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CLINICAL TRIAL REPORT

Acupuncture as Add-on Therapy to SSRIs Can Improve Outcomes of Treatment for Anxious Depression: Subgroup Analysis of the AcuSDep Trial

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Purpose: Anxious depression (AD) is a common, distinct depression subtype. This exploratory subgroup analysis aimed to explore the effects of acupuncture as an add-on therapy of selective serotonin reuptake inhibitors (SSRIs) for patients with AD or non-anxious depression (NAD).

Patients and Methods: Four hundred and sixty-five patients with moderate-to-severe depression from the AcuSDep pragmatic trial were included in analysis. Patients were randomly assigned to receive MA+SSRIs, EA+SSRIs, or SSRIs alone (1:1:1) for six weeks. AD was defined by using dimensional criteria. The measurement instruments included 17-items Hamilton Depression Scale (HAMD-17), Self-Rating Depression Scale (SDS), Clinical Global Impression (CGI), Rating Scale for Side Effects (SERS), and WHO Quality of Life-BREF (WHOQOL-BREF). Comparison between AD and NAD subgroups and comparisons between groups within either AD or NAD subgroups were conducted.

Results: Eighty percent of the patients met the criteria for AD. The AD subgroup had poorer clinical manifestations and treatment outcomes compared to those of the NAD subgroup. For AD patients, the HAMD response rate, remission rate, early onset rate, and the score changes on each scale at most measurement points on the two acupuncture groups were significantly better than the SSRIs group. For NAD patients, the HAMD early onset rates of the two acupuncture groups were significantly better than the SSRIs group.

Conclusion: For AD subtype patients, either MA or EA add-on SSRIs showed comprehensive improvements, with small-to-medium effect sizes. For NAD subtype patients, both the add-on acupuncture could accelerate the response to SSRIs treatment. The study contributed to the existing literature by providing insights into the potential benefits of acupuncture in combination with SSRIs, especially for patients with AD subtypes. Due to its limited nature as a post hoc subgroup analysis, prospectively designed, high-quality trials are warranted.

Clinical Trials Registration: ChiCTR-TRC-08000297.

Keywords: anxious depression, non-anxious depression, acupuncture, SSRIs, subgroup analysis

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Introduction

Major depressive disorder (MDD) is a heterogeneous mental disorder with various subtypes,[1] including the common anxious depression (AD).[2,3] With more severe depressive symptoms and functional impairment,[4–6] AD patients experience longer duration of current depressive episode,[6–8] and less likely to achieve remission compared with those with non-anxious depression (NAD).[6,7,9] In addition, AD also diminishes patients' quality of life,[4,7] and increases the risk of suicide as well as the incidence of adverse events.[7,9] Therefore, carefully assessing anxiety in depressed patients plays an essential part in treatment decision-making.

In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study for MDD, the remission rate for AD patients was significantly lower than NAD patients according to both the Hamilton Depression Scale (HAMD) criterion (22% vs 33%) and the self-report version of the Quick Inventory of Depressive Symptomatology (QIDS-SR) criterion (28% vs 39%).[7] For patients who did not achieve remission or were unable to tolerate citalopram were switched to cognitive therapy or citalopram combined cognitive therapy, and the remission rate was only 14%–21%.[10] It suggests that treatments either alone or combined traditional antidepressants and psychotherapy for AD are far from satisfactory. Although ketamine therapy and transdiagnostic combination therapies (such as antidepressants plus atypical antipsychotics) showed better therapeutic effects, they are more prone to safety issues.[11–13] Therefore, an AD treatment strategy that covers both effectiveness and safety is urgently in demand. Additionally, an accumulating body of research indicates that AD has distinct neurobiological findings that separate it from NAD.[3,14,15] Notably, acupuncture therapy has been widely used to treat depression. The findings from several systematic reviews have shown that acupuncture, as an adjuvant treatment for antidepressant therapy, demonstrated significant benefits in reducing the severity of symptoms in depression patients compared with those by antidepressants alone.[16,17]

We recently published the results of a multicenter pragmatic randomized controlled trial (PRCT) – the Acupuncture as add-on treatment of SSRIs for Depression (AcuSDep) trial (477 participants) – that provides new evidence for add-on acupuncture therapy. During at least 10 weeks in this study, it was found manual acupuncture (MA) or electroacupuncture (EA) added onto selective serotonin reuptake inhibitors (SSRIs) had more prompt response, better therapeutic effects, less adverse reactions, and higher quality of life compared with using SSRIs alone, for patients suffering from moderate-to-severe depression.[18,19] Since about 80% of the patients included in the AcuSDep study were of AD subtype, we conducted this post-hoc subgroup analysis to further explore the treatment outcomes of acupuncture add-on SSRIs treatments in depressed patients with or without obvious anxiety symptoms.

Materials and Methods

Design

The AcuSDep study is a three-arm trial. Via simple randomization and central telephone randomization, patients with moderate-to-severe depression were randomly allocated in MA+SSRIs group (161 cases), EA+SSRIs group (160 cases), and SSRIs alone group (156 cases) to receive respective treatment for 6 weeks and thereafter were followed up till week 10. The randomization sequence was generated using SAS 9.2 (SAS Institute, Cary, NC, USA) and was concealed in sequentially numbered, opaque, sealed envelopes. In this AcuSDep study, the data analysts were blinded, while the patients and acupuncturists were not blinded. The study protocol was approved by the Medical Ethics Committee of Peking University Sixth Hospital (No.2009–26) and conducted according to the Declaration of Helsinki. Written informed consent was obtained from all patients. More details regarding the methodology can be found in the previously published article[18] and trial registration (ChiCTR-TRC-08000297). This study is a subgroup analysis on the AcuSDep trial. All analyses were performed based on a modified intention-to-treat (mITT) analysis dataset, including 465 patients who were randomized and completed at least one treatment session.[20] In this study, a 1:1:1 random allocation on the AcuSDep trial was maintained, and patients were specified in two subtypes according to dimensional criteria.[21,22] Those whose anxiety/somatization factor (ASF) score ≥7 on baseline were defined as AD subtype according to 17-item Hamilton Depression Scale (HAMD-17),[23] and those of ASF <7 were defined as NAD subtype.

Participants

This study included patients aged 18–60 years suffering from first-episode depression with a score ≥17 based on HAMD-17, which therefore were classified as moderate-to-severe depression according to this scale. Patients were excluded who were diagnosed with bipolar disorder, took antidepressants or remained unwashed out pharmacological effects, had other brain diseases and serious illness, or had suicidal thoughts or behaviors. Patients were recruited from the outpatient departments of six Chinese hospitals.

Interventions

Patients in each of the three treatment groups received usual dosage of oral SSRIs for 6 weeks. The dosage of SSRIs was individually adjusted according to the severity of symptoms. For patients with severe insomnia, small dosages of sedative-hypnotics were allowed at bedtime if necessary. The MA+SSRIs group and EA+SSRIs group received 18 sessions of MA or EA treatments on top of SSRIs treatment respectively, 3 sessions of 30 minutes per week, for 6 weeks. Two main acupoints and five compulsory auxiliary acupoints were used in both EA and MA groups. The main acupoints included Baihui (GV20) and Yintang (EX-HN3). The compulsory auxiliary acupoints included Fengfu (GV16), bilateral Fengchi (GB20), Dazhui (GV14), bilateral Neiguan (PC6), and bilateral Sanyinjiao (SP6).

Outcome Measures

The measurement instruments for this subgroup analysis were derived from the AcuSDep study.[18,19] The primary outcome was response rate (≥50% total score reduction from baseline at the end of week 6) of HAMD-17. Secondary outcomes included: (1) HAMD-17: Remission rate (at the end of week 6 total score≤7), early onset rate (≥20% total score reduction from baseline at the end week 1),[24] and total score change from baseline at the end of week 1, 2, 4, 6, and week 10; (2) Self-Rating Depression Scale (SDS):[25] Total score change from baseline at the end of week 1, 2, 4, 6, and week 10; (3) Clinical Global Impression (CGI):[26] Score change from baseline in severity of illness (SI) at the end of week 6; (4) Rating Scale for Side Effects (SERS):[27] Total score change from baseline at the end of week 2, 4, and 6 week; (5) WHO Quality of Life-BREF (WHOQOL-BREF):[28] Score change from baseline in overall quality of life, general health, physical health, psychological health, social relationships, and environment at the end of week 6; (6) Adverse events, dropout rate, and medication during treatment.

Data Analysis

In this study, we first explored the proportion of AD and NAD patients among total sample and their distribution in the three arms, as well as the characteristics on baseline of AD and NAD subgroups (without distinguishing interventions) in the total sample. Second, we analyzed the overall treatment outcomes, adverse events, dropout rate and medication use of each subgroup. And finally, the treatment outcomes were analyzed for three treatments on each of the two subgroups separately.

All analyses were performed using SPSS 22.0 software (IBM, Armonk, NY, USA). The method of last observation carried forward (LOCF) was used to fill in missing values. For comparison of dichotomous variables between groups, the Chi-square (χ^2) test or Fisher's exact test was adopted. Binary logistic regression models were applied to adjust baseline severity of depression then response rate, remission rate, and early onset rate between the two subgroups were analyzed. The possible interaction between the subgroups and treatment modes are also examined. For continuous variables, comparisons of baseline variables between the two subgroups were conducted by using two-sample *t* test or Mann–Whitney *U*-test. Within the two subgroups, comparisons among the three treatment groups were carried out with one-way ANOVA or Kruskal–Wallis test. If the global test among the three treatment groups was found significant, then the Bonferroni correction or Nemenyi test was utilized for multiple comparisons. Generalized linear mixed model (GLMM) was adopted to analyze those repeatedly measured data. Between-group Cohen's *d* effect sizes were calculated on mean change scores of HAMD-17 and SDS (baseline to 6 weeks, and baseline to 10 weeks) divided by the pooled standard deviation. Cohen's *d* of 0.2, 0.5 and 0.8 indicates small, medium and large effect size, respectively.[29] All analyses in this study were in the nature of exploratory with the statistical significance set at $P<0.05$ (two-tailed).

Results

The Impact of Anxiety Baseline Level on General Baseline Severity of Health Condition and Outcomes of Treatment

According to the baseline level, 374 (80.4%) patients met the criteria for AD. The distribution of AD patients took 128 (81.5%) in the MA+SSRIs group, 123 (80.4%) in the EA+SSRIs group, and 123 (82.0%) in the SSRIs group respectively (P=0.889). The two subgroups of AD and NAD were comparable in respect of gender and age (P=0.939; P=0.882). Most variables in the AD subgroup reflected longer duration of current depressive episode, more severe depression, and lower quality of life. Less history of self-injury was also observed within patients in the AD subgroup (Table 1).

After 6 weeks of treatment, the remission rate among the AD subgroup was significantly lower than that in the NAD subgroup (26.2% vs 58.2%, OR=0.26 [95% CI, 0.16–0.42], P<0.001). The response rate did not differ significantly between the two subgroups. The early onset rate at end of week 1 was significantly lower in AD subgroup compared with that in NAD subgroup (39.0% vs 50.5%, OR=0.60 [95% CI, 0.38–0.95], P=0.029). The interaction between these two subgroups and treatment modes among the above indicators was not significant (Table 2).

During the 6 weeks' treatment, the incidence of adverse events in the AD and NAD subgroups was 7.0% and 2.2%, respectively (RR=3.16 [95% CI, 0.76–13.08], P=0.087). One serious adverse event (abnormal behavior and confusion) was observed in the AD subgroup related to drug discontinuation. The most common non-serious adverse events associated with antidepressants were digestive symptoms, while transient fainting during needling and subcutaneous bleeding were the most common ones related to acupuncture. The dropout rate in the AD and NAD subgroups was 7.0% and 12.1%, respectively (RR=0.58 [95% CI, 0.30–1.12], P=0.104). No significant difference was observed between the two subgroups in terms of average dosage of SSRIs and concomitant use of sedative-hypnotics at most time points (Table S1).

The Impact of MA Add-on or EA Add-on Strategies to Treatment Outcomes for Patients with AD or NAD

The baseline characteristics were statistically comparable among the three treatment groups for AD subtype patients, except for self-injury history, which was no significant difference in post hoc comparisons. For duration of depression, although there was no statistically significant difference (p=0.061), the duration in SSRIs was 2–4 months shorter than the acupuncture groups. For the NAD subtype, baseline characteristics were comparable among the three treatment groups, except the WHOQOL-BREF social relationships baseline score was found significantly lower in the EA+SSRIs group compared with that in the SSRIs group (P=0.048) (Table 1).

HAMD-17

The repeated-measures analysis revealed significant differences in total HAMD-17 scores over 10-week period among the three treatment groups for both subtypes (P<0.001). In the AD subgroup, the two acupuncture groups were significantly better than the SSRIs alone group in response rate (Week 6), remission rate (Week 6), and early onset rate (Week 1). Both acupuncture groups were significantly better than the SSRIs group in total score improvement from baseline on week 1, 2, 4, 6, and week 10 (P<0.05). Compared with the SSRIs group, the MA+SSRIs group showed small effect sizes in total score at the end of week 6 (d=0.37) and week 10 (d=0.41), and the EA+SSRIs group showed medium effect sizes at the end of week 6 (d=0.58) and week 10 (d=0.66). For the NAD subtype, the early onset rate was significantly better in both acupuncture groups in comparison with that of the SSRIs alone group (P≤0.01). As for the response and remission rates no significant difference was observed among the three groups. Both acupuncture groups were significantly better than the SSRIs group in total score improvement from baseline at the end of week 1 (P<0.05). There was no significant difference in total score changes at other time points among the three groups. Between the two acupuncture groups, no significant difference was observed for either subtype in terms of the above indicators (Figure 1A and B, Tables 3 and 4).

SDS

For repeatedly measured data, significant differences in SDS total scores were observed among the three treatment groups for both subtypes during a period of 10 weeks (P<0.001). In the AD subgroup, both acupuncture groups were

Table 1 Baseline Characteristics of Patients, by Presence of Anxious Depression and Treatment Option

Variables	Anxious Depression Subgroup					Nonanxious Depression Subgroup					Between Subgroups *P*
	MA+SSRIs (N=128)	EA+SSRIs (N=123)	SSRIs Alone (N=123)	Inter-Group Comparison *P*	Subtotal (N=374)	MA+SSRIs (N=29)	EA+SSRIs (N=30)	SSRIs Alone (N=32)	Inter-Group Comparison *P*	Subtotal (N=91)	
Female, n (%)	86 (67.2)	86 (69.9)	73 (59.3)	0.194	245 (65.5)	16 (55.2)	18 (60.0)	26 (81.2)	0.070	60 (65.9)	0.939
Psychiatric history, n (%)	1 (0.8)	3 (2.4)	2 (1.6)	0.536	6 (1.6)	0 (0)	1 (3.3)	0 (0)	0.648	1 (1.1)	1.000
Self-injury history, n (%)	6 (4.7)	3 (2.4)	0 (0)	**0.047***	9 (2.4)	3 (10.3)	1 (3.3)	3 (9.4)	0.621	7 (7.7)	**0.031**
Family history, n (%)	14 (11.0)	13 (10.6)	17 (13.8)	0.692	44 (11.8)	3 (10.3)	5 (16.7)	2 (6.3)	0.451	10 (11.1)	0.856
Major adverse events in life, n (%)	12 (9.4)	10 (8.2)	5 (4.1)	0.231	27 (7.3)	1 (3.4)	2 (6.7)	6 (18.8)	0.139	9 (9.9)	0.401
Age, mean (SD)	41.39 (12.78)	40.75 (12.21)	41.80 (12.78)	0.798	41.32 (12.57)	41.75 (11.60)	41.14 (11.14)	42.25 (12.95)	0.856	41.73 (11.84)	0.882
Duration of depression, mean (SD), mo	13.70 (18.04)	11.53 (16.41)	9.43 (13.92)	0.061	11.56 (16.27)	9.68 (13.32)	8.71 (10.95)	10.13 (13.95)	0.911	9.52 (12.70)	0.070
HAMD-17 total score, mean (SD)	25.73 (5.03)	26.29 (4.68)	25.54 (5.15)	0.345	25.85 (4.95)	20.66 (3.45)	21.03 (3.27)	20.72 (2.76)	0.773	20.80 (3.13)	**<0.001**
HAMD-17 ASF score, mean (SD)	9.92 (2.05)	9.88 (2.06)	9.65 (2.22)	0.419	9.82 (2.11)	5.48 (0.74)	5.40 (0.89)	5.28 (0.85)	0.497	5.38 (0.83)	**<0.001**
SDS total score, mean (SD)	66.40 (10.58)	67.56 (9.79)	66.04 (9.91)	0.467	66.66 (10.10)	63.45 (10.07)	64.17 (10.44)	61.25 (8.00)	0.170	62.91 (9.51)	**0.002**
CGI-SI, mean (SD)	4.30 (0.94)	4.38 (1.02)	4.25 (0.82)	0.404	4.31 (0.93)	3.83 (0.81)	3.47 (0.82)	3.69 (0.82)	0.189	3.66 (0.82)	**<0.001**
SERS total score, mean (SD)	11.21 (5.63)	11.45 (5.32)	10.86 (5.32)	0.679	11.17 (5.42)	8.17 (5.89)	8.70 (3.91)	7.53 (3.90)	0.305	8.12 (4.60)	**<0.001**
WHOQOL-BREF, mean (SD)											
Overall quality of life	2.28 (0.86)	2.14 (0.92)	2.22 (0.86)	0.333	2.21 (0.88)	2.28 (0.80)	2.17 (0.95)	2.38 (0.75)	0.518	2.27 (0.83)	0.414
General health	1.87 (0.64)	1.77 (0.66)	1.89 (0.76)	0.367	1.84 (0.69)	2.03 (0.78)	1.83 (0.59)	2.13 (0.42)	0.119	2.00 (0.61)	**0.024**
Physical health	9.58 (2.39)	9.44 (2.14)	9.47 (1.80)	0.977	9.50 (2.12)	10.19 (2.18)	9.90 (1.94)	10.30 (1.63)	0.706	10.14 (1.91)	**0.006**
Psychological health	9.27 (2.25)	9.20 (2.18)	9.17 (1.90)	0.736	9.22 (2.11)	9.43 (2.13)	9.62 (2.15)	10.40 (1.69)	0.135	9.83 (2.02)	**0.007**
Social relationships	11.77 (2.83)	11.71 (2.35)	11.47 (2.36)	0.557	11.65 (2.52)	12.02 (2.62)	10.89 (2.16)	12.31 (2.38)	**0.041****	11.75 (2.44)	0.632
Environment	12.02 (1.93)	11.89 (1.92)	12.18 (1.82)	0.238	12.03 (1.89)	12.19 (2.07)	11.93 (2.25)	12.89 (2.06)	0.420	12.35 (2.15)	0.059

Notes: Values in bold type show statistical significance. *There was no significant difference in post hoc comparisons. **The score was significantly lower in EA+SSRIs group than in SSRIs group (P=0.048), while there was no significant difference between other post hoc comparisons.

Abbreviations: MA, manual acupuncture; SSRIs, selective serotonin reuptake inhibitors; EA, electroacupuncture; SD, standard deviation; HAMD-17, 17-item Hamilton Rating Scale for Depression; ASF, anxiety/somatization factor; SDS, Self-Rating Depression Scale; CGI-SI, Clinical Global Impression-severity of illness; SERS, Rating Scale for Side Effects; WHOQOL-BREF, WHO Quality of Life-BREF.

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Table 2 Response, Remission, Early Onset of Patients (HAMD-17), by Presence of Anxious Depression (Logistic Regression Model)

Variables	Anxious Depression (N=374) n (%)	Nonanxious Depression (N=91) n (%)	Between Subgroups				Anxiety*Treatment (MA+SSRIs/EA+SSRIs/ SSRIs) Interaction			
			Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)*	*P**	Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)*	*P**
Response (Week 6)	266 (71.1)	71 (78.0)	0.69 (0.40, 1.20)	0.188	0.69 (0.40, 1.19)	0.178	1.26 (0.64, 2.49)	0.505	1.26 (0.64, 2.48)	0.508
Remission (Week 6)	98 (26.2)	53 (58.2)	0.26 (0.16, 0.41)	**<0.001**	0.26 (0.16, 0.42)	**<0.001**	1.55 (0.87, 2.80)	0.140	1.58 (0.88, 2.84)	0.129
Early onset (Week 1)	146 (39.0)	46 (50.5)	0.63 (0.40, 0.99)	**0.047**	0.60 (0.38, 0.95)	**0.029**	0.80 (0.43, 1.48)	0.479	0.79 (0.43, 1.47)	0.463

Notes: *Adjusted for baseline severity of depression (HAMD-17 scale without anxiety/somatization factor).
Abbreviations: HAMD-17, 17-item Hamilton Rating Scale for Depression; MA, manual acupuncture; SSRIs, selective serotonin reuptake inhibitors; EA, electroacupuncture; OR, odds ratio; CI, confidence interval. Values in bold type show statistical significance.

significantly better than that of the SSRIs alone group in total score improvement compared with baseline in general, except in the week 6 for the MA+SSRIs group ($P<0.05$). Compared with the SSRIs group, the MA+SSRIs group showed small effect size in total score at the end of week 10 ($d=0.48$), and the EA+SSRIs group showed small-to-medium effect sizes at the end of week 6 ($d=0.38$) and week 10 ($d=0.51$). For the NAD subtype, the total score in the EA+SSRIs group were significantly improved compared with that of the SSRIs alone group at all time points ($P<0.05$), and the total score changes in MA+SSRIs group were also significant better than that of the SSRIs group at the end of week 1 and week 4 ($P<0.05$). Large effect sizes for the EA+SSRIs group compared with the SSRIs group were observed in total score at the end of week 6 ($d=0.99$) and week 10 ($d=1.25$). No significant difference was found all the way between the two acupuncture groups for either subtype (Figure 1C and D, Tables 3 and 4).

CGI-SI

For the AD subtype, the score improvements of either acupuncture group in comparison with baseline were significantly better than that of the SSRIs alone group in week 6 ($P<0.001$), while no significant difference was observed between the two acupuncture groups. No significant difference was found among the three groups in terms of the score changes in the NAD subtype (Tables 3 and 4).

SERS

The repeated-measures analysis revealed significant difference in total scores achieved over a period of 6 weeks' treatment among the three treatment groups for either subtype ($P<0.001$). For total score changes in comparison with baseline for the AD subtype, the two acupuncture groups were significantly better than the SSRIs group all alone ($P<0.05$). The EA+SSRIs group was significantly better than the SSRIs group at the end of week 4 for the NAD subtype ($P=0.030$). No significant difference was found in other pair-wise comparisons for both subtypes (Figure 1E and F, Tables 3 and 4).

WHOQOL-BREF

For the AD subtype, the environmental domain score changes at the end of week 6 were significantly improved referring baseline in the MA+SSRIs group in comparison with that of SSRIs group ($P=0.014$), alone with the score changes in overall quality of life, general health and environmental domain of the EA+SSRIs group were more significant compared to those of the SSRIs group ($P<0.05$). As for the NAD subtype, the score improvement in social relationships from baseline was significantly better in the EA+SSRIs group than the one in SSRIs group ($P=0.0497$). There was no significant difference in other pair-wise comparisons for both subgroups (Tables 3 and 4).

Discussion

Summary of results

This study expanded as well as deepened the findings from the AcuSDep trial.[18,19] It was indicated that AD subtype took a high proportion (80.4%) of 465 depressed patients. In comparison with NAD patients at the baseline evaluation, AD patients suffered from more severe and longer depressive episodes with lower quality of life (Table 1). During 6 weeks'

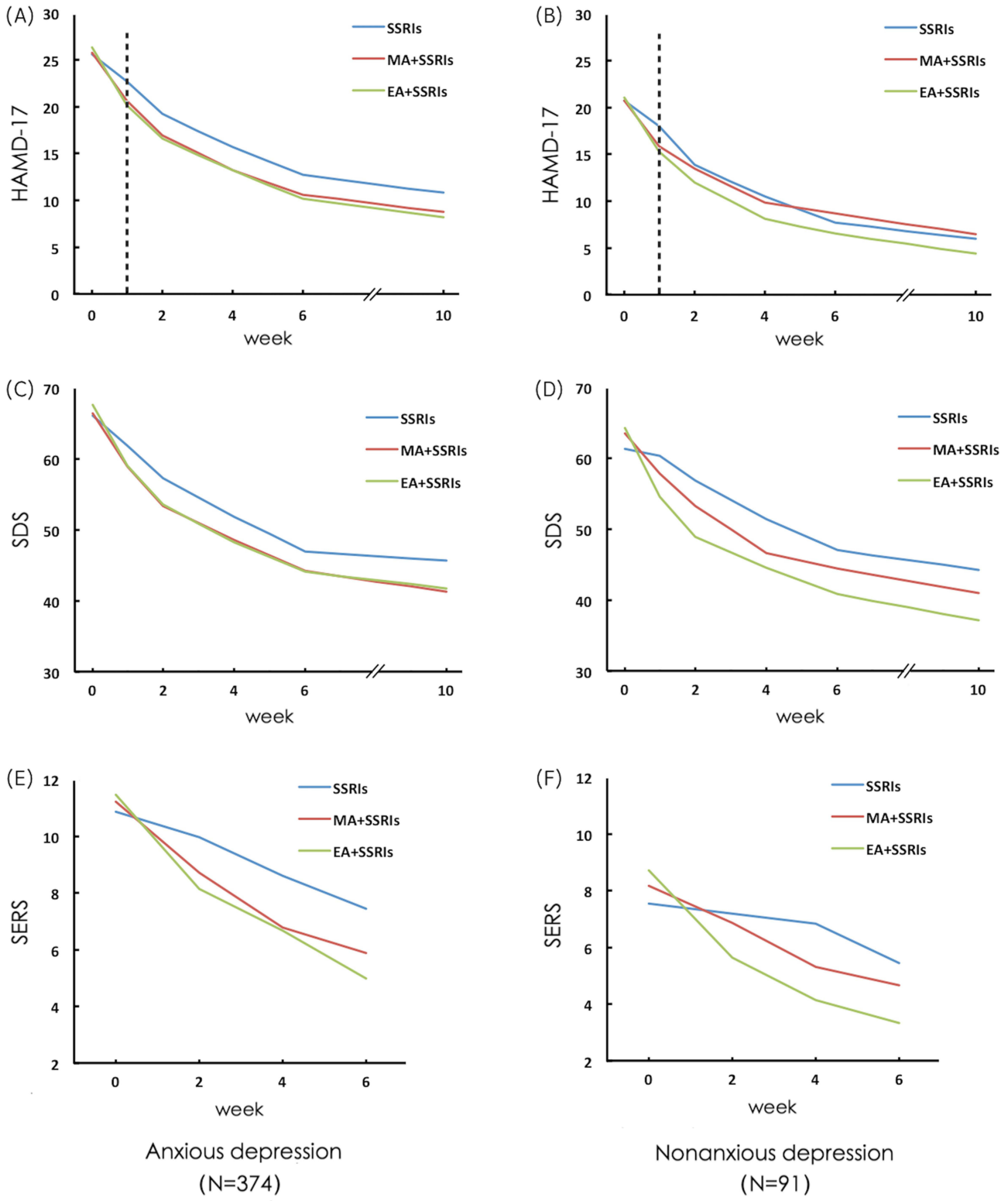

Figure 1 Trend of HAMD-17 (**A** and **B**), SDS (**C** and **D**) and SERS (**E** and **F**) total scores during six weeks' treatment and four weeks' follow-up in anxious and nonanxious depression patients.

Abbreviations: HAMD-17, 17-item Hamilton Rating Scale for Depression; SDS, Self-Rating Depression Scale; SERS, Rating Scale for Side Effects; SSRIs, Selective serotonin reuptake inhibitors; MA, manual acupuncture; EA, electroacupuncture.

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Table 3 Treatment Outcomes in Patients with Anxious Depression, by Treatment Option

Variables	MA+SSRIs (N=128)	EA+SSRIs (N=123)	SSRIs (N=123)	Inter-Group Comparison *P*	Pairwise Comparison					
					MA+SSRIs vs SSRIs		EA+SSRIs vs SSRIs		MA+SSRIs vs EA+SSRIs	
					RR/MD (95% CI)	*P**	RR/MD (95% CI)	*P**	RR/MD (95% CI)	*P**
HAMD-17, n (%)										
Response (Week 6)	98 (76.6)	98 (79.7)	70 (56.9)	**<0.001**	1.35 (1.12, 1.61)	**0.003**	1.40 (1.17, 1.67)	**<0.001**	0.96 (0.84, 1.10)	1.000
Remission (Week 6)	40 (31.2)	41 (33.3)	17 (13.8)	**<0.001**	2.26 (1.36, 3.77)	**0.003**	2.41 (1.45, 4.00)	**<0.001**	0.94 (0.66, 1.34)	1.000
Early onset (Week 1)	54 (42.2)	65 (52.8)	27 (22.0)	**<0.001**	1.92 (1.30, 2.84)	**0.002**	2.41 (1.66, 3.49)	**<0.001**	0.80 (0.61, 1.04)	1.000
Change from baseline in HAMD-17 total score, mean (SD)										
Week 1	−5.12 (4.92)	−6.15 (4.57)	−2.88 (3.94)	**<0.001**	−2.24 (−3.34, −1.14)	**0.002**	−3.27 (−4.32, −2.22)	**<0.001**	1.03 (−0.14, 2.20)	0.103
Week 2	−8.84 (6.11)	−9.74 (5.60)	−6.29 (4.74)	**<0.001**	−2.55 (−3.90, −1.20)	**0.005**	−3.45 (−4.75, −2.15)	**<0.001**	0.90 (−0.55, 2.35)	0.267
Week 4	−12.50 (6.80)	−13.12 (5.84)	−9.89 (5.19)	**<0.001**	−2.61 (−4.10, −1.12)	**0.004**	−3.23 (−4.61, −1.85)	**<0.001**	0.62 (−0.95, 2.19)	0.342
Week 6	−15.15 (6.91)	−16.15 (5.95)	−12.84 (5.44)	**<0.001**	−2.31 (−3.85, −0.77)	**0.011**	−3.31 (−4.73, −1.89)	**<0.001**	1.00 (−0.59, 2.59)	0.257
Week 10	−16.82 (5.68)	−18.10 (5.49)	−14.65 (4.93)	**<0.001**	−2.17 (−3.48, −0.86)	**0.022**	−3.45 (−4.75, −2.15)	**<0.001**	1.28 (−0.10, 2.66)	0.165
Change from baseline in SDS total score, mean (SD)										
Week 1	−7.55 (9.16)	−8.54 (9.51)	−4.28 (6.81)	**<0.001**	−3.27 (−5.26, −1.28)	**0.017**	−4.26 (−6.33, −2.19)	**<0.001**	0.99 (−1.32, 3.30)	0.607
Week 2	−13.12 (11.00)	−14.02 (12.72)	−8.77 (8.64)	**<0.001**	−4.35 (−6.79, −1.91)	**0.010**	−5.25 (−7.97, −2.53)	**0.002**	0.90 (−2.05, 3.85)	0.840
Week 4	−17.84 (12.28)	−19.37 (13.02)	−14.25 (9.04)	**<0.001**	−3.59 (−6.25, −0.93)	**0.044**	−5.12 (−7.92, −2.32)	**0.002**	1.53 (−1.60, 4.66)	0.896
Week 6	−22.22 (13.48)	−23.50 (13.22)	−19.10 (10.02)	**0.008**	−3.12 (−6.05, −0.19)	0.138	−4.40 (−7.33, −1.47)	**0.017**	1.28 (−2.02, 4.58)	1.000
Week 10	−25.39 (10.95)	−26.01 (12.05)	−20.47 (9.62)	**<0.001**	−4.92 (−7.47, −2.37)	**0.003**	−5.54 (−8.26, −2.82)	**<0.001**	0.62 (−2.23, 3.47)	1.000
Change from baseline in CGI-SI, mean (SD)										
Week 6	−2.08 (1.21)	−2.17 (1.21)	−1.51 (0.94)	**<0.001**	−0.57 (−0.84, −0.30)	**<0.001**	−0.66 (−0.93, −0.39)	**<0.001**	0.09 (−0.21, 0.39)	0.742
Change from baseline in SERS total score, mean (SD)										
Week 2	−2.52 (4.01)	−3.30 (3.81)	−0.90 (3.83)	**<0.001**	−1.62 (−2.59. −0.65)	**0.006**	−2.40 (−3.35, −1.45)	**<0.001**	0.78 (−0.19, 1.75)	0.172
Week 4	−4.45 (5.03)	−4.77 (4.23)	−2.28 (4.77)	**<0.001**	−2.17 (−3.38, −0.96)	**0.002**	−2.49 (−3.62, −1.36)	**<0.001**	0.32 (−0.83, 1.47)	0.634
Week 6	−5.34 (5.78)	−6.47 (4.72)	−3.42 (5.13)	**<0.001**	−1.92 (−3.27, −0.57)	**0.016**	−3.05 (−4.28, −1.82)	**<0.001**	1.13 (−0.17, 2.43)	0.185

Change from baseline in WHOQOL-BREF, mean (SD)										
Overall quality of life (Week 6)	0.79 (0.96)	1.01 (0.95)	0.67 (0.84)	**0.023**	0.12 (−0.10, 0.34)	0.677	0.34 (0.12, 0.56)	**0.027**	−0.22 (−0.46, 0.02)	0.185
General health (Week 6)	1.04 (0.90)	1.18 (1.01)	0.85 (0.92)	**0.031**	0.19 (−0.04, 0.42)	0.320	0.33 (0.09, 0.57)	**0.031**	−0.14 (−0.38, 0.10)	0.518
Physical health (Week 6)	2.68 (2.48)	3.00 (2.56)	2.40 (1.85)	0.427	NA	NA	NA	NA	NA	NA
Psychological health (Week 6)	3.27 (2.74)	3.31 (2.61)	2.72 (2.12)	0.084	NA	NA	NA	NA	NA	NA
Social relationships (Week 6)	1.63 (2.81)	1.63 (2.45)	1.61 (2.04)	0.808	NA	NA	NA	NA	NA	NA
Environment (Week 6)	1.16 (2.02)	1.33 (1.78)	0.44 (1.53)	**0.001**	0.72 (0.28, 1.16)	**0.014**	0.89 (0.48, 1.30)	**0.004**	−0.17 (−0.64, 0.30)	0.895

Notes: Values in bold type show statistical significance. *For categorical data, Bonferroni correction was used for pairwise comparisons. For continuous data, Bonferroni correction or Nemenyi Rank-Sum test were used for pairwise comparisons.

Abbreviations: MA, manual acupuncture; SSRIs, selective serotonin reuptake inhibitors; EA, electroacupuncture; RR, relative risk; CI, confidence interval; HAMD-17, 17-item Hamilton Rating Scale for Depression; SD, standard deviation; MD, mean difference; SDS, Self-Rating Depression Scale; CGI-SI, Clinical Global Impression-severity of illness; SERS, Rating Scale for Side Effects; WHOQOL-BREF, WHO Quality of Life-BREF; NA, not applicable.

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Table 4 Treatment Outcomes in Patients with Nonanxious Depression, by Treatment Option

Variables	MA+SSRIs (N=29)	EA+SSRIs (N=30)	SSRIs (N=32)	Inter-Group Comparison *P*	Pairwise Comparison					
					MA+SSRIs vs SSRIs		EA+SSRIs vs SSRIs		MA+SSRIs vs EA+SSRIs	
					RR/MD (95% CI)	*P**	RR/MD (95% CI)	*P**	RR/MD (95% CI)	*P**
HAMD-17, n (%)										
Response (Week 6)	21 (72.4)	26 (86.7)	24 (75.0)	0.366	NA	NA	NA	NA	NA	NA
Remission (Week 6)	13 (44.8)	20 (66.7)	20 (62.5)	0.196	NA	NA	NA	NA	NA	NA
Early onset (Week 1)	18 (62.1)	20 (66.7)	8 (25.0)	**0.001**	2.48 (1.28, 4.82)	**0.010**	2.67 (1.39, 5.11)	**0.003**	0.93 (0.64, 1.36)	1.000
Change from baseline in HAMD-17 total score, mean (SD)										
Week 1	−4.79 (2.81)	−5.77 (3.41)	−2.75 (2.82)	**<0.001**	−2.04 (−3.45, −0.63)	**0.025**	−3.02 (−4.58, −1.46)	**<0.001**	0.98 (−0.61, 2.57)	0.624
Week 2	−7.17 (4.00)	−9.03 (3.93)	−6.88 (3.06)	0.051	NA	NA	NA	NA	NA	NA
Week 4	−10.86 (5.12)	−12.93 (5.34)	−10.25 (3.94)	0.080	NA	NA	NA	NA	NA	NA
Week 6	−11.97 (5.80)	−14.50 (5.51)	−13.06 (3.54)	0.156	NA	NA	NA	NA	NA	NA
Week 10	−13.96 (5.16)	−16.83 (4.64)	−14.93 (2.72)	0.127	NA	NA	NA	NA	NA	NA
Change from baseline in SDS total score, mean (SD)										
Week 1	−5.69 (10.19)	−9.67 (7.88)	−0.97 (5.00)	**<0.001**	−4.72 (−8.81, −0.63)	**0.004**	−8.70 (−12.01, −5.39)	**<0.001**	3.98 (−0.68, 8.64)	0.654
Week 2	−10.21 (13.36)	−15.33 (9.95)	−4.47 (6.15)	**<0.001**	−5.74 (−11.05, −0.43)	0.089	−10.86 (−15.01, −6.71)	**<0.001**	5.12 (−0.91, 11.15)	0.166
Week 4	−16.83 (14.40)	−19.63 (10.51)	−9.94 (7.02)	**<0.001**	−6.89 (−12.67, −1.11)	**0.048**	−9.69 (−14.17, −5.21)	**0.002**	2.80 (−3.65, 9.25)	0.982
Week 6	−19.03 (16.35)	−23.40 (11.37)	−14.28 (6.62)	**0.001**	−4.75 (−11.13, 1.63)	0.374	−9.12 (−13.79, −4.45)	**0.011**	4.37 (−2.84, 11.58)	0.494
Week 10	−21.35 (15.05)	−28.30 (10.91)	−17.25 (6.29)	**<0.001**	−4.10 (−10.00, 1.80)	0.055	−11.05 (−15.52, −6.58)	**<0.001**	6.95 (0.22, 13.68)	0.390
Change from baseline in CGI-SI, mean (SD)										
Week 6	−1.83 (1.07)	−1.73 (1.26)	−1.81 (1.00)	0.977	NA	NA	NA	NA	NA	NA

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Change from baseline in SERS total score, mean (SD)										
Week 2	−1.31 (6.46)	−3.07 (3.92)	−0.34 (3.87)	**0.030**	−0.97 (−3.68, 1.74)	0.996	−2.73 (−4.67, −0.79)	0.074	1.76 (−0.98, 4.50)	0.068
Week 4	−2.86 (6.37)	−4.57 (4.25)	−0.69 (5.13)	**0.017**	−2.17 (−5.09, 0.75)	0.948	−3.88 (−6.22, −1.54)	**0.030**	1.71 (−1.06, 4.48)	0.076
Week 6	−3.52 (6.71)	−5.37 (4.23)	−2.09 (5.25)	0.061	NA	NA	NA	NA	NA	NA
Change from baseline in WHOQOL-BREF, mean (SD)										
Overall quality of life (Week 6)	0.76 (0.87)	1.10 (0.99)	0.63 (0.91)	0.165	NA	NA	NA	NA	NA	NA
General health (Week 6)	0.93 (0.80)	1.07 (0.91)	0.56 (0.76)	0.070	NA	NA	NA	NA	NA	NA
Physical health (Week 6)	2.36 (1.97)	2.69 (2.19)	1.91 (2.11)	0.338	NA	NA	NA	NA	NA	NA
Psychological health (Week 6)	3.08 (2.32)	2.84 (2.52)	1.60 (1.97)	**0.045**	1.48 (0.39, 2.57)	0.053	1.24 (0.11, 2.37)	0.253	0.24 (−1.00, 1.48)	0.744
Social relationships (Week 6)	1.22 (2.42)	1.96 (2.09)	0.73 (2.04)	**0.039**	0.49 (−0.65, 1.63)	0.208	1.23 (0.20, 2.26)	**0.0497**	−0.74 (−1.90, 0.42)	0.811
Environment (Week 6)	0.91 (1.56)	1.05 (1.17)	0.22 (1.73)	0.114	NA	NA	NA	NA	NA	NA

Notes: Values in bold type show statistical significance. *For categorical data, Bonferroni correction was used for pairwise comparisons. For continuous data, Bonferroni correction or Nemenyi Rank-Sum test were used for pairwise comparisons.

Abbreviations: MA, manual acupuncture; SSRIs, selective serotonin reuptake inhibitors; EA, electroacupuncture; RR, relative risk; CI, confidence interval; HAMD-17, 17-item Hamilton Rating Scale for Depression; SD, standard deviation; MD, mean difference; SDS, Self-Rating Depression Scale; CGI-SI, Clinical Global Impression-severity of illness; SERS, Rating Scale for Side Effects; WHOQOL-BREF, WHO Quality of Life-BREF; NA, not applicable.

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treatment period, patients of AD subtype showed slower onset of actions, poorer remissions, and higher incidence of adverse events (Table 2). Although the differences between EA add-on and MA add-on treatments in both AD and NAD subtypes did not reach the statistical significance level, AD subtype patients who accepted either MA add-on or EA add-on treatments demonstrated accelerated response in treatment effect onset, enhanced therapeutic effects (small-to-medium effect sizes), improved quality of life, and reduced side effects of antidepressants (Table 3). As for the NAD patients, both acupuncture add-on treatments had an early onset of action. Furthermore, all the way throughout the entire treatment period of NAD patients, EA add-on treatment also enhanced self-reported treatment effects (large effect size) as well. For the NAD subtype group, there was no significant difference in most of the other outcome indicators between these two acupuncture add-on treatments and the SSRIs alone treatment (Table 4).

Strengths and Limitations

The study was derived from a large sample size PRCT. And to our knowledge, up to present time this is the first study to explore the outcomes of two acupuncture add-on to SSRIs treatment strategies for moderate to severe depressed patients with or without obvious anxiety symptoms. Many previous studies on AD subtype highlighted the necessity to search for novel treatment strategies for this major subtype of depression,[5,7,10,30] which prompted us to conduct this subgroup analysis. The depression subtypes were identified based on baseline characteristics of the patients. The baseline data showed that the main prognostic factors were comparable to a large extent among the treatment strategies for these two subtypes. Both clinician-rated and self-reported instruments were adopted to obtain more comprehensive information. The dimensional criteria used in this study are time-saving and easy operation[5,9] and are in line with clinical practice.[6,21] Therefore, these facts enhanced the credibility of the study results.[28]

It must be admitted that although we hypothesized before conduction of this subgroup analysis that both acupuncture add-on treatments could be more effective than SSRIs alone for AD patients, and this was the only subgroup hypotheses we made, this subgroup analysis is not originally planned in the AcuSDep trial, thus the results may have the risk of misleading.[31,32] However, the *P* values for significant results are generally small, this indicate that the possibility that chance can explain the subgroup difference is small. Besides this, our findings are not only consistent with studies testing acupuncture for anxiety, which showed better effects for acupuncture than anti-anxiety drugs,[33,34] our findings are also consistent with relevant previous small sample-sized studies testing effects of acupuncture for depression.[35,36] Mechanism studies also revealed that by regulating neuro-endocrine-immune system, acupuncture relieved anxiety and depression.[37,38] According to the guidelines for deciding whether apparent differences in subgroup response are real,[31] the rational of our analysis is basically acceptable. Since the sample size was not estimated by individual subtype group in advance, this study might lack statistical power to confirm the differences between treatment strategies for the two subtype groups (especially in the NAD subgroup), neither covered is the interaction between anxiety level and treatment modes. Additionally, considering the substantial risk of failure in blinding of Chinese patients with rich acupuncture experience,[39,40] a sham control was not used, therefore the placebo effect could not be excluded.

Relationship to Literature

In this study, approximately 80% of patients with moderate-to-severe depression had high levels of anxiety symptoms, which is similar to the results from previous Chinese study in the term of prevalence.[41] Also, in line with the previous studies,[4–8,30] patients of AD subtype in our study exhibited more severe clinical manifestations. Previous studies held different views on whether the response of AD patients to drug therapy is similar to or worse than that of NAD patients.[6–8,42] However, no significant difference was found in this study, in the term of response rate between these two subtype groups, which suggests that the degree of overall improvement is similar. Like previous antidepressant studies,[6,7,9] the remission rate of the AD subgroup was significantly lower compared with NAD subgroup in this study. We also found the early onset rate in the AD subgroup was significantly lower. The AD subgroup in this study was more likely to have adverse events, but its dropout rate and SSRIs dosage were not significantly different to the ones in NAD subgroup, which are consistent with previous studies.[4,6,7,9]

In this study, both MA add-on and EA add-on strategies accelerated onset of action, enhanced therapeutic effects, improved quality of life, as well as reduced side effects of medication in AD patients, which are consistent with the results of previous small-scale trials that the two acupuncture as add-on therapies to SSRIs could improve anxiety symptoms on

depressed patients.[35,36] For NAD patients, only EA add-on strategy showed sustained improvement on the SDS scale, suggesting that these patients may have more positive self-evaluations related to EA treatment. For NAD subtype group, different treatment strategies did not result much differences in most outcome indicators, that could be due to SSRIs were more effective in "pure" depression and then appeared a ceiling effect. It also could lead to insufficient statistic power due to the small sample size. In previous study, only EA add-on SSRIs showed a significant improvement over SSRIs alone in depressed patients at week 1.[43] However, in this study, the early onset rates of both two acupuncture add-on strategies were approximately twice than those of the SSRIs alone strategy for either AD or NAD subtype group.

Implications for Clinical Practice and Future Research

As a first-line antidepressant, SSRIs showed limited effectiveness and poorer safety in AD patients than in NAD patients.[7] For patients of AD subtype, we recommend either EA or MA as a synergistic therapy with SSRIs, since either acupuncture add-on approaches provided the dual advantages in effectiveness and safety. For patients of NAD subtype, we suggest EA add-on to shorten the onset time of treatment, since EA add-on strategy not only accelerating onset of action but continuously improved patients' subjective experience. As an exploratory subgroup analysis, the results of this study need to be applied with caution.[31]

Potential Biological Mechanisms of Acupuncture Add-on Strategy for AD Treatment

In this study, the treatment outcomes for the two subtype groups were significantly different, which might be due to their different neurobiological characteristics.[3,14] Studies have shown that AD patients have more severe HPA axis dysfunction and immune activation than NAD patients.[2,44] Several functional magnetic resonance imaging studies revealed aberrant connectivity pattern in brain default mode network and in cortical-limbic network in patients with AD.[45–48] One study found that EA stimulation can modulate abnormal default mode network activity in depressed patients.[49] Researchers also found that MA add-on SSRIs can regulate the balance between anti- and pro-inflammatory cytokines in depressed patients,[38] and may achieve antidepressant effects by modulating limbic system and corticostriatal reward circuitry.[50,51] These findings are provided with some indirect explanations to the prominent outcome improvements after acupuncture add-on treatment on AD patients in this study.

Conclusion

In our study, 465 patients with moderate-to-severe depression were enrolled from six Chinese hospitals. AD subtype patients accounted for a high proportion and had more severe clinical manifestations and poorer treatment outcomes compared with NAD subtype patients. For AD subtype patients, either MA or EA add-on SSRIs showed comprehensive improvements, with small-to-medium effect sizes. Therefore, these combined treatment strategies may form new, effective and safe therapies. For NAD subtype patients, both the add-on acupuncture could accelerate the response to SSRIs treatment. Due to its limited nature as a post hoc subgroup analysis, prospectively designed, high-quality trials are warranted.

Abbreviations

AD, anxious depression; NAD, non-anxious depression; MDD, major depressive disorder; STAR*D, Sequenced Treatment Alternatives to Relieve Depression; AcuSDep, Acupuncture as add-on treatment of SSRIs for Depression; PRCT, pragmatic randomized controlled trial; MA, manual acupuncture; EA, electroacupuncture; SSRIs, selective serotonin reuptake inhibitors; HAMD-17, 17-items Hamilton Depression Scale; ASF, anxiety/somatization factor; SDS, Self-Rating Depression Scale; CGI, Clinical Global Impression; SI, severity of illness; SERS, Rating Scale for Side Effects; WHOQOL-BREF, WHO Quality of Life-BREF; mITT, modified intention-to-treat; LOCF, last observation carried forward; GLMM, Generalized linear mixed model.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to their containing information that could compromise the privacy of participants.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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