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Can acupuncture combined with SSRIs improve clinical symptoms and quality of life in patients with depression? Secondary outcomes of a pragmatic randomized controlled trial

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ABSTRACT

Objectives: To explore the effects of acupuncture (manual acupuncture or electroacupuncture) combined with SSRIs for moderate to severe depression improving major clinical symptoms and life quality of the patients on secondary outcomes.
Design: Pragmatic, parallel, randomized controlled trial.
Setting: 6 hospitals in China.
Interventions: 6 weeks of manual acupuncture (MA) + selective serotonin reuptake inhibitors (SSRIs), electroacupuncture (EA) + SSRIs, and SSRIs alone.
Main outcome measures: The primary outcome was response rate of 17-item Hamilton Depression Scale (HAMD-17) total score at 6th week. The secondary outcomes reported in this analysis were HAMD-17 factor scores at 1st, 2nd, 4th, 6th, 10th week and WHO Quality of Life-BREF (WHOQOL-BREF) scores at 6th week.
Results: 477 patients were randomly assigned into MA + SSRIs (n = 161), EA + SSRIs (n = 160), or SSRIs alone (n = 156) groups. For HAMD-17 (at 6th week), the MA + SSRIs group was significantly better than the SSRIs alone group in retardation factor ($p = 0.008$), while the EA + SSRIs group was significantly better than the SSRIs alone group in anxiety/somatization factor ($p < 0.001$) and sleep disturbance factor ($p = 0.002$). For WHOQOL-BREF (at 6th week), the EA + SSRIs group, compared with the SSRIs alone group, produced a more significant improvement in the overall quality of life, general health, physical health, and psychological health ($p < 0.05$). While, the MA + SSRIs group, compared to the SSRIs alone group, showed significant advantage only in psychological health ($p = 0.023$).
Conclusions: Either MA or EA combined SSRIs treatment could improve symptoms and quality of life for patients with moderate to severe depression. The main limitation of this trial was not using a sham control therefore the placebo effect could not be excluded.

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1. Introduction

Depression is typically manifested as constant low mood, loss of interest, and chronic fatigue. An estimate of 322 million patients globally suffer from depression and this number increased by 18.4% from 2005 to 2015.[1] Depression is considered the largest independent contributor to non-fatal health loss.[1]

More and more psychiatrists believe that the main goal of treatment for depression shall focus on symptomatic remission for individual patient. [2–4] So that investigate in patients' symptom profile is the key to personalized treatment.[2] Second-generation antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs), are the most commonly prescribed antidepressants. Despite improved tolerability of new antidepressants,[5] 63% of patients did not achieve remission after initial treatment, and the likelihood of remission descents along with steps of later treatment.[6] Most non-remitters suffered from residual symptoms, such as core mood symptoms, somatic symptoms, anxiety, and insomnia,[3,7] which increased the risks of recurrence that usually associate with more severe and chronic disease course.[8,9] Considering the burden of depression disease and limitations of available treatments, new strategies to enhance the efficacy of antidepressants in the early stage of treatment are greatly in need.[7]

With or without antidepressants, acupuncture has been widely used for treating depression for many years, in two main styles, manual acupuncture (MA) and electroacupuncture (EA). MA is the most traditional form of acupuncture in China and is characterized by manual manipulation of fine needles after insertion into specific acupoints for therapeutic purposes.[10] EA is to apply a small electric current between a pair of acupuncture needles after manual manipulating the needles as in MA in order to restore and maintain health.[11]

We conducted a three-armed pragmatic RCT (AcuSDep, n = 477) to compare MA plus SSRIs, EA plus SSRIs versus SSRIs alone in a period of ten weeks. In this paper, we aimed to explore major clinical symptoms measured by factor scores of 17-item Hamilton Depression Scale (HAMD-17)[12] and quality of life measured by WHO Quality of Life-BREF (WHOQOL-BREF).[13] Five factors in HAMD-17 were examined: retardation, cognitive impairment, anxiety/somatisation, sleep disturbance, and weight. In addition, we also examined overall quality of life, general health, physical health, psychological health, social relationships, and environment in WHOQOL-BREF. Evaluating improvements of certain specific clinical symptoms and quality of life measures could help us understand in which areas MA/EA plus SSRIs treatments could contribute most.[10] Identifying the most responsive domains of each of the two combined treatments would allow us to provide specific evidence and, therefore, suggest the targeted intervention strategy for individualized and effective clinical practice.

2. Materials and methods

2.1. Design

In this three-arm (MA + SSRIs, EA + SSRIs, SSRIs) pragmatic RCT, eligible patients with clear diagnosis of depression were recruited from the outpatient departments of Sixth Hospital of Peking University, the Sixth Hospital of Baotou City, Guangdong 999 Brain Hospital, Guangzhou Overseas Chinese Hospital, Nanfang Hospital, and Nanjing Brain Hospital affiliated to Nanjing Medical University. Patients (18–60 years old) were eligible if they fulfilled ICD-10 (F32) criteria for depressive episodes,[14] confirmed to be during the first episode, and had a HAMD-17 score ≥ 17. Patients were excluded if diagnosed with bipolar depression, suicidal tendencies, pregnant or lactating, other severe diseases requiring treatment, suffering from other brain diseases, or participated in other clinical trials within a prior period of four weeks, taking antidepressants or the pharmacological effects of such antidepressants had not been washed out.

The protocol of this trial was approved by the medical ethics committees of participating centres. The CONSORT statement (Text S1) and the STRICTA criteria (Text S2) were followed in this trial. Informed consent in writing was delivered to and signed by all participating patients before enrolment.

2.2. Randomization and blinding

Simple randomization method was used. Random sequence was generated by SAS 9.2 (SAS Institute, Cary, NC, USA). Eligible patients were randomly allocated (1:1:1) via a central telephone randomization to receive either MA + SSRIs, or EA + SSRIs, or SSRIs alone. The treatments were for six weeks and attached a follow-up for another four weeks thereafter. Data analysts were blinded. Outcome assessors for HAMD-17 were blinded in five hospitals. The patients and acupuncturists were not blinded.

2.3. Intervention

The usual dosage of oral SSRIs was prescribed for all these three groups for a period of six weeks. On top of SSRIs treatment, MA or EA treatments were add on to the MA + SSRIs group and the EA + SSRIs group respectively. The add-on acupuncture treatments were applied as 30 min per session, three sessions per week for a period of six weeks (Fig. S1). Further details of the interventions are presented in Method S1 and Method S2.

2.4. Outcomes

For the whole trial, response rate of HAMD-17 total score at 6^{th} week was defined as the primary outcome, which will be presented together with other outcomes (HAMD-17 remission rate, early onset rate, and total score; Self-Rating Depression Scale (SDS) total score; Clinical Global Impression (CGI: SI, GI, EI) score, Rating Scale for Side Effects (SERS) total and domain score) in another separate paper. For this paper, we aim to report HAMD-17 factors and WHOQOL-BREF scores.

HAMD-17 factors were rated at baseline, 1^{st}, 2^{nd}, 4^{th}, 6^{th}, and 10^{th} week. And scores by WHOQOL-BREF were collected at baseline and 6^{th} week.

The five factors of HAMD-17 include: retardation, cognitive impairment, anxiety/somatisation, sleep disturbance, and weight. The retardation (14 points) consists of (1) depressed mood; (2) loss of interest in activity, hobbies or work; (3) slowness of thought and speech, impaired ability to concentrate, decreased motor activity; and (4) sexual symptoms. The cognitive impairment (12 points) consists of (1) feelings of guilt; (2) suicide; and (3) agitated behaviour. The anxiety/somatisation (18 points) consists of (1) psychic anxiety (subjective tension and irritability, loss of concentration, worrying about minor matters, apprehension, fears expressed without questioning, feelings of panic, and feeling jumpy); (2) somatic anxiety (physiological concomitants of anxiety: dry mouth, abdominal distension, diarrhea, belching, cramps, palpitations, headaches, hyperventilation, sighing, urinary frequency, and sweating); (3) gastro-intestinal symptoms; (4) general somatic symptoms (heaviness in limbs, back or head, backaches, headaches, muscle aches, loss of energy, and fatigability); (5) hypochondriasis; and (6) insight (acknowledge/deny being ill). The sleep disturbance (6 points) consists of (1) difficulty in falling asleep; (2) light sleep; and (3) early awakening. The weight (2 points) refers to loss of weight.

WHOQOL-BREF scores were collected in two independent items including overall quality of life (5 points) and general health (5 points), and four domains covering physical health (20 points), psychological health (20 points), social relationships (20 points), and environment (20 points).

2.5. Statistical analysis

160 patients were required for each group for 0.9 power to detect a significant difference ($\alpha = 0.05$, two-tailed test, dropout rate of 20%) based on the response rate (defined as reduction of HAMD-17 total score ≥ 50% from baseline) of 60%[15] in the control group and 80%[16–18] in the acupuncture add-on groups. A modified intention-to-treat (mITT) approach was taken using last observation carried forward (LOCF) to handle missing data. Participants who completed baseline evaluation and at least one treatment were included in mITT analysis. The Kruskal-Wallis test was used for inter-group comparisons among all three groups. The Nemenyi Rank-Sum test and mean difference with 95% confidence intervals (95% CIs) were used for pair-wise comparisons between any of two groups. The generalized linear mixed model was used to detect repeatedly measured data. Categorical variables were analysed with the Chi-square (χ^2) test. Significance was defined as a two-tailed $p < 0.05$. All analyses were carried out exploratorily using SPSS 22.0 software (IBM Corporation, Armonk, NY, USA).

3. Results

3.1. Participant characteristics

Interested patients (number not documented) were screened for eligibility and randomly assigned to MA + SSRIs group (n = 161), EA + SSRIs group (n = 160), and SSRIs group (n = 156). The mITT sample included 465 (97.5%) patients (157, 153, and 155 each). 385 (80.7%) patients (129, 122, and 134 each) completed four weeks' follow-ups. There was no significant imbalance at baseline among the three groups (Fig. S2, Table 1). The types of SSRIs and drug combinations used during six weeks' treatment are listed in Table S1. Details of acupuncturists are revealed in Result S1.

3.2. Outcomes

3.2.1. HAMD-17 factors

For repeatedly measured data, significantly differences were observed among the three groups in every HAMD factors ($p < 0.001$). For retardation factor, significant differences were observed at the 1st, 4th, 6th, 10th week among all three groups ($p < 0.05$). The improvement in the MA + SSRIs group was significantly better than that of the SSRIs alone group in general, except for the 2nd week ($p < 0.05$). The improvement in the EA + SSRIs group was also significantly better than the SSRIs alone group at the 4th and 10th week ($p < 0.05$). No significant difference was observed in other pair-wise comparisons for retardation. For anxiety/somatization factor, significant differences were noticed for each of all three groups at the 1st, 2nd, 4th, 6th, 10th week ($p < 0.05$). The improvement in the EA + SSRIs group was significantly better than that of the SSRIs group ($p < 0.05$). No significant differences were observed between the MA + SSRIs group and the SSRIs alone group as well as in between the two acupuncture add-on groups in this aspect. For sleep disturbance factor, significant differences were observed throughout the six weeks of treatment as well as the four weeks of follow-up ($p < 0.01$). The improvement in the EA + SSRIs group was all the way significantly better than that in the SSRIs alone group ($p < 0.01$), and it was also significantly better than that in the MA + SSRIs group at the 10th week ($p = 0.024$). The improvement in the MA + SSRIs group was also significantly better than that in the SSRIs alone group at the 1st and 2nd week ($p < 0.05$). No significant differences were revealed in other pair-wise comparisons. The cognitive impairment as well as the weight factors made no difference at all among all these three groups (Fig. 1, Fig. S3, Table 2).

3.2.2. WHOQOL-BREF scores

Significant differences were observed at the 6th week among these three groups in the fields of overall quality of life, general health, physical health, and psychological health ($p < 0.05$). The EA + SSRIs group produced a significantly improvement in these fields compared with the SSRIs alone group ($p < 0.05$). However, in the MA + SSRIs group, only improvement in psychological health was superior to the SSRIs alone group ($p = 0.023$). There was no significant difference in other pair-wise comparisons. Also no significant differences were observed in the fields of social relationships and environment domains among these three groups (Table 3).

4. Discussion

4.1. Summary of findings

The outcomes showed that acupuncture (both MA and EA) combined with SSRIs were effective to improve depressive symptoms in moderate to severe depression with little cognitive impairment. Retardation symptoms, for instance, were improved by applying either practice, though better improvements shown by MA plus SSRIs. And symptoms in anxiety, somatization, and sleep disturbance were improved by EA plus SSRIs. No significant effect on patients' weight was

Table 1
Baseline characteristics of patients with depression (ITT).

Variables	MA + SSRIs (N = 161)	EA + SSRIs (N = 160)	SSRIs alone (N = 156)	Inter-group comparison *p* value	Total (N = 477)
Female [a] (n, %)	105, 65.2	108, 67.5	99, 63.5	0.751	312, 65.4
Age [b]	41.42 ± 12.53	41.18 ± 12.00	41.76 ± 12.85	0.886	41.45 ± 12.44
Duration of depression [b] (months)	12.83 ± 17.09	10.77 ± 15.32	9.52 ± 13.85	0.113	11.05 ± 15.51
HAMD-17					
Retardation [b] (14 points)	6.98 ± 1.84	7.25 ± 1.80	7.03 ± 1.64	0.135	7.09 ± 1.76
Cognitive impairment [b] (12 points)	3.56 ± 1.87	3.53 ± 1.86	3.31 ± 1.72	0.437	3.47 ± 1.82
Anxiety / somatization [b] (18 points)	9.04 ± 2.61	8.97 ± 2.62	8.75 ± 2.68	0.511	8.92 ± 2.63
Sleep disturbance [b] (6 points)	4.43 ± 1.59	4.51 ± 1.65	4.60 ± 1.68	0.372	4.51 ± 1.64
Weight [b] (2 points)	0.71 ± 0.75	0.83 ± 0.81	0.83 ± 0.77	0.362	0.79 ± 0.78
WHOQOL-BREF					
Overall quality of life [b] (5 points)	2.29 ± 0.84	2.19 ± 0.95	2.26 ± 0.84	0.378	2.24 ± 0.88
General health [b] (5 points)	1.91 ± 0.67	1.79 ± 0.65	1.94 ± 0.71	0.134	1.88 ± 0.68
Physical health [b] (20 points)	9.70 ± 2.34	9.53 ± 2.09	9.64 ± 1.79	0.967	9.62 ± 2.09
Psychological health [b] (20 points)	9.30 ± 2.20	9.29 ± 2.15	9.44 ± 1.93	0.734	9.34 ± 2.10
Social relationships [b] (20 points)	11.85 ± 2.77	11.60 ± 2.38	11.67 ± 2.38	0.695	11.71 ± 2.52
Environment [b] (20 points)	12.07 ± 1.95	11.93 ± 1.95	12.34 ± 1.89	0.148	12.11 ± 1.94

ITT, intention-to-treat; MA, manual acupuncture; EA, electroacupuncture; SSRIs, selective serotonin reuptake inhibitors; HAMD-17, 17-item Hamilton Rating Scale for Depression; WHOQOL-BREF, WHO Quality of Life-BREF. a. Categorical data were analyzed using the Chi-square (χ^2) test; b. Continuous data were evaluated by the Kruskal-Wallis test.

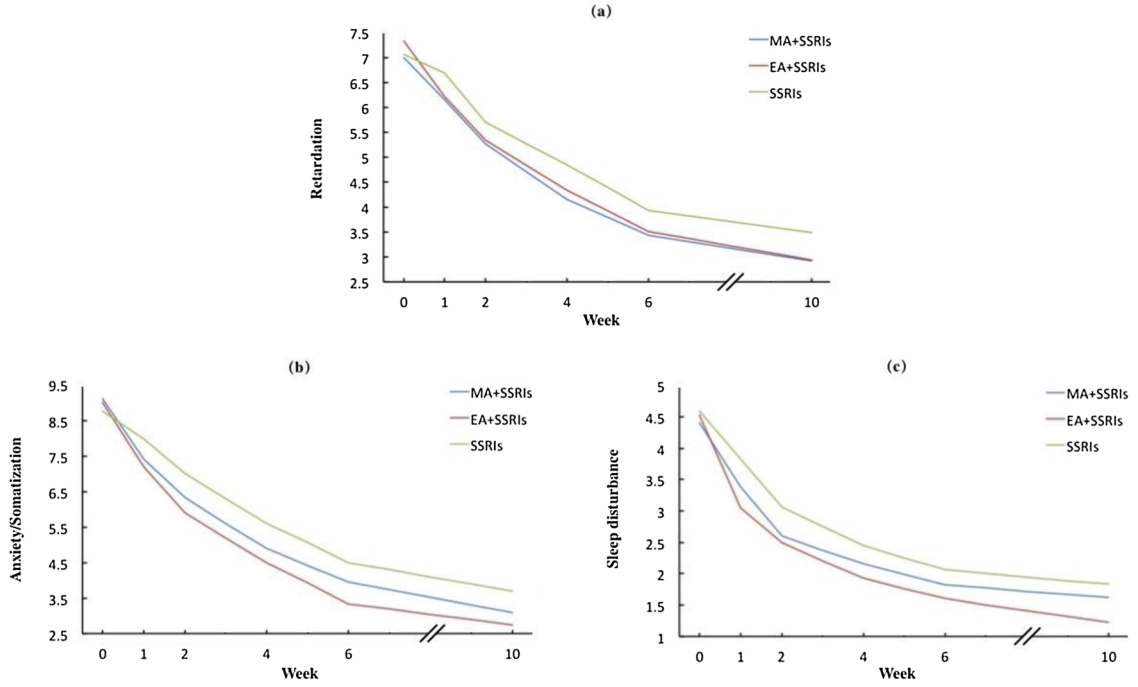

Fig. 1. Trend of HAMD-17 factor scores during six weeks of treatment and four weeks of follow-up (mITT). (a) Retardation; (b) Anxiety/Somatization; (c) Sleep disturbance. HAMD-17, 17-item Hamilton Rating Scale for Depression; mITT, modified intention-to-treat; MA, manual acupuncture; EA, electroacupuncture; SSRIs, Selective serotonin reuptake inhibitors.

noticed in applying either practice (Fig. 1, Fig. S3, Table 2). In life quality perspective, psychological health of patients showed improvement in the cases of both combined acupuncture treatments. Additionally, the overall quality of life, general health and physical health, were improved by EA plus SSRIs as well (Table 3).

4.2. Strength and limitations

In this study, a comprehensive comparison was conducted in the dominant clinical targets for depression between MA plus SSRIs and EA plus SSRIs. The objective assessments on disease-related symptoms by doctors (HAMD-17) were complemented with the overall health-related subjective experiences of patients in physical, psychological, social, and environmental aspects (WHOQOL-BREF). Our treatment protocols were derived from, therefore representative and compliance with, routine treatment recipes of acupuncture and SSRIs in China. The rational sample size and a completion rate throughout this trial are also support the confidence level of the outcomes. However, for a limitation, considering the substantial risk of failure in blinding of Chinese patients with rich acupuncture experience,[19,20] a sham control was not used, thus the placebo effect could not be excluded. The post treatment follow-up was limited to only four weeks beginning from the end of six weeks' treatment, thus the long-term antidepressant effects of acupuncture combined therapies remained unknown beyond that point. Also a relatively low baseline score on cognitive impairment factor due to the exclusion of patients with suicidal tendencies in our study lead to, therefore, a necessity of an evaluation on the effectiveness and safety of acupuncture combined with SSRIs for such patients. More studies have recently confirmed the correlation between depression and obesity.[21] Obesity increases the risk of depression and depression in turn predicts the development of obesity.[22] Both gain and loss weight were listed as manifestations of major depressive disorder in the DSM-V diagnostic criteria.[23] The influence on weight gain was not evaluated in this study, however only loss weight is referred as a factor in HAMD-17.

4.3. The implications of future practice and research

The heterogeneity of the depression subtypes plays a key role in the first treatment remission.[7] Personalized treatment should target specific symptoms or symptom clusters to help patients achieve completely functional recovery.[7] Our study observed different characteristics and advantages of MA plus SSRIs and EA plus SSRIs via detailed analysis of HAMD factors and quality of life, suggesting that psychiatrists could select treatment strategies according to patients' clinical features and main symptoms at the beginning of treatment. In depressed patients who responded to antidepressant treatment without achieving remission, 96% suffered residual core mood symptoms, 94% suffered residual anxiety symptoms, 76% suffered residual insomnia symptoms, and 70% suffered residual somatization symptoms.[3] Typical depressive symptoms included depressed mood, loss of interest and pleasure, and fatigue,[14] which are closely related to part items of HAMD-17 retardation factor ("depressed mood" and "loss of interest in activity, hobbies or work"). For patients without suicidal tendencies, but characterized by typical depressed emotional symptoms with impaired psychological health, add-on MA treatment might be a recommended choice. It was reported that depression with high levels of anxiety was associated with severe illness, longer course, and less likelihood of remission,[24,25] and might also increase the risk of recurrence.[27] Residual somatic symptoms were related to functional impairment.[3] Insomnia was indicated a poor clinical outcome,[7] and would lead to depressive recurrence.[26] For patients suffering from these symptoms as well as physical and psychological threats, add-on EA treatment could be recommended by psychiatrists and acupuncturists. Future research in HAMD factors targeted at in individual subgroups would promote deeper understanding and lead to more effective heterogeneity treatment. It is worth noting that the different results between add-on acupuncture groups with SSRIs group should not be attributed solely to the effects of MA and EA. There may be other possibilities, such as the Hawthorne effect and synergistic effect. Further studies are needed to explore the component of the extra add-on therapeutic effects.

Table 2
HAMD factor scores in six weeks' treatment and four weeks' follow-up (mITT).

Variables	MA + SSRIs (N)	EA + SSRIs (N)	SSRIs alone (N)	Inter-group comparison *p* value [a]	Pair-wise comparison						Repeatedly measured data *p* value [c]
					MA + SSRIs vs. SSRIs (95% CI)	*p1* value [b]	EA + SSRIs vs. SSRIs (95% CI)	*p2* value [b]	MA + SSRIs vs. EA + SSRIs (95% CI)	*p3* value [b]	
Retardation (14 points)											< 0.001
Baseline	7.00 ± 1.85 (157)	7.33 ± 1.75 (153)	7.06 ± 1.59 (155)	0.072	−0.06 (-0.44, 0.32)	0.750	0.27 (-0.10, 0.64)	0.329	−0.33 (-0.73, 0.07)	0.079	
1 week	6.16 ± 1.77 (157)*	6.22 ± 1.81 (153)	6.69 ± 1.68 (155)	0.013	−0.53 (-0.91, -0.15)	0.020	−0.47 (-0.86, -0.08)	0.099	−0.06 (-0.46, 0.34)	0.817	
2 week	5.27 ± 1.86 (157)	5.34 ± 1.91 (153)	5.70 ± 1.58 (155)	0.064	−0.43 (-0.81, -0.05)	0.084	−0.36 (-0.75, 0.03)	0.219	−0.07 (-0.49, 0.35)	0.894	
4 week	4.15 ± 2.05 (157)*	4.34 ± 1.89 (153)*	4.85 ± 1.65 (155)	0.002	−0.70 (-1.11, -0.29)	0.003	−0.51 (-0.91, -0.11)	0.046	−0.19 (-0.63, 0.25)	0.633	
6 week	3.43 ± 1.96 (157)*	3.51 ± 1.88 (153)	3.93 ± 1.70 (155)	0.005	−0.50 (-0.91, -0.09)	0.008	−0.42 (-0.82, -0.02)	0.068	−0.08 (-0.96, 0.80)	0.734	
10 week (follow-up)	2.92 ± 1.59 (132)*	2.94 ± 1.59 (125)*	3.49 ± 1.52 (135)	0.002	−0.57 (-0.94, -0.20)	0.006	−0.55 (-0.93, -0.17)	0.018	−0.02 (-0.41, 0.37)	0.952	
Cognitive impairment (12 points)											< 0.001
Baseline	3.57 ± 1.89 (157)	3.58 ± 1.84 (153)	3.30 ± 1.72 (155)	0.343	0.27 (-0.13, 0.67)	0.448	0.28 (-0.12, 0.68)	0.444	−0.01 (-0.44, 0.42)	0.999	
1 week	2.46 ± 1.57 (157)	2.38 ± 1.60 (153)	2.77 ± 1.75 (155)	0.190	−0.31 (-0.68, 0.06)	0.441	−0.39 (-0.76, -0.02)	0.213	0.08 (-0.27, 0.43)	0.887	
2 week	1.83 ± 1.47 (157)	1.69 ± 1.57 (153)	2.11 ± 1.64 (155)	0.052	−0.28 (-0.63, 0.07)	0.430	−0.42 (-0.78, -0.06)	0.051	0.14 (-0.20, 0.48)	0.517	
4 week	1.25 ± 1.27 (157)	1.28 ± 1.37 (153)	1.52 ± 1.55 (155)	0.341	−0.27 (-0.58, 0.04)	0.454	−0.24 (-0.57, 0.09)	0.435	−0.03 (-0.32, 0.26)	0.999	
6 week	0.93 ± 1.26 (157)	0.88 ± 1.10 (153)	1.03 ± 1.41 (155)	0.814	−0.10 (-0.40, 0.20)	0.856	−0.15 (-0.43, 0.13)	0.871	−0.05 (-0.21, 0.31)	1.000	
10 week (follow-up)	0.64 ± 0.87 (132)	0.54 ± 0.87 (125)	0.68 ± 0.96 (135)	0.407	−0.04 (-0.26, 0.18)	0.997	−0.14 (-0.36, 0.08)	0.482	0.10 (-0.11, 0.31)	0.533	
Anxiety / somatization (18 points)											< 0.001
Baseline	9.10 ± 2.55 (157)	9.00 ± 2.60 (153)	8.75 ± 2.69 (155)	0.408	0.35 (-0.23, 0.93)	0.457	0.25 (-0.34, 0.84)	0.586	0.10 (-0.47, 0.67)	0.978	
1 week	7.41 ± 2.70 (157)	7.20 ± 2.67 (153)*	7.97 ± 2.71 (155)	0.040	−0.56 (-1.16, 0.04)	0.213	−0.77 (-1.37, -0.17)	0.048	0.21 (-0.39, 0.81)	0.771	
2 week	6.33 ± 2.69 (157)	5.90 ± 2.80 (153)*	6.99 ± 2.67 (155)	< 0.001	−0.66 (-1.25, -0.07)	0.057	−1.09 (-1.70, -0.48)	< 0.001	0.43 (-0.18, 1.04)	0.288	
4 week	4.89 ± 2.69 (157)	4.50 ± 2.71 (153)*	5.61 ± 2.76 (155)	0.001	−0.72 (-1.32, -0.12)	0.094	−1.11 (-1.72, -0.50)	0.001	0.39 (-0.21, 0.99)	0.338	
6 week	3.94 ± 2.45 (157)	3.34 ± 2.28 (153)*	4.50 ± 2.79 (155)	< 0.001	−0.56 (-1.14, 0.02)	0.224	−1.16 (-1.73, -0.59)	< 0.001	0.60 (0.07, 1.13)	0.069	
10 week (follow-up)	3.09 ± 1.75 (132)	2.74 ± 1.77 (125)*	3.69 ± 2.17 (135)	< 0.001	−0.60 (-1.07, -0.13)	0.076	−0.95 (-1.43, -0.47)	0.001	0.35 (-0.08,0.78)	0.261	
Sleep disturbance (6 points)											< 0.001
Baseline	4.41 ± 1.59 (157)	4.54 ± 1.62 (153)	4.59 ± 1.69 (155)	0.310	−0.18 (-0.54, 0.18)	0.313	−0.05 (-0.42, 0.32)	0.836	−0.13 (-0.49, 0.23)	0.656	
1 week	3.38 ± 1.57 (157)*	3.05 ± 1.57 (153)*	3.83 ± 1.59 (155)	< 0.001	−0.45 (-0.80, -0.10)	0.047	−0.78 (-1.13, -0.43)	< 0.001	0.33 (-0.02, 0.68)	0.257	
2 week	2.60 ± 1.44 (157)*	2.49 ± 1.55 (153)*	3.06 ± 1.44 (155)	0.001	−0.46 (-0.78, -0.14)	0.012	−0.57 (-0.90, -0.24)	0.003	0.11 (-0.22, 0.44)	0.876	
4 week	2.16 ± 1.38 (157)	1.93 ± 1.40 (153)*	2.45 ± 1.28 (155)	0.001	−0.29 (-0.59, 0.11)	0.082	−0.52 (-0.82, -0.22)	0.001	0.23 (-0.08, 0.54)	0.339	

(*continued on next page*)

Table 2 (*continued*)

Variables	MA + SSRIs (N)	EA + SSRIs (N)	SSRIs alone (N)	Inter-group comparison *p* value [a]	Pair-wise comparison						Repeatedly measured data *p* value [c]
					MA + SSRIs vs. SSRIs (95% CI)	*p1* value [b]	EA + SSRIs vs. SSRIs (95% CI)	*p2* value [b]	MA + SSRIs vs. EA + SSRIs (95% CI)	*p3* value [b]	
6 week	1.82 ± 1.35 (157)	1.60 ± 1.22 (153)[*]	2.06 ± 1.14 (155)	0.002	−0.24 (-0.52, 0.04)	0.090	−0.46 (-0.72, -0.20)	0.002	0.22 (-0.07, 0.51)	0.422	
10 week (follow-up)	1.62 ± 1.16 (132)	1.22 ± 0.93 (125)[*,#]	1.83 ± 1.13 (135)	< 0.001	−0.21 (-0.48, 0.06)	0.304	−0.61 (-0.86, -0.36)	< 0.001	0.40 (0.14, 0.66)	0.024	
Weight (2 points)											< 0.001
Baseline	0.71 ± 0.75 (157)	0.82 ± 0.81 (153)	0.83 ± 0.77 (155)	0.364	−0.12 (-0.29, 0.05)	0.398	−0.01 (-0.19, 0.17)	0.955	−0.11 (-0.28, 0.06)	0.577	
1 week	0.33 ± 0.57 (157)	0.35 ± 0.61 (153)	0.42 ± 0.61 (155)	0.274	−0.09 (-0.22, 0.04)	0.370	−0.07 (-0.21, 0.07)	0.384	−0.02 (-0.15, 0.11)	1.000	
2 week	0.23 ± 0.47 (157)	0.24 ± 0.48 (153)	0.26 ± 0.46 (155)	0.568	−0.03 (-0.13, 0.07)	0.646	−0.02 (-0.13, 0.09)	0.656	−0.01 (-0.12, 0.10)	1.000	
4 week	0.14 ± 0.38 (157)	0.12 ± 0.34 (153)	0.15 ± 0.37 (155)	0.723	−0.01 (-0.09, 0.07)	0.938	−0.03 (-0.11, 0.05)	0.727	0.02 (-0.06, 0.10)	0.906	
6 week	0.11 ± 0.34 (157)	0.11 ± 0.37 (153)	0.14 ± 0.37 (155)	0.496	−0.03 (-0.22, 0.16)	0.763	−0.03 (-0.11, 0.05)	0.522	0.00 (-0.08, 0.08)	0.919	
10 week (follow-up)	0.06 ± 0.27 (132)	0.02 ± 0.15 (125)	0.06 ± 0.24 (135)	0.355	0.00 (-0.06, 0.06)	0.977	−0.04 (-0.09, 0.01)	0.439	0.04 (-0.01, 0.09)	0.568	

HAMD-17, 17-item Hamilton Rating Scale for Depression; mITT, modified intention-to-treat; MA, manual acupuncture; EA, electroacupuncture; SSRIs, selective serotonin reuptake inhibitors. *p1*, MA + SSRIs vs. SSRIs alone; *p2*, EA + SSRIs vs. SSRIs alone; *p3*, MA + SSRIs vs. EA + SSRIs. [*] $p < 0.05$ vs. SSRIs alone; [#] $p < 0.05$ vs. MA + SSRIs. a. Inter-group comparisons were evaluated by the Kruskal-Wallis test; b. Pair-wise comparisons between two groups were assessed by the Nemenyi Rank-Sum test; c. Repeatedly measured data (10 weeks' period) were tested through the generalized linear mixed model.

Table 3
WHOQOL-BREF scores at 6th week (mITT).

WHOQOL-BREF	MA + SSRIs (n = 157)	EA + SSRIs (n = 153)	SSRIs alone (n = 155)	Inter-group comparison *p* value [a]	Pair-wise comparison					
					MA + SSRIs vs. SSRIs (95% CI)	*p1* value [b]	EA + SSRIs vs. SSRIs (95% CI)	*p2* value [b]	MA + SSRIs vs. EA + SSRIs (95% CI)	*p3* value [b]
Overall quality of life (5 points)										
Baseline	2.28 ± 0.85	2.14 ± 0.92	2.25 ± 0.84	0.225	0.03 (-0.16, 0.22)	0.971	−0.11 (-0.31, 0.09)	0.396	0.14 (-0.06, 0.34)	0.274
6 week	3.06 ± 0.68	3.17 ± 0.78*	2.91 ± 0.73	0.003	0.15 (-0.01, 0.31)	0.180	0.26 (0.09, 0.43)	0.004	−0.11 (-0.27, 0.05)	0.310
General health (5 points)										
Baseline	1.90 ± 0.67	1.78 ± 0.65	1.94 ± 0.71	0.116	−0.04 (-0.19, 0.11)	0.888	−0.16 (-0.31, -0.01)	0.135	0.12 (-0.03, 0.27)	0.315
6 week	2.92 ± 0.77	2.94 ± 0.83*	2.73 ± 0.72	0.021	0.19 (0.02, 0.36)	0.101	0.21 (0.04, 0.38)	0.035	−0.02 (-0.20, 0.16)	0.900
Physical health (20 points)										
Baseline	9.69 ± 2.36	9.53 ± 2.11	9.64 ± 1.80	0.971	0.05 (-0.42, 0.52)	0.997	−0.11 (-0.55, 0.33)	0.980	0.16 (-0.34, 0.66)	0.963
6 week	12.31 ± 2.09	12.47 ± 2.27*	11.94 ± 1.82	0.031	0.37 (-0.06, 0.80)	0.368	0.53 (0.07, 0.99)	0.032	−0.16 (-0.65, 0.33)	0.470
Psychological health (20 points)										
Baseline	9.30 ± 2.22	9.29 ± 2.18	9.42 ± 1.92	0.766	−0.12 (-0.58, 0.34)	0.955	−0.13 (-0.59, 0.33)	0.759	0.01 (-0.48, 0.50)	0.907
6 week	12.53 ± 2.27*	12.50 ± 2.14*	11.92 ± 1.67	0.002	0.61 (0.17, 1.05)	0.023	0.58 (0.15, 1.01)	0.004	0.03 (-0.46, 0.52)	0.825
Social relationships (20 points)										
Baseline	11.82 ± 2.79	11.55 ± 2.33	11.65 ± 2.38	0.688	0.17 (-0.41, 0.75)	0.887	−0.10 (-0.63, 0.43)	0.939	0.27 (-0.30, 0.84)	0.700
6 week	13.37 ± 2.51	13.25 ± 2.10	13.08 ± 1.95	0.352	0.29 (-0.21, 0.79)	0.359	0.17 (-0.28, 0.62)	0.704	0.12 (-0.39, 0.63)	0.842
Environment (20 points)										
Baseline	12.05 ± 1.95	11.90 ± 1.98	12.32 ± 1.89	0.136	−0.27 (-0.70, 0.16)	0.399	−0.42 (-0.85, 0.01)	0.149	0.15 (-0.29, 0.59)	0.832
6 week	13.25 ± 2.01	13.17 ± 2.03	12.72 ± 1.75	0.051	0.53 (0.11, 0.95)	0.130	0.45 (0.03, 0.87)	0.090	0.08 (-0.37, 0.53)	0.982

WHOQOL-BREF, WHO Quality of Life-BREF; mITT, modified intention-to-treat; MA, manual acupuncture; EA, electroacupuncture; SSRIs, selective serotonin reuptake inhibitors. *p1*, MA + SSRIs vs. SSRIs alone; *p2*, EA + SSRIs vs. SSRIs alone; *p3*, MA + SSRIs vs. EA + SSRIs. * $p < 0.05$ vs. SSRIs alone; # $p < 0.05$ vs. MA + SSRIs, however there was none. a. Inter-group comparisons were evaluated by the Kruskal-Wallis test; b. Pair-wise comparisons between two groups were assessed by the Nemenyi Rank-Sum test.

5. Conclusions

Either MA or EA combined with SSRIs could improve symptoms and quality of life for patients with moderate to severe depression. Based on HAMD-17, MA combined with SSRIs demonstrated an advantage in improving retardation, while EA combined with SSRIs was superior in improving anxiety, somatization, and sleep disturbance. By WHOQOL-BREF, both combined acupuncture treatments could improve psychological health, while EA combined with SSRIs could also improve the overall quality of life, general health, and physical health.

Data availability

The dataset used to support the findings of this study are available from the corresponding authors upon request.

Author contributions

Tuya Bao generated the idea. Zhigang Li and Xiangqun Wang participated in the design of the trial. Bingcong Zhao, Yutong Fei, Yilin Liang, and Yang Sun all contributed to the drafting of the manuscript. Yuanzheng Wang, Xuehong Ma, and Xueqin Wang were chief investigators at individual clinical centres. Yutong Fei contributed to the methodology. Bingcong Zhao, Yutong Fei, Xinjing Yang, Meng Song, and Tianwei Guo did the statistical analysis. All authors critically reviewed the manuscript and approved the final version.

Conflict of interest

All authors claim no conflict of financial interest. Bingcong Zhao, Zhigang Li, Yuanzheng Wang, Xuehong Ma, Meng Song, Xinjing Yang, and Tianwei Guo are practicing acupuncturists. Bingcong Zhao, Zhigang Li, Xinjing Yang, Yang Sun, Meng Song, Tianwei Guo, and Tuya Bao work or study in an acupuncture education organization. Yutong Fei is the methodologist work in a traditional Chinese medicine university. Xueqin Wang is the consultant of Traditional Chinese Medicine health promotion project by Beijing Administration of Traditional Chinese Medicine.

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Appendix A. Supplementary data

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