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Manual or electroacupuncture as an add-on therapy to SSRIs for depression: A randomized controlled trial

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ABSTRACT

Selective serotonin reuptake inhibitors (SSRIs) are first-line antidepressants, however, only around 60% of patients could benefit from them. Acupuncture is supported by insufficient evidence to help with symptom relieving and SSRIs tolerance. This pragmatic randomized controlled trial compared SSRIs alone versus SSRIs together with manual acupuncture (MA) or electroacupuncture (EA) in moderate to severe depressed patients. Patients were randomly allocated to receive MA + SSRIs (161), EA + SSRIs (160), or SSRIs alone (156) for six weeks, and then followed up for another four weeks. The primary outcome was response rate of the 17-item Hamilton Depression Scale (HAMD-17) at 6th week. The secondary outcomes were HAMD-17 (remission rate, early onset rate, total score), Self-Rating Depression Scale (SDS: total score), Clinical Global Impression (CGI), Rating Scale for Side Effects (SERS: total and domain scores), number of patients with adjusted dosage of SSRIs and adverse events (AEs). Both MA + SSRIs and EA + SSRIs were significantly better than SSRIs at 6th week on HAMD-17 response rate (RR = 1.21, 95% CI 1.04, 1.42, $P = 0.013$; RR = 1.27, 95% CI 1.09, 1.48, $P = 0.0014$), HAMD-17 early onset rate ($P < 0.0001$), HAMD-17 and SDS total scores ($P < 0.05$), CGI ($P < 0.01$), SERS total score ($P < 0.01$), number of patients with increased dosage of SSRIs ($P < 0.01$). For HAMD-17 remission rate, EA + SSRIs was significantly higher than SSRIs ($P = 0.0083$), while MA + SSRIs showed no significant difference at 6th week ($P = 0.092$). No unintended acupuncture-related severe AE was observed. This study identified that both MA and EA showed beneficial effects in addition to SSRIs alone in patients with moderate to severe depression, and were well tolerated.

Clinical trials registration: ChiCTR-TRC-08000297.

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1. Introduction

Depressive disorders are characterized by low mood, loss of interest, guilty feelings or low self-esteem, sleep and appetite disorders, fatigue, and impaired concentration (WHO, 2017). In 2015, an estimated 4.4% of the global population suffered from depressive disorder, and there were about 54.8 million cases in China, accounting for 4.2% of the Chinese population (WHO, 2017). The financial burden of depression is considerable (Krauth et al., 2014). In China, the total cost was estimated at US $6,264 million in 2002, with direct US $986 million and indirect US $5,278 million spends associated with depressive disorders (Hu et al., 2007).

Selective serotonin reuptake inhibitors (SSRIs), such as paroxetine, fluoxetine, sertraline, fluvoxamine, citalopram, and escitalopram, are the first-line antidepressants. The response rate to SSRIs, defined as at least a 50% improvement from baseline, was only around 60% with documented side effects such as nausea, weight gain, and sexual function recession, which limited compliance of the patients to the treatment (Cipriani et al., 2009; Gartlehner et al., 2011).

Acupuncture treatment for depression has been provided alone or together with antidepressants in China and worldwide for years. Manual acupuncture (MA) and electroacupuncture (EA) are two major forms. MA is the most traditional form of acupuncture in China, characterized by manual manipulation of needles after insertion in certain acupuncture points in the body to help with health conditions (Smith et al., 2018). EA is applied with a small electric current passing through one or several sets of two acupuncture needles after basic manipulation of MA acupuncture treatment to achieve treatment goals (China Food and Drug Administration, 2011). Randomized controlled trials (RCTs) revealed some valuable benefits of MA and EA for depression, in increasing response rates and decreasing side effects of antidepressants, compared to antidepressants used alone (Liu et al., 2015; Wang et al., 2013, 2014; Zhang et al., 2012). However, systematic reviews indicated potential benefits supporting MA or EA as add-on therapy, but failed to demonstrate high certainty evidence. This was mainly limited by lack of large-scale trials, high risk of bias, and inconsistent results of the included studies (Chan et al., 2015; Smith et al., 2018; Zhang et al., 2010). More evidence is needed.

The objective of our trial was to evaluate the difference between SSRIs alone versus SSRIs together with MA or EA for patients with moderate to severe depression.

2. Material and methods

2.1. Study design and participants

We conducted a multi-centre pragmatic RCT. Eligible patients with clear diagnosis were enrolled from the outpatients departments of the Sixth Hospital of Peking University (Beijing), the Sixth Hospital of Baotou City (Baotou), Guangdong 999 Brain Hospital (Guangzhou), Guangzhou Overseas Chinese Hospital (Guangzhou), Nanfang Hospital (Guangzhou), and Nanjing Brain Hospital affiliated to Nanjing Medical University (Nanjing).

Patients with depressive episodes were diagnosed according to the International Classification of Diseases 10th Edition (ICD-10, F32) by professional psychiatrists at every centre (WHO, 1992). The inclusion criteria were as follows: (1) confirmed to be during the first episode; (2) had moderate to severe illness, with a score of ≥17 on the 17-item Hamilton Depression Scale (HAMD-17)(Tang and Zhang, 1984); (3) aged 18–60 years. Patients were excluded when they: (1) were diagnosed as bipolar depression; (2) had participated in other clinical trials (all conditions) in the previous four weeks; (3) were taking antidepressants or the pharmacological effects of antidepressants had not been washed out; (4) were pregnant or lactating; (5) were diagnosed with other serious diseases that needed to be treated; (6) had other brain diseases; (7) presented or suspected to have suicidal plan or behaviour.

The protocol of this trial (Supplementary Text S1) was approved by the Medical Ethics Committee (Supplementary Text S2). All patients provided written informed consent prior to being enrolled in the trial, with detail of interventions fully explained. This trial is reported following the CONSORT statement (Supplementary Text S3) and the STRICTA criteria (Supplementary Text S4).

2.2. Randomization and masking

Simple randomization method was used. Random sequence was generated by SAS 9.2 (SAS Institute, Cary, NC, USA). Allocation concealment was achieved by central telephone randomization. Patients were allocated into MA + SSRIs group, EA + SSRIs group, and SSRIs group with the ratio of 1:1:1. Patients and acupuncturists were not blinded. Blinding of outcome assessors for clinician-administered rating scales (HAMD-17, CGI and SERS) were achieved at the Beijing, Nanjing and Guangzhou centres (n = 405). HAMD-17, CGI, and SERS were assessed by acupuncturists at the Baotou centre (n = 72).

2.3. Treatments

Usual dosage of oral paroxetine was prescribed for six weeks in all participating centres, except for the Nanjing centre, where one of the SSRIs medications were selected from paroxetine, fluoxetine, sertraline, fluvoxamine, citalopram, and escitalopram (see explanations in the *Results*). The usual dosage of paroxetine was 10 mg/d in the first two days, and 20 mg/d from the third day. The dosage of all SSRIs was individualised to suit variations in severity of the symptoms. Small dosages of sedative-hypnotics (zolpidem, zopiclone, and short-acting benzodiazepine class of sedatives) were allowed for severe insomnia patients at bedtime when necessary.

In addition to SSRIs, manual acupuncture treatments were given to the MA + SSRIs group 30 min per session, three sessions per week, for a period of six weeks. The locations of acupoints followed WHO standard acupuncture point locations in the Western Pacific regions (World Health Organization Western Pacific Region, 2008). Needle manipulation techniques followed a well-accepted acupuncture textbook in China (Shen, 2007). The acupuncture recipes were developed based on TCM theories, scientific research evidence (Duan et al., 2008; Lv and Wang, 2003), and the consensus among experts from both inside and outside of the research team.

Main acupuncture points: GV20 (Baihui) and EX-HN3 (Yintang). Compulsory auxiliary acupuncture points: GV16 (Fengfu), bilateral GB20 (Fengchi), GV14 (Dazhui), bilateral PC6 (Neiguan), and bilateral SP6 (Sanyinjiao, Fig. 1).

Acupuncture was performed at GV20 with needle tips horizontally toward the back, 0.5–0.8 cun; at EX-HN3 upward perpendicularly, 0.5–0.8 cun; at GV16 toward the mandible, 0.8–1 cun; at GB20 toward the opposite GB20, 1–1.2 cun; at GV14 perpendicularly, 1–1.2 cun; at PC6 and SP6 perpendicularly, 0.5–1 cun. Sequence of needling: GV14 first, GV16 second, and the rest from head to toe. Needles were twirled at GV14 and GV16 slowly with a small angle (90 °–180°) between 60 and 90 times/min for 30 s, and then withdrew slowly.

Needles at GV20, EX-HN3, GB20, PC6, and SP6 were retained for 30 min after achieving a needling sensation. Needles were manipulated for 5–10 s at the 15th minute. One or two additional acupuncture points were permitted to suit patients' symptoms.

In EA + SSRIs group, GV14, GV16, PC6, and SP6 were stimulated following the same rules as in the MA + SSRIs group. EA was applied using Han's Acupuncture Point Nerve Stimulator (LH-202H) at GV20, EX-HN3 and the bilateral GB20 for 30 min with disperse-dense waves and an alternative of low (2 Hz) and high (15 Hz) frequencies. The stimulus intensity depended on the tolerance of patients. Disposable sterile stainless steel needles (0.32 mm in diameter, 1 cun and 1.5 cun in length, Hwato brand) were used in all the centres.

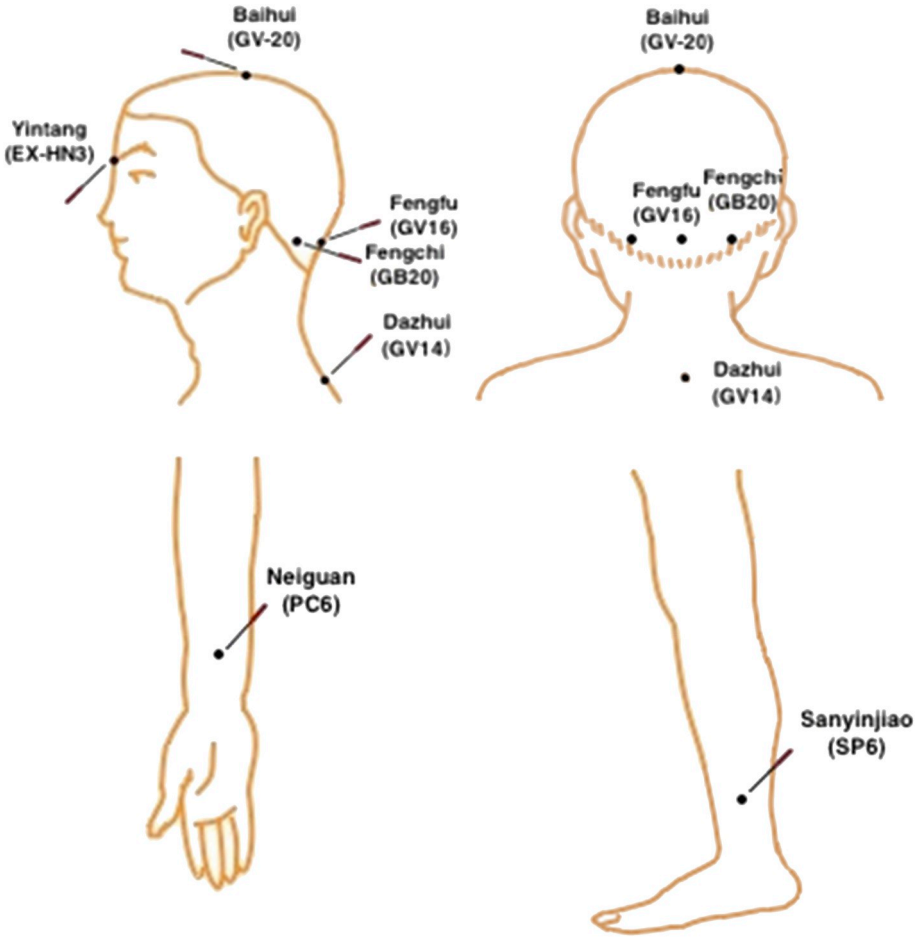

Fig. 1. Acupuncture points used in MA and EA groups. MA, manual acupuncture; EA, electroacupuncture.

Standard operating procedures were followed with systematic training. Certificated acupuncturists from all centres, with at least five years' Chinese medical degree and one-year clinical experience were gathered and given standardized training courses by two senior acupuncturists before launching the trial.

2.4. Outcomes

The primary outcome was response rate (defined as reduction of HAMD total score ≥50% from baseline score) of HAMD-17 (Tang and Zhang, 1984) at 6th week.

Secondary outcomes were remission rate (defined as HAMD total score ≤7) of HAMD-17 at 6th week; early onset rate (defined as reduction of HAMD total score ≥20% from baseline score)(Montgomery et al., 2002; Stassen et al., 1993) of HAMD-17 at 1st week; HAMD-17 total scores, and Self-Rating Depression Scale (SDS)(Wang and Chi, 1984) total scores at baseline, 1st, 2nd, 4th, 6th, and 10th week; Clinical Global Impression (CGI)(Wu, 1984) which includes severity of illness (SI), global improvement (GI) and efficacy index (EI) at baseline and 6th week, and the number of patients who adjusted SSRIs dosage due to varied symptoms during six weeks' treatment.

Safety: adverse events (AEs); total scores of Rating Scale for Side Effects (SERS)(Asberg et al., 1970) at baseline, 2nd, 4th, and 6th week; the domain scores of SERS at the 6th week.

2.5. Follow-ups

After six weeks' treatments, patients were followed for another four weeks. During follow-ups, the patients could choose freely to continue acupuncture or not freely. On the 10th week, patients were approached by telephone interviews.

2.6. Statistical analysis

Sample size was calculated to be 160 per group, taking the response rate of paroxetine hydrochloride as 60% (Golden et al., 2002) and acupuncture (MA, EA) as 80% (Li et al., 2004, 2006; Wang et al., 2003) at 6th week, $\alpha = 0.05$, two-tailed test, power of 90%, allocation ratio of 1:1:1, and dropout rate of 20%. For primary outcome and dichotomous variables of secondary outcomes, all randomized participants were included in intention-to-treat (ITT) analysis. For continuous variable of secondary outcomes, modified intention-to-treat (mITT) analysis was used, which included participants who completed baseline evaluation and at least one treatment (either one session of acupuncture or one dosage of SSRIs). Worst-case imputation, which imputed treatment failure for missing data of the acupuncture plus SSRIs groups, but imputed treatment success for missing data of the SSRIs group, was adopted to handle missing data for primary outcomes and dichotomous variables of secondary outcomes. Last observation carried forward (LOCF) method was utilized to handle missing data of continuous variable. Per protocol analysis was conducted as supplementary analysis, with dataset defined as patients who received at least 80% of allocated treatments. All patients who had been randomized were included in safety set when analysing AEs. All analyses were performed with SPSS 22.0 software (IBM Corporation, Armonk, NY, USA). For continuous variables, comparisons between the three groups were evaluated by the Kruskal-Wallis test. Comparisons between two groups were assessed by the Nemenyi Rank-Sum test. Repeatedly measured

data were tested through the generalized linear mixed model. For dichotomous variables, the Chi-square (χ^2) test was used. The significance level for all tests was defined as P less than 0.05 (two-tailed). Absolute difference and 95% CIs of relative risks (RRs) for dichotomous data and Cohen's d for continuous data were used to express the effect size (Cohen, 1988; Mauri et al., 2014; Spencer et al., 2015). Absolute differences of RRs were calculated by multiplying RRs and 95% CIs by the control group rate of outcomes in our RCT (Guyatt et al., 2015; Spencer et al., 2015).

3. Results

3.1. Participant characteristics

477 patients were enrolled and randomized to MA + SSRIs group (n = 161), EA + SSRIs group (n = 160), and SSRIs group (n = 156), among which 465 (97.5%) patients (157, 153, and 155 each) were included in mITT analysis; 428 (89.7%) patients (140, 138, and 150) who completed at least 80% of allocated treatments were included into per protocol analysis (Supplementary Text S5); 385 (80.7%) patients (129, 122, and 134) completed all the follow-ups. Twelve patients (4, 7, and 1) were excluded from mITT analysis since no intervention was received. It was comparable at baseline among the three groups (Fig. 2, Table 1).

The types of SSRIs used during six weeks' treatment are shown in Supplementary Table S1. Except for one centre, paroxetine as the solely prescribed SSRIs, was given to a total of 313 patients. In Nanjing centre (n = 152), paroxetine (n = 61), citalopram (n = 24), sertraline (n = 20), fluoxetine (n = 17), escitalopram (n = 15), and fluvoxamine (n = 13) were prescribed. This deviation was made by an agreement among local investigators (2 psychiatrists and 3 acupuncturists) before the enrolment of the first patient in their centre, in order to facilitate patient compliance.

Nine acupuncturists (six males) contributed in the treatment of patients. The average age was 33.78 ± 10.18 (24–57) years old. The average clinical experience was 10.44 ± 8.95 (3–30) years.

3.2. Primary outcome

HAMD-17 response rate: There were significant differences among the three groups at 6th week ($P = 0.0030$). MA + SSRIs group (73.9%) and EA + SSRIs group (77.5%) were significantly higher than SSRIs group (60.9%. RR = 1.21, 95% CI 1.04, 1.42, $P = 0.013$; RR = 1.27, 95% CI 1.09, 1.48, $P = 0.0014$). There was no significant difference between the two acupuncture groups. According to the absolute differences calculated from RRs and 95% CIs, approximately 13 more patients will benefit by half reduced depression severity every 100 patients treated by adding manual acupuncture, as fewer as 2, as much as 25. Approximately 16 (5–29) more patients will benefit in every 100 patients treated by adding electroacupuncture (Table 2, Supplementary Table S2).

3.3. Secondary outcomes

HAMD-17 remission rate, early onset rate, and total scores: There were significant differences among the three groups at 6th week in term of remission rate ($P = 0.030$). The remission rate was significantly higher in EA + SSRIs group (38.1%) than in SSRIs group (24.4%. $P = 0.0083$), while there was no significant difference between MA + SSRIs group (32.9%) and SSRIs group ($P = 0.092$). No significant difference was observed between MA + SSRIs group and EA + SSRIs group. Approximately 8 more patients will benefit by clinical symptoms disappearance every 100 patients treated by adding manual acupuncture, as fewer as 0, as much as 22. Approximately 14 (3–29) more patients will benefit in every 100 patients treated by adding electroacupuncture (Table 2, Supplementary Table S2). There were significant differences among the three groups at the end of 1st week in terms of early onset rate ($P < 0.0001$). MA + SSRIs group (44.7%) and EA + SSRIs group (53.1%) were significantly higher than SSRIs group (23.1%. $P < 0.0001$; $P < 0.0001$). There was no significant difference between the two acupuncture groups. Approximately 21 more patients will benefit by early improvement of clinical symptoms every 100 patients treated by adding manual acupuncture, as fewer as 9, as much as 39. Approximately 29 (15–49) more patients will benefit in every 100 patients treated by adding electroacupuncture (Table 2, Supplementary Table S2). Significant differences across groups were observed in terms of HAMD-17 total scores at 1st, 2nd, 4th, and 6th week ($P < 0.001$). Two acupuncture groups were significantly better than SSRIs group all along ($P < 0.05$). No significant difference was observed between MA + SSRIs group and EA + SSRIs group (Fig. 3a, Table 2, Supplementary Table S2). Small effect sizes for the two acupuncture groups compared with the SSRIs group were observed in HAMD-17 total score at 6th week (Cohen's $d_{MS} = 0.25$; Cohen's $d_{ES} = 0.41$, Table 2).

SDS: There were significant differences in terms of SDS total scores among the three groups at 1st, 2nd, 4th, and 6th week ($P < 0.01$). Both MA + SSRIs and EA + SSRIs groups were significantly better than SSRIs group from the 1st week ($P < 0.05$), while there was no significant difference between the two acupuncture groups (Fig. 3b, Table 2, Supplementary Table S2). Small effect sizes for the two acupuncture groups compared with SSRIs group were observed in SDS total score at 6th week (Cohen's $d_{MS} = 0.28$; Cohen's $d_{ES} = 0.41$, Table 2).

CGI: Significant differences were presented on SI, GI, and EI among the three groups at 6th week ($P < 0.0001$). There was no significant difference between the two acupuncture groups, but both of them were better than SSRIs group ($P < 0.01$, Table 2, Supplementary Table S2).

3.4. Outcomes at follow-up

During four weeks' follow-up, 84% and 83% of patients of MA + SSRIs and EA + SSRIs groups turned to SSRIs alone respectively. There were significant differences in HAMD-17 and SDS total scores among three groups ($P < 0.0001$) at the end of follow-up. Both MA + SSRIs and EA + SSRIs groups were significantly better than SSRIs alone ($P < 0.01$), while no significant difference was observed between the two acupuncture groups (Fig. 3a and b, Table 2, Supplementary Table S2). Small to moderate effect sizes for the two acupuncture groups compared with the SSRIs group were observed in HAMD-17 (Cohen's $d_{MS} = 0.35$; Cohen's $d_{ES} = 0.58$) and SDS (Cohen's $d_{MS} = 0.58$; Cohen's $d_{ES} = 0.65$) total scores at 10th week (Table 2).

3.5. Safety

SERS: There were significant differences in SERS total scores among the three groups at 2nd, 4th, and 6th week ($P < 0.001$). Comparing to the SSRIs group, fewer side effects were observed in MA + SSRIs and EA + SSRIs groups as early as the 2nd week until the end of treatment (week 2, MA, $P = 0.057$, EA, $P = 0.0003$; week 4, MA, $P = 0.0013$, EA, $P < 0.0001$; week 6, MA, $P = 0.0015$, EA, $P < 0.0001$). There was no significant difference between the two acupuncture groups (Fig. 3c, Table 2, Supplementary Table S2). After six weeks' treatment, physical tiredness, tremor, dry mouth, constipation, and somnolence were less severe in the two acupuncture groups than in the group taking SSRIs alone ($P < 0.05$). There were significantly fewer sexual problems in MA + SSRIs group than in SSRIs group ($P < 0.01$). There were significantly fewer headaches, sleep disorders, and episodes of dizziness in EA + SSRIs group than in SSRIs group ($P < 0.05$, Table 3, Supplementary Table S2).

Adverse events: There were 28 cases of adverse events in total, 9, 10, and 9 each in MA + SSRIs, EA + SSRIs and SSRIs groups. One serious adverse event (hospitalization due to abnormal behaviours and confusion of mind) was observed in a 21 year-old male patient in the

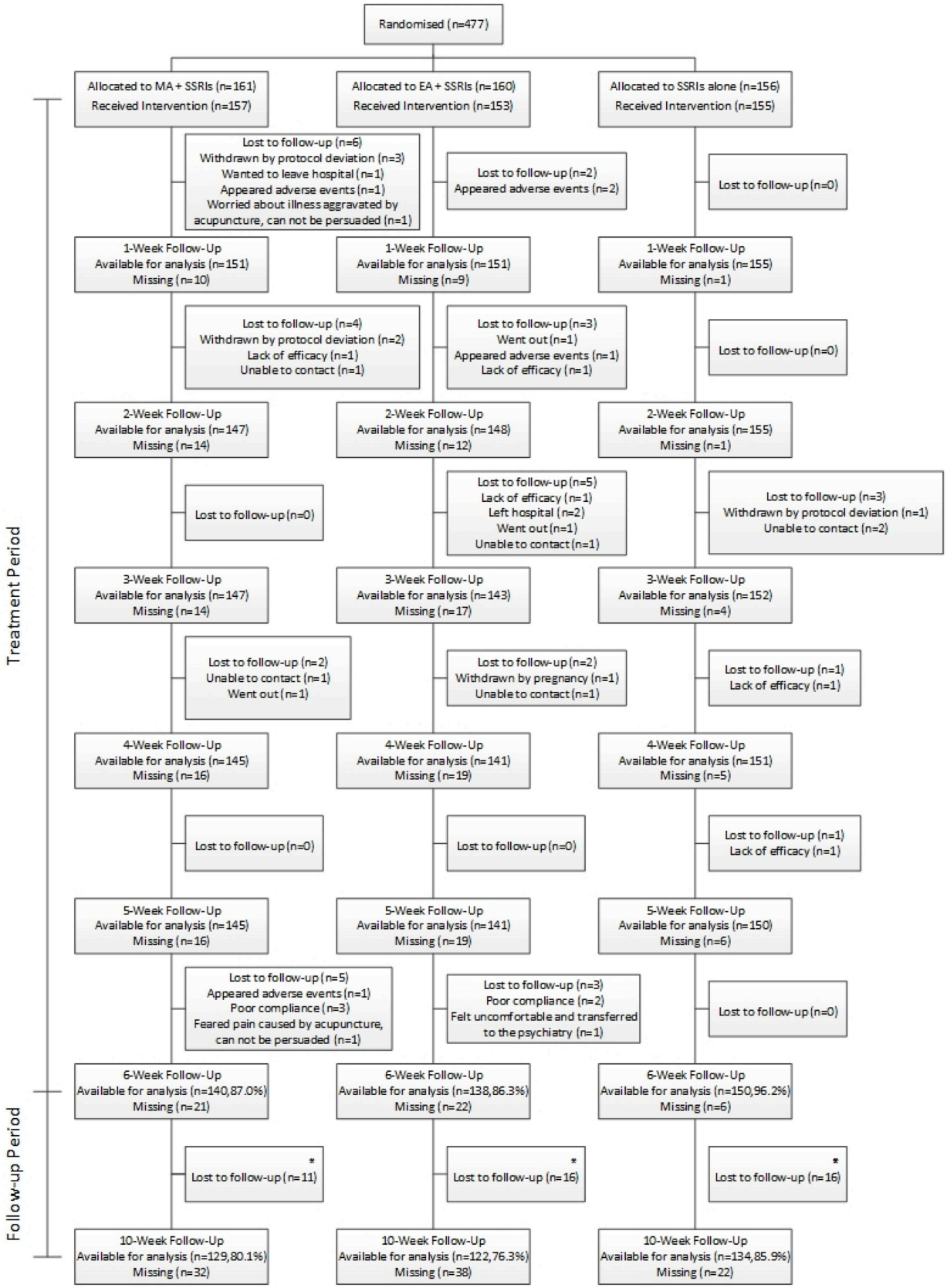

Fig. 2. Flowchart for the study participants. MA, manual acupuncture; EA, electroacupuncture; SSRIs, selective serotonin reuptake inhibitors. * Not approachable by phone.

Table 1
Baseline characteristics of patients (ITT).

Variables	MA + SSRIs	EA + SSRIs	SSRIs alone
	(n = 161)	(n = 160)	(n = 156)
Female, n (%)	105 (65.2)	108 (67.5)	99 (63.5)
Age, Mean (SD)	41.42 (12.53)	41.18 (12.00)	41.76 (12.85)
Duration of depression (months), Mean (SD)	12.83 (17.09)	10.77 (15.32)	9.52 (13.85)
Psychiatric history, n (%)	1 (0.6)	5 (3.1)	2 (1.3)
Self-injury history, n (%)	9 (5.6)	4 (2.5)	3 (1.9)
Family history, n (%)	17 (10.6)	19 (11.9)	19 (12.3)
Major adverse events in life, n (%)	13 (8.1)	12 (7.5)	11 (7.1)
HAMD-17 total score, Mean (SD)	24.80 (5.16)	25.26 (4.90)	24.54 (5.13)
SDS score, Mean (SD)	65.85 (10.52)	66.90 (9.98)	65.05 (9.72)
CGI-SI score, Mean (SD)	4.22 (0.94)	4.20 (1.05)	4.14 (0.85)
SERS score, Mean (SD)	10.65 (5.78)	10.91 (5.18)	10.17 (5.22)

ITT, intention-to-treat; MA, manual acupuncture; EA, electroacupuncture; SSRIs, selective serotonin reuptake inhibitors; SD, standard deviation; HAMD-17, 17-item Hamilton Rating Scale for Depression; SDS, Self-Rating Depression Scale; CGI-SI, Clinical Global Impression-severity of illness; SERS, Rating Scale for Side Effects.

MA + SSRIs group at day 30 after 13 sessions of acupuncture treatments and 17 days of 20 mg/d paroxetine. This patient had stopped medication by himself for 12 days before such symptoms occurred.

Non-serious adverse events probably caused by antidepressants were 4, 4, and 9 in MA + SSRIs, EA + SSRIs, and SSRIs groups each, with an average duration of symptoms for 12 days (11.59 ± 13.72 days). Non-serious adverse events probably caused by acupuncture treatment were 4 and 5 in MA + SSRIs and EA + SSRIs groups each, with an average duration of 1.33 ± 0.71 days. The most common non-serious AEs associated with antidepressants were nausea and vomiting and constipation, while transient fainting during needling and subcutaneous bleeding were the most common ones associated with acupuncture. A case of limbs twitching for an uncertain reason, lasting for one day, was observed in EA + SSRIs group. It was considered not related to the treatments.

3.6. Medication

In MA + SSRIs and EA + SSRIs groups, 4.5% and 9.8% of patients increased the dosage of SSRIs within the six weeks of treatment, while the dosage of 21.9% patients in SSRIs group had been increased ($P < 0.001$, Supplementary Table S3). Supplementary Table S1 shows the type of drug combinations during six weeks' treatment.

4. Discussion

As add-on therapies with SSRIs, MA and EA both enhanced the therapeutic effects (response rate, week 6, $P = 0.0030$; remission rate, week 6, $P = 0.030$; HAMD and SDS total scores, week 6, 10, $P < 0.001$; CGI, week 6, $P < 0.0001$, Fig. 3a and b, Table 2), accelerated response to treatment (early onset rate, week 1, $P < 0.0001$, Table 2), potentially reduced the adverse effects of SSRIs (SERS, week 2, 4, 6, $P < 0.001$, Fig. 3c, Table 2, Table 3) and decreased the proportion of patients who needed to increase the dosage of SSRIs ($P < 0.0001$, Supplementary Table S3) after six weeks of treatment with small to moderate effects. This trial provides evidence for short-term effects of add-on acupuncture for patients with moderate to severe depression.

This multi-centre pragmatic RCT demonstrated a small to moderate effect size of combined acupuncture therapies, with a reasonable sample size and completion rate. The acupuncture treatment protocol with personalized characteristics and SSRIs utilized in this trial reflected routine practice in China. Both clinician-assessed and patients' self-assessed scales were adopted taking consideration of the advantages and disadvantages in both measures (Duan and Sheng, 2012; Dunlop et al., 2010, 2011; Keller et al., 2007), and they showed consistent results.

This study has several limitations. Outcome assessor blinding was not fully achieved (15% patients not achieved), which might lead to over estimation of combined acupuncture treatment effects, although the clinician-rated HAMD-17 results were concordant with the patient-rated SDS results. The decision not to use a sham control was supported by public concerns on the methodology of sham or placebo acupuncture design (Day and Altman, 2000; Hopton and Macpherson, 2011; White et al., 2001), as well as the substantial risk of failure in blinding of participants, who are usually very experienced with acupuncture treatment in Chinese medical culture and settings (Fei et al., 2013; Zhang et al., 2018). The occurrences of AEs in this trial were relatively low, especially in SSRIs group, partly because of most drug-induced AEs overlapped with the items of SERS scale, it might also related to the lower dosages of antidepressants. We followed patients for only 4 weeks after the end of treatments, thus evidence of long-term effects of combined acupuncture treatments beyond one month cannot be provided by our study.

There were some previous relevant studies. A recent systematic review (Chan et al., 2015) included 13 RCTs (1046 patients with moderate to severe depression) comparing MA/EA plus SSRIs versus SSRIs alone with an average of 6 weeks of treatment. Meta-analysis showed low quality evidence of statistically significant benefits for each of the two combined treatments in terms of HAMD-17 response rate (MA + SSRIs vs. SSRIs, 6 RCTs, 394 cases, RR = 1.27, 95% CI 1.01, 1.61, $I^2 = 78\%$; EA + SSRIs vs. SSRIs, 8 RCTs, 523 cases, RR = 1.22, 95% CI 1.05, 1.42, $I^2 = 63\%$), and better effects for MA/EA plus SSRIs in terms of HAMD total score at week 6 (6 RCTs, 339 cases, MD = −2.52, 95% CI -4.12, −0.92, $I^2 = 71\%$). Another most up-to-date systematic review (Smith et al., 2018) reported remission rate rather than response rate. It showed no significant difference between MA/EA plus SSRIs and SSRIs alone in HAMD remission rate (MA + SSRIs vs. SSRIs, 5 RCTs, 299 cases, RR = 1.33, 95% CI 0.65, 2.73, $I^2 = 76\%$; EA + SSRIs vs. SSRIs, 5 RCTs, 273 cases, RR = 1.17, 95% CI 0.75, 1.80, $I^2 = 49\%$).

Compared with Chan review (Chan et al., 2015), our two combined acupuncture treatments showed similar effects in HAMD response rate (MA + SSRIs vs. SSRIs, 317 cases, RR = 1.21, 95% CI 1.04, 1.42, $P = 0.013$; EA + SSRIs vs. SSRIs, 316 cases, RR = 1.27, 95% CI 1.09, 1.48, $P = 0.0014$). Compared with Smith review (Smith et al., 2018), for HAMD remission rate in our study, MA plus SSRIs treatment showed a similar effect (RR = 1.35, 95% CI 0.95, 1.92, $P = 0.092$), but EA plus SSRIs treatment showed a statistically positive effect (RR = 1.57, 95% CI 1.11, 2.20, $P = 0.0083$).

Our trial shared some similarities in the characteristics of patients and interventions with the above two reviews (all trials were conducted in China; similar eligibility criteria, including HAMD-17 score ≥17 and no secondary depression; and six weeks' treatment) (Chan et al., 2015; Smith et al., 2018). However, the sample size of our trial (477 patients) was much larger than any of the included studies, which ranged from 20 to 56 patients per group per trial (Chan et al., 2015; Smith et al., 2018). We treated patients three sessions per week, while about half trials in the reviews (Chan et al., 2015; Smith et al., 2018) provided acupuncture treatment for 5–6 sessions per week. Having acupuncture treatment every the other day is more practical and cheaper than continuous treatments. None of the acupuncture recipes was identical with ours, although, our main points Baihui (GV20) and Yintang (EX-HN3) were the most commonly used points documented in the systematic reviews (Chan et al., 2015; Smith et al., 2018). Different acupuncture treatment protocols are more likely to be the reason for the differences between our results and the systematic reviews (Chan et al., 2015; Smith et al., 2018).

Table 2
HAMD-17, SDS, CGI and SERS scores overtime.

Variables	MA + SSRIs	EA + SSRIs	SSRIs alone	Between -group differences	*P* value	Repeatedly measured data [c]	*P* value [c]	RR (95% CI) RR_{MS}, RR_{ES}	Cohen's *d* d_{MS}, d_{ES}
HAMD-17									
Response rate [a], n (%) 6 week	161 (73.9) *	160 (77.5) *	156 (60.9)	11.642	0.0030			1.21 (1.04, 1.42), 1.27 (1.09, 1.48)	
Remission rate [a], n (%) 6 week	161 (32.9)	160 (38.1) *	156 (24.4)	7.018	0.030			1.35 (0.95, 1.92), 1.57 (1.11, 2.20)	
Early onset rate [a], n (%) 1 week	161 (44.7) *	160 (53.1) *	156 (23.1)	31.434	<0.0001			1.94 (1.39, 2.71), 2.30 (1.67, 3.17)	
Total score [b], n, Mean (SD)						13.892	<0.001		
1 week	157 19.74 (5.48) *	153 19.19 (5.59) *	155 21.69 (5.53)	15.952	0.0003				
6 week	157 10.24 (5.79) *	153 9.44 (5.18) *	155 11.66 (5.54)	16.207	0.0003				0.25, 0.41
10 week (follow-up)	132 8.33 (4.12) *	125 7.48 (3.72) *	135 9.75 (4.09)	23.059	<0.0001				0.35, 0.58
SDS [b], n, Mean (SD)						13.838	<0.001		
1 week	157 58.64 (9.40) *	153 58.13 (9.40) *	155 61.45 (9.94)	11.247	0.0036				
6 week	157 44.22 (11.05) *	153 43.42 (8.84) *	155 46.95 (8.34)	17.870	0.0001				0.28, 0.41
10 week (follow-up)	132 41.18 (7.68) *	125 40.85 (7.17) *	134 45.34 (6.63)	35.283	<0.0001				0.58, 0.65
CGI [b], n, Mean (SD)									
SI (6 week)	157 2.18 (1.13) *	153 2.12 (1.08) *	155 2.56 (0.93)	20.107	<0.0001				
GI (6 week)	142 1.49 (0.80) *	139 1.36 (0.61) *	147 1.97 (0.83)	49.201	<0.0001				
EI (6 week)	142 3.26 (0.92) *	139 3.18 (0.90) *	147 2.84 (0.92)	18.639	<0.0001				
SERS [b], n, Mean (SD)						15.141	<0.001		
6 week	157 5.64 (4.24) *	153 4.65 (3.49) *	155 7.03 (4.11)	34.608	<0.0001				

HAMD-17, 17-item Hamilton Rating Scale for Depression; SDS, Self-Rating Depression Scale; CGI, Clinical Global Impression; SERS, Rating Scale for Side Effects; MA, manual acupuncture; EA, electroacupuncture; SSRIs, selective serotonin reuptake inhibitors; SD, standard deviation; SI, severity of illness; GI, global improvement; EI, efficacy index; RR_{MS}, relative risk of MA + SSRIs vs. SSRIs; RR_{ES}, relative risk of EA + SSRIs vs. SSRIs; Cohen's *d*, 0.2, 0.5 and 0.8 indicates small, moderate and large effect size respectively.

*$P < 0.05$ vs. SSRIs alone.

#$P < 0.05$ vs. MA + SSRIs, however there was none.

[a] Categorical data were analyzed using Chi-square (χ^2) test.

[b] Continuous data were examined using Kruskal-Wallis test.

[c] Repeatedly measured data of HAMD-17, SDS (10 weeks' period) and SERS (6 weeks' period) were tested through the generalized linear mixed model.

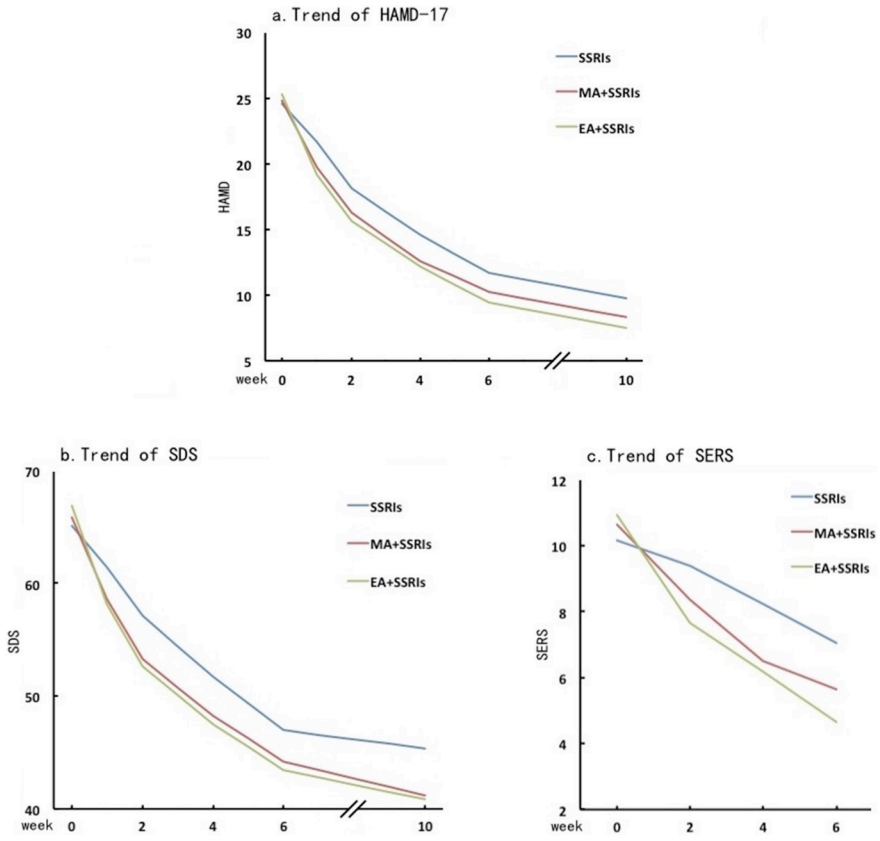

Fig. 3. Trend of HAMD-17 (a), SDS (b) and SERS (c) total scores during six weeks' treatment and four weeks' follow-up (mITT). HAMD-17, 17-item Hamilton Rating Scale for Depression; SDS, Self-Rating Depression Scale; SERS, Rating Scale for Side Effects; mITT, modified intention-to-treat; SSRIs, Selective serotonin reuptake inhibitors; MA, manual acupuncture; EA, electroacupuncture.

A meta-analysis reported a rapid onset of therapeutic effects in combined EA and SSRIs for primary depression (Zhang et al., 2016). Six RCTs with 431 moderate to severe cases were included (among them, only one RCT was included in the above two reviews (Chan et al., 2015; Smith et al., 2018)). All the outcomes that this meta-analysis investigated, including HAMD (week 1, 2, 4), SDS (week 1, 2, 4) and SERS (week 2, 4) total scores, showed significant benefits for EA plus SSRIs compared to SSRIs alone.

Our trial showed a similar effect size compared with the above meta-analysis (Zhang et al., 2016) in the first week (EA + SSRIs vs. SSRIs, HAMD and SDS total scores) and demonstrated a rapid response in MA plus SSRIs and EA plus SSRIs groups in the first week of treatment with a decrease in the HAMD and SDS total scores approximately twice as large as in the group taking SSRIs alone.

Our trial also revealed that both combined acupuncture treatments reduced the side effects of SSRIs (SERS total and domain scores) during the 6 weeks' treatment. Another add-on EA trial with 41 patients found similar results in patients taking fluoxetine (Liu et al., 2009).

Table 3
SERS total and domain scores at the baseline and 6th week (mITT).

Variables	MA + SSRIs (n = 157)		EA + SSRIs (n = 153)		SSRIs alone (n = 155)		χ^2 (Week 6)	*P* value (Week 6)
	Week 0	Week 6	Week 0	Week 6	Week 0	Week 6		
Physical tiredness, Mean (SD)	1.61 (0.86)	0.98 (0.59) *	1.75 (0.75)	0.82 (0.64) *	1.70 (0.82)	1.19 (0.62)	24.715	<0.0001
Headache, Mean (SD)	0.81 (0.86)	0.36 (0.58)	0.82 (0.95)	0.28 (0.56) *	0.80 (1.00)	0.46 (0.65)	8.806	0.012
Sleep disturbance, Mean (SD)	1.86 (0.95)	0.76 (0.67)	1.90 (0.93)	0.67 (0.67) *	1.83 (0.94)	0.91 (0.60)	13.188	0.0014
Vertigo, Mean (SD)	0.73 (0.86)	0.33 (0.57)	0.87 (0.84)	0.24 (0.54) *	0.86 (0.91)	0.42 (0.57)	12.475	0.0020
Orthostatic symptoms, Mean (SD)	0.28 (0.65)	0.08 (0.34)	0.21 (0.52)	0.06 (0.29)	0.15 (0.42)	0.08 (0.30)	1.261	0.532
Palpitations, Mean (SD)	0.95 (0.83)	0.47 (0.64)	0.97 (0.85)	0.35 (0.56)	0.85 (0.90)	0.41 (0.54)	2.958	0.228
Tremor, Mean (SD)	0.30 (0.60)	0.12 (0.35) *	0.27 (0.56)	0.10 (0.30) *	0.23 (0.55)	0.22 (0.43)	9.780	0.0075
Sweating, Mean (SD)	0.66 (0.83)	0.37 (0.57)	0.78 (0.85)	0.29 (0.51)	0.68 (0.84)	0.46 (0.63)	5.690	0.058
Dryness of mouth, Mean (SD)	1.00 (0.90)	0.64 (0.64) *	0.82 (0.84)	0.55 (0.64) *	0.74 (0.78)	0.83 (0.69)	20.415△	<0.0001△
Constipation, Mean (SD)	0.59 (0.87)	0.41 (0.62) *	0.64 (0.85)	0.32 (0.51) *	0.53 (0.82)	0.63 (0.75)	14.774	0.0006
Dysuria, Mean (SD)	0.25 (0.63)	0.10 (0.34)	0.19 (0.52)	0.08 (0.29)	0.15 (0.52)	0.10 (0.36)	0.349	0.840
Somnolence, Mean (SD)	0.15 (0.51)	0.14 (0.43) *	0.18 (0.46)	0.10 (0.33) *	0.14 (0.38)	0.25 (0.50)	12.189	0.0023
Sexual problem, Mean (SD)	0.87 (0.96)	0.46 (0.67) *	0.86 (0.89)	0.52 (0.69)	0.88 (0.83)	0.70 (0.72)	11.513	0.0032
Other symptoms, Mean (SD)	0.61 (0.71)	0.42 (0.56)	0.65 (0.71)	0.27 (0.49) #	0.65 (0.74)	0.35 (0.53)	6.948	0.031
Total, Mean (SD)	10.65 (5.78)	5.64 (4.24) *	10.91 (5.18)	4.65 (3.49) *	10.17 (5.22)	7.03 (4.11)	34.608	<0.0001

SERS, Rating Scale for Side Effects; mITT, modified intention-to-treat; MA, manual acupuncture; EA, electroacupuncture; SSRIs, selective serotonin reuptake inhibitors; SD, standard deviation.
P value (Week 6): *P* value between three groups detected by Kruskal-Wallis test from the scores at 6th week.
△χ^2 and *P* value were detected from the differences between the baseline and 6th week of each group.
*$P < 0.05$ vs. SSRIs alone.
#$P < 0.05$ vs. MA + SSRIs.

There are several implications for future clinical practice and research. Acupuncture, including MA and EA, is a significant add-on therapy for patients with moderate to severe depression on SSRIs, for improving symptoms with less adverse effect scores. There are acceptable mild safety concerns of needling specific adverse events, such as transient pain or trivial bleeding of the acupuncture points. For patients who require SSRIs but are vulnerable to drug side effects, add-on acupuncture might be a preferable solution to help to improve drug tolerance and to reduce the number of patients who need to increase SSRIs dosage at least in a 6-week time period. For patients requiring a quick treatment response, acupuncture is a preferable add-on treatment; and EA plus SSRIs might be a prior choice.

Acupuncture was reasonably tolerated and acceptable in our trial. In every 100 patients, approximately 13 (MA + SSRIs) and 16 (EA + SSRIs) patients benefited from a reduction of at least half in their depression severity, while approximately 3 patients (MA + SSRIs, 2.5%; EA + SSRIs, 3.1%) suffered from non-severe acupuncture-related adverse events (average duration, 1.33 ± 0.71 days). The dropout rates of two acupuncture groups were 13.0% (MA + SSRIs) and 13.7% (EA + SSRIs) at 6th week, higher than in SSRIs group (3.8%), but were still acceptable. One reason for the higher dropout rates might be the time taken to attend. Another concern might the transient pain when needling.

Based on clinical experience and previous studies (Smith and Hay, 2005), a six-week acupuncture treatment protocol with a follow-up of four weeks was decided. It is important that future researches include longer follow-up, such as three months and six months. In this study, we selected 2/15 Hz disperse-dense wave for EA. 2/15 Hz EA could activate the release of multiple endogenous opioid peptides (enkephalin and dynorphin), which were closely related to rapid onset of acupuncture for depression (Chen et al., 1993; Chen and Han, 1992; Wang and Wang, 2010). And compared with continuous wave, disperse-dense wave could reduce the patients' tolerance to needling sensation (Chen et al., 2011; Hu et al., 2015; Liu et al., 2013). 2/100 Hz EA has similar effects (Chen et al., 1993), however researchers suggested that patients might not tolerate high-frequency electroacupuncture (100 Hz) (Mayor, 2013).

Some researchers attempted to explore the possible mechanisms underlying the effects of acupuncture plus SSRIs in depressed patients. The direct pharmacological effect of SSRIs is to increase synaptic serotonin (Andrews et al., 2015). It was found that MA plus SSRIs increased serum serotonin faster than SSRIs alone in depressed patients (Liu et al., 2015). The brain limbic network and reward network, which are modulated by serotonin and dopamine respectively (Kupfer et al., 2012), may play important roles in the pathophysiology of depression (Kupfer et al., 2012; Naranjo et al., 2001), and are both important pathways for acupuncture to take effect (Hui et al., 2000; Lundeberg et al., 2007). Comparing to sham MA plus fluoxetine, the effects of verum MA plus fluoxetine might have been achieved through modulating limbic system and corticostriatal reward circuits (Wang et al., 2016, 2017). These studies suggested there might be potential synergistic effect between MA and SSRIs. We did not find relative findings in EA plus SSRIs intervention.

It is worth noting that we didn't use a sham control, thus the placebo effect could not be excluded. However previous studies compared MA/EA plus SSRIs with sham MA/EA plus SSRIs, and found that the effects of combined MA/EA treatments were better (Liu et al., 2018; Wang et al., 2016, 2017; Zhang et al., 2012). This indicates verum acupuncture induced therapeutic effects beyond placebo effects in depression.

In conclusion, evidence provided by this trial showed that MA and EA as add-on therapies of SSRIs antidepressants probably enhanced therapeutic effectiveness, accelerated response to treatment, and potentially reduced adverse effects of SSRIs, with small to moderate effect sizes for moderate to severe primary depression patients, comparing with SSRIs used alone, at six-week treatment and four-week follow-up. Both combined acupuncture treatment protocols were reasonably tolerated and accepted.

Conflicts of interest

All authors claim no conflict of financial interest. B.C.Z., Z.G.L., Y.Z.W., X.H.M., Y.H., J.B.Z., X.Y.H., J.F.J., S.S.Q., M.S., and X.J.Y. are practicing acupuncturists. B.C.Z., Z.G.L., Y.H., J.B.Z., J.F.J., S.S.Q., M.S., X.J.Y, and T.Y.B. work or study in an acupuncture education organization. Y.T.F. and J.P.L are the methodologists work in a traditional Chinese medicine university. X.Q.W. (Xueqin Wang) is the consultant of Traditional Chinese Medicine health promotion project by Beijing Administration of Traditional Chinese Medicine.

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Author Contributions

T.Y.B. generated the idea. Z.G.L. and X.Q.W. (Xiangqun Wang) were involved in the design of the trial. B.C.Z. and Y.T.F. drafted the manuscript. Y.Z.W., X.H.M., Y.H., J.B.Z., L.Q.L., X.Q.W. (Xueqin Wang), J.F.J., and S.S.Q. were chief investigators on the clinical sites. Y.T.F. and J.P.L. helped with the methodology. B.C.Z., Y.T.F., Q.Y.C., M.S., and X.J.Y. did the statistical analysis. All authors contributed to and approved the final manuscript.

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Appendix A. Supplementary data

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