | 14.1±2.0                          | 14.8±2.0*                         | 5.903 | 0.004 |
| $F$             | 0.006                         | 7.202                             | 36.639                             |     |     |
| $P$             | 0.940                         | 0.010                             | 0.000                              |     |     |
| Social          |                               |                                   |                                    |     |     |
| Baseline        | 11.9±2.6                      | 12.2±2.9                          | 11.1±2.5                           | 2.055 | 0.132 |
| 6 weeks         | 13.2±2.1                      | 14.0±2.1*                         | 12.8±1.9                          | 4.313 | 0.015 |
| $F$             | 10.574                        | 16.041                            | 15.079                             |     |     |
| $P$             | 0.002                         | 0.000                             | 0.000                              |     |     |
| Environment     |                               |                                   |                                    |     |     |
| Baseline        | 11.2±1.7                      | 10.8±1.9                          | 10.7±1.9                           | 0.599 | 0.551 |
| 6 weeks         | 11.7±1.4                      | 11.4±1.1                          | 11.6±1.4                          | 0.572 | 0.566 |
| $F$             | 3.787                         | 5.125                             | 5.672                              |     |     |
| $P$             | 0.059                         | 0.029                             | 0.022                              |     |     |

a $P < 0.05$, vs. drug control group; b $P < 0.05$, vs. electroacupuncture group. Higher scores represent better quality of life. Measurement data are expressed as mean ± SD.

Intergroup comparison was conducted using one-way analysis of variance; intragroup differences were compared using analysis of variance of repeated measurements. Intergroup comparison of data with significant differences compared with baseline was conducted using covariance analysis.
The sample size in the present study was small, so we did not include sham needling + paroxetine or needling + placebo groups. Thus, we cannot exclude the possibility of an effect of acupuncture on paroxetine treatment. Moreover, we did not assess the patients’ quality of life regularly, so information during treatment was not obtained. However, we confirmed efficacy of acupuncture in combination with paroxetine in treating depression. In addition, four-domain evaluation eliminated the influence of an unstable baseline and was superior to the six-domain WHOQOL-BREF. In conclusion, adjuvant treatment with acupuncture can significantly improve quality of life in patients receiving paroxetine, and electroacupuncture was superior to verum acupuncture. Verum acupuncture + paroxetine was predominantly effective on physical function and social relationships, whereas electroacupuncture + paroxetine mainly improved psychological status.

SUBJECTS AND METHODS

Design
Prospective randomized, controlled study.

Time and setting
The study was performed in Nanfang Hospital, First Hospital of Southern Medical University, Guangzhou Overseas Chinese Hospital, First Hospital of Jinan University, and Guangdong 999 Brain Hospital, China from December, 2008 to October, 2010.

Subjects
Depressed patients admitted to Nanfang Hospital, First Hospital of Southern Medical University, Guangzhou Overseas Chinese Hospital, First Hospital of Jinan University and Guangdong 999 Brain Hospital were enrolled.

Diagnostic standards
Depression was diagnosed according to the International Classification of Disease and Diagnostic Standards for depression. The depression had persisted for ≥ 2 weeks and the patients had no history of hypomania or mania.

Inclusion criteria
Patients with scores of 17 or more on the 17 items of the Hamilton Depression Rating Scale, of either gender and aged between 18 and 60 years, were selected.

Exclusion criteria
Patients with bipolar depression, who had participated in other clinical trials in 4 weeks before the present study, or who were taking or coming off antidepressant drugs. Neither pregnant nor lactating women were included. People suffering severe diseases of the brain or other systems, and those who had planned or attempted suicide were also excluded.

Participation criteria
Treatment was terminated in subjects with poor compliance, who did not undergo acupuncture according to regulations, who experienced physiopathological changes, who was intolerant of or hypersensitive to paroxetine, who developed adverse effects or who may have become pregnant during the treatment. Informed consent was obtained from all participants. The study was approved by the Administrative Regulations on Medical Institution, issued by the State Council of China.

Methods
Random grouping
Randomization method: centralized randomization and random number allocation were conducted by the Center for Evidence-Based Medicine, Beijing University of Chinese Medicine. Once the 157 subjects had signed their informed consent, the researchers called the center to obtain random numbers, which were generated using SAS 6.12 statistical software (Raleigh, NC, USA). Randomization concealment: patients were grouped during centralized randomization by the Center for Evidence-Based Medicine, Beijing University of Chinese Medicine and coded as A, B or C. Random codes were also assigned according to research center number and subject number, and the patients received the corresponding intervention according to the research workbook and random codes. Single blind setting: blinding was not used in patients, but in outcome evaluation and data input and for the statistics researcher. All data were checked and logged in. The principal researchers and statisticians discussed the statistical plan, followed by unblinding and signing of the allocation concealment.

Intervention
Patients in the drug control group were treated with paroxetine (Glaxo Smith Kline, London, UK; No. H10950043). The verum acupuncture and electroacupuncture groups were treated with paroxetine combined with acupuncture. The drug dose was 10 mg/d for the first 2 days, then 20 mg/d until the end of the treatment, administrated orally once per day after breakfast for 6 consecutive weeks.
Electroacupuncture group:

Acupoints: Baihui and Yintang were the principal points; Fengfu (GV16), bilateral Fengchi (GB20), Dazhui (GV14), bilateral Neiguan (PC6) and bilateral Sanyinjiao (SP6) were the acupoints of coordination, selected according to current data on acupoints for the treatment of clinical depression[36]. The location of the acupoints was confirmed in accordance with the Name and Location of Acupoints: Chinese National Standards[37]. Baihui was located at the intersection of the highest point of the ear lobe and the medial line of the head; Yintang was located between the frontal region and the two eyebrows; Fengfu was located 1 cun vertically superior to the medial posterior hair margin; Fengchi was inferior to the nuchal occipital bone; Dazhui was at the hollow of the posterior medial vertebral spine at the seventh cervical vertebra; Neiguan was at the medial forearm, 2 cun superior to the wrist crease; and Sanyinjiao was located 3 cun superior to the medial malleolus of the medial leg.

Needles: Hwato stainless steel acupuncture needles (Suzhou, Jiangsu, China), (25–40) × (0.25–0.30) mm.

Acupuncture methods: the patient was placed in a sitting position for acupuncture at Fengfu and Dazhui. The needle was not left in place at the acupoints. The patient was then placed in the dorsal position for acupuncture at Baihui, Yintang and other acupoints.

During needling of Fengfu, the patient was asked to sit with his or her arms on the table, head sloping slightly anterior and nuchal muscle relaxed. The needle was inserted slowly in the submaxillary direction to a depth of 2.0–3.0 cm. After Deqi, the needle was slowly and gently twisted through 90°–180°, 60–90 times/minute for 30 seconds. It was then withdrawn slowly and pressure was applied to needle hole.

During needling of Dazhui, the patient was sitting or prone with the head bowed to expose the spinous process of the seventh cervical vertebrae. The needle was inserted vertically from the inferior spinous process to a depth of 3.0–3.5 cm. After Deqi, the needle was slowly and gently twisted through 90°–180°, 60–90 times/minute for 30 seconds. It was then withdrawn slowly and pressure was applied to the needle hole.

During needling of Baihui, the patient was placed in the dorsal position. The needle was inserted slowly backward to a depth of 1.5–2.5 cm. It was not lifted or thrusted, but only twisted gently until Deqi.

During needling of Yintang, the patient was placed in the dorsal position. The needle was inserted slowly upward to a depth of 1.5–2.5 cm. It was not lifted or thrusted, but only twisted gently until Deqi.

During needling of Fengchi, the patient was placed in the dorsal position. The needle was inserted from the left and right Fengchi acupoints to a depth of 2.0–2.5 cm, then twisted gently until Deqi.

During needling of Neiguan, the needle was inserted vertically to a depth of 1.5–2.5 cm, then twisted gently until Deqi.

During needling of Sanyinjiao, the needle was inserted vertically to a depth of 2.0–2.5 cm, then twisted gently until Deqi.

Baihui, Yintang and bilateral Fengchi were stimulated using Han's acupuncture nerve stimulator (LH-202H; Beijing, China). The positive electrode of one set of electric wires was connected to Baihui and the negative electrode was connected to Yintang; the other set of wires was connected to bilateral Fengchi, with the positive and negative electrodes alternated between the left and right sides at each treatment. A disperse-dense wave, 2/15 Hz, was used, and the current was controlled within tolerance (skin micromovement). Each electroacupuncture lasted for 30 minutes. The needle was left in place for 30 minutes at the other acupoints, with needling once after 15 minutes for 5–10 seconds.

Duration of treatment: Acupuncture was conducted every 2 days, three times per week, for 6 weeks in addition to drug treatment.

Verum acupuncture group: The principal points, acupoints of coordination, needles, acupuncture methods and duration of treatment were the same as for electroacupuncture. Needles at all acupoints were left in place for 30 minutes.

**WHOQOL-BREF evaluation of quality of life**

The WHOQOL-BREF originally covered six domains: physical function, psychological domain, level of independence, social relationships, environment and spirituality. Following modifications, level of independence and spirituality were included in the physical function and psychological domains[27, 38-39] to produce a four-domain evaluation. Patients were assessed at the beginning of treatment and 6 weeks after treatment to investigate changes in their quality of life.

**Statistical analysis**

Measurement data were expressed as the mean ± SD and analyzed using SPSS 13.0 software (SPSS, Chicago, IL, USA). The data set used for evaluation of efficacy and safety was the per protocol set. Subjects who withdrew from the study were excluded. Intergroup differences in scale evaluation scores, age and duration of illness were compared using one-way analysis of
variance; repeated measurements data were analyzed using analysis of variance of repeated measurements. Intergroup comparison of data with significant differences compared with baseline was conducted using covariance analysis. Gender data were analyzed using the chi-square test. All statistical analyses were conducted using two-sided tests, with an alpha level of 0.05.

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Author contributions: Yong Huang was the mentor and designer for this trial. Shenchang Guo recruited patients. Junqi Chen, Ganlong Li and Canghuan Zhao conducted the experiment and the result was evaluated by Shenchang Guo and Congqi Wang. Renyong Lin recorded the data. Shenghui Ma and Shanshan Qu analyzed the data. Shenghui Ma wrote the first draft of the manuscript and it was validated by Yong Huang and Zhangjin Zhang.

Conflicts of interest: None declared.

Ethical approval: This study received permission from the Ethics Committee of Guangzhou Overseas Chinese Hospital, First Hospital of Jinan University, China. The study is registered at the Chinese Clinical Trial Register (No. ChiCTR-TRC-00000278).

REFERENCES

[1] Gabilondo A, Rojas-Farreras S, Vilagut G, et al. Epidemiology of major depressive episode in a southern European country: results from the ESEMeD-Spain project. J Affect Disord. 2010;120(1-3):76-85.

[2] Guo WJ, Tsang A, Li T, et al. Psychiatric epidemiological surveys in China 1960-2010: how real is the increase of mental disorders? Curr Opin Psychiatry. 2011;24(4):324-330.

[3] Song Y, Huang Y, Liu D, et al. Depression in college: depressive symptoms and personality factors in Beijing and Hong Kong college freshmen. Compr Psychiatry. 2008;49(5):496-502.

[4] Cheung YB, Law CK, Chan B, et al. Suicidal ideation and suicidal attempts in a population-based study of Chinese people: risk attributable to hopelessness, depression, and social factors. J Affect Disord. 2006;90(2-3):193-199.

[5] Zhang WJ, Yang XB, Zhong BL. Combination of acupuncture and fluoxetine for depression: a randomized, double-blind, sham-controlled trial. J Altern Complement Med. 2009;15(8):837-844.

[6] Phillips MR, Shen Q, Liu X, et al. Assessing depressive symptoms in persons who die of suicide in mainland China. J Affect Disord. 2007;98(1-2):73-82.

[7] Jakobsen JC, Hansen JL, Simonsen E, et al. The effect of adding psychodynamic therapy to antidepressants in patients with major depressive disorder. A systematic review of randomized clinical trials with meta-analyses and trial sequential analyses. J Affect Disord. 2012;137(1-3):1-4.

[8] Berlim MT, Turecki G. What is the meaning of treatment resistant/refractory major depression (TRD)? A systematic review of current randomized trials. Eur Neuropsychopharmacol. 2007;17(11):696-707.

[9] Davis JM, Chen N. Old versus new: weighing the evidence between the first- and second-generation antipsychotics. Eur Psychiatry. 2005;20(1):7-14.

[10] Keltner NL, Johnson V. Biological perspectives. Aripiprazole: a third generation of antipsychotics begins? Perspect Psychiatr Care. 2002;38(4):157-159.

[11] Cepoiu M, Mccusker J, Cole MG, et al. Recognition of depression by non-psychiatric physicians—a systematic literature review and meta-analysis. J Gen Intern Med. 2008;23(1):25-36.

[12] Han JS, Ho YS. Global trends and performances of acupuncture research. Neurosci Biobehav Rev. 2011;35(3):680-687.

[13] Leo RJ, Ligot JJ. A systematic review of randomized controlled trials of acupuncture in the treatment of depression. J Affect Disord. 2007;97(1-3):13-22.

[14] Zhang ZJ, Chen HY, Yip KC, et al. The effectiveness and safety of acupuncture therapy in depressive disorders: systematic review and meta-analysis. J Affect Disord. 2010;124(1-2):9-21.

[15] Manni L, Albanesi M, Guaragna M, et al. Neurotrophins and acupuncture. Auton Neurosci. 2010;157(1-2):9-17.

[16] Utter GA, Han S, Han JS. Electroacupuncture: mechanisms and clinical application. Biol Psychiatry. 1998;44(2):129-138.

[17] Zhang J, Shang H, Gao X, et al. Acupuncture-related adverse events: a systematic review of the Chinese literature. Bull World Health Organ. 2010;88(12):915-921.

[18] Whiting M, Leavey G, Scammell A, et al. Using acupuncture to treat depression: a feasibility study. Complement Ther Med. 2008;16(2):87-91.

[19] Pilkington K. Anxiety, depression and acupuncture: a review of the clinical research. Auton Neurosci. 2010;157(1-2):91-95.
[20] Yeung AS, Ameral VE, Chuzi SE, et al. A pilot study of acupuncture augmentation therapy in antidepressant partial and non-responders with major depressive disorder. J Affect Disord. 2011;130(1-2):285-289.

[21] Duan DM, Tu Y, Chen LP. Assessment of effectiveness of electroacupuncture and fluoxetine for treatment of depression with physical symptoms. Zhongguo Zhen Jiu. 2008;28(3):167-170.

[22] Zhang WJ, Yang XB, Zhong BL. Combination of acupuncture and fluoxetine for depression: a randomized, double-blind, sham-controlled trial. J Altern Complement Med. 2009;15(8):837-844.

[23] Zhang GJ, Shi ZY, Liu S, et al. Clinical observation on treatment of depression by electro-acupuncture combined with Paroxetine. Chin J Integr Med. 2007;13(3):228-230.

[24] Nierenberg AA, Ostacher MJ, Huffman JC, et al. A brief review of antidepressant efficacy, effectiveness, indications, and usage for major depressive disorder. J Occup Environ Med. 2008;50(4):428-436.

[25] Fang Y, Yuan C, Xu Y, et al. Comparisons of the efficacy and tolerability of extended-release venlafaxine, mirtazapine, and paroxetine in treatment-resistant depression: a double-blind, randomized pilot study in a Chinese population. J Clin Psychopharmacol. 2010;30(4):357-364.

[26] Stor W, Irnich D. Acupuncture: basics, practice, and evidence. Schmerz. 2009;23(4):405-417, 418.

[27] The World Health Organization Quality of Life Assessment (WHOQOL): development and general psychometric properties. Soc Sci Med. 1998;46(12):1569-1585.

[28] Naumann VJ, Byrne GJ. WHOQOL-BREF as a measure of quality of life in older patients with depression. Int Psychogeriatr. 2004;16(2):159-173.

[29] Roschke J, Wolf C, Muller M J, et al. The benefit from whole body acupuncture in major depression. J Affect Disord. 2000;57(1-3):73-81.

[30] Nahas R, Sheikh O. Complementary and alternative medicine for the treatment of major depressive disorder. Can Fam Physician. 2011;57(6):659-663.

[31] Paterson C, Dieppe P. Characteristic and incidental (placebo) effects in complex interventions such as acupuncture. BMJ. 2005;330(7501):1202-1205.

[32] Wang XJ, Wang LL. A mechanism of endogenous opioid peptides for rapid onset of acupuncture effect in treatment of depression. Zhong Xi Yi Jie He Xue Bao. 2010;8(11):1014-1017.

[33] ICD-10 (International Classification of Disease): a new way with speed bumps? Discussed on the example of depression, anxiety and sleep disorders. Psychiatr Prax. 1996;23(1 Suppl):1-8.

[34] Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;23:56-62.

[35] State Council of the People's Republic of China. Administrative Regulations on Medical Institution. 1994-09-01.

[36] Liu LG, Gu J, Wong ZM. Analysis on acupuncture treatment characteristics for depression syndrome in ancient medical literature. Zhong Xi Yi Jie He Xue Bao. 2004;2(5):339, 342.

[37] GB/T12346-2006, Name and location of Acupoints: Chinese National Standards. 2006.

[38] Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group. Psychol Med. 1998;28(3):551-558.

[39] Ohaeri JU, Awadalla AW, El-Abassi AH, et al. Confirmatory factor analytical study of the WHOQOL-Bref: experience with Sudanese general population and psychiatric samples. BMC Med Res Methodol. 2007;7:37.

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