Electroacupuncture and cognitive behavioural therapy for sub-syndromal depression among undergraduates: a controlled clinical trial

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Accepted 25 March 2016
Published Online First 15 April 2016

To cite: Guo T, Guo Z, Zhang W, *et al*. *Acupunct Med* 2016;**34**:356–363.

ABSTRACT

Background Individuals with sub-syndromal depression (SSD) are at increased risk of incident depressive disorders; however, the ideal therapeutic approach to SSD remains unknown.

Objective To evaluate the effects of electroacupuncture (EA) and cognitive behavioural therapy (CBT), alone or in combination, on depressive symptoms.

Methods Undergraduate students with SSD were recruited and allocated to one of four groups based on their preferences: EA (n=6), CBT (n=10), EA+CBT (n=6), and untreated control (n=11) groups. Six weeks of treatment were provided in the first three groups. Clinical outcomes were measured using the 17-item Hamilton Depression (HAMD-17) rating scale, Center for Epidemiologic Depression (CES-D) scale, WHO Quality of Life-Brief version (WHOQOL-BREF) questionnaire, and clinical remission rate.

Results All 33 subjects were included in an intent-to-treat analysis. Statistically significant improvements in HAMD-17, CES-D, and WHOQOL-BREF scores and a higher remission rate were found in the EA, CBT, and EA+CBT intervention groups compared with the control group (all $p<0.05$). No significant differences were found between the three intervention groups. HAMD-17 factor score analysis revealed that EA reduced sleep disturbance scores more than CBT or EA+CBT ($p<0.05$), and CBT reduced retardation scores more than EA ($p<0.01$). EA +CBT reduced anxiety/somatisation scores more than EA or CBT ($p<0.05$) and retardation scores more than EA ($p<0.05$).

Conclusions Early intervention may alleviate depressive symptoms in SSD. EA and CBT may have differential effects on certain symptoms. Combination therapy targeting both physical and psychological symptoms may represent an ideal strategy for SSD intervention. However, randomised trials with larger sample sizes are needed.

Trial registration number ChiCTR-TRC-10000889; Results.

INTRODUCTION

Sub-syndromal depression (SSD) is characterised by clinical symptoms of major depression that are of insufficient severity to meet full diagnostic criteria. SSD is linked to various adverse functional outcomes, as well as an increased risk of incident psychiatric disorders, a high socioeconomic burden, and decreased quality of life.[1–3] However, research into interventions for SSD remains scarce. Given the relatively high prevalence of SSD and its associated risks,[3] there is a need to develop effective therapeutic strategies.

Electroacupuncture (EA) may be an effective adjuvant therapy for psychiatric disorders.[4] The putative antidepressant actions of EA are believed to involve modulation of neurotransmitters, hormones and/or cytokines.[5 6] Observations from clinical trials indicate that EA can reduce side effects and accelerate the clinical response to antidepressant medications.[7–9] In addition, it has been suggested that EA may alleviate symptoms such as pain, insomnia, and

digestive dysfunction.[6] Cognitive behavioural therapy (CBT) has been used in clinical practice for decades.[10 11] Systematic reviews support the use of CBT as a first-line psychological treatment for depression compared with other psychotherapies.[12 13] Neuroimaging studies have indicated that CBT restores metabolic abnormalities in the brain circuits that regulate mood.[14 15]

Despite evidence of efficacy for EA and CBT in the treatment of depression, their respective roles in the prevention of depression remain unknown. We hypothesised that EA and CBT (alone or in combination) would contribute to the prevention of depression via potential improvement in SSD.

METHODS

Settings

This study was conducted at the Inner Mongolia Medical University between October 2011 and March 2012. The study protocol was approved by the Medical Ethical Committee of the Third Affiliated Hospital of Beijing University of Chinese Medicine in June 2009 and was prospectively registered in the Chinese Clinical Trial Registry at http://www.chictr.org.cn/enindex.aspx (reference no. ChiCTR-TRC-10000889) in June 2010.

Subjects and group allocation

Undergraduates aged between 18 and 22 years completed questionnaires incorporating the Center for Epidemiologic Studies Depression Scale (CES-D)[16] and the WHO Quality of Life-Brief version (WHOQOL-BREF).[17] Individuals with a CES-D score ≥16 were selected for further evaluation, including the 17-item Hamilton Rating Scale for Depression (HAMD-17)[18] and the Mini International Neuropsychiatric Interview (M.I.N.I.),[19] which were conducted by experienced psychiatrists. The inclusion criteria were: (1) presence of ≥1 but <5 symptoms required for the diagnosis of major depression as detailed in the China Diagnostic Criteria for Mental Disorders-3 (CCMD-3), including loss of interest/enjoyment, reduction of energy or marked tiredness, psychomotor retardation or agitation, feelings of guilt or worthlessness, reduced concentration, recurrent suicidal thoughts, sleep disturbance, loss of appetite and body weight reduction, and loss of libido; (2) symptoms lasting at least 2 weeks; (3) HAMD-17 score between 7 and 16; (4) informed consent. Subjects were excluded if they had: (1) a history of psychiatric disorders; (2) a history of brain injury or surgery; (3) unstable medical conditions; (4) involvement in any other clinical trial in the past 4 weeks; (5) suicidal attempts or aggressive behaviour; or (6) a family history of psychiatric disorders. The study was designed as a pragmatic non-randomised controlled trial. All participants were informed in detail about the four available treatment strategies (EA, CBT, EA combined with CBT, and no treatment) and self-selected which group they were allocated to, based on their personal preferences.

Blinding

Neither the participants nor the acupuncturist/therapist were blinded; however, outcome assessors and the statistical analyst were kept blind to treatment allocation. Outcome assessors were not permitted to ask participants about group allocation or any treatment (s) received.

EA and CBT interventions

A total of 18 EA treatments were provided (three sessions per week for six consecutive weeks). Based on empirical evidence and previous clinical studies,[20] GV20 (*Baihui*) and *Yintang* were selected as mandatory acupuncture points. Other acupuncture points were added based on individualised syndrome differentiation and included: LR3 (*Taichong*), LI4 (*Hegu*), PC6 (*Neiguan*), HT7 (*Shenmen*), KI3 (*Taixi*), KI6 (*Zhaohai*), SP6 (*Sanyinjiao*), and ST36 (*Zusanli*). Disposable stainless steel acupuncture needles (0.25 mm in diameter and 25–40 mm in length) (Hwato, Suzhou Medicine Co, Ltd, Suzhou, Jiangsu, China) were inserted perpendicularly or obliquely to a depth of 10–30 mm. Manual manipulation was performed to achieve characteristic needling sensation (*de qi*). The needles inserted at GV20 and *Yintang* were attached to a Han's Acupuncture Nerve Stimulator (HANS; model no. LH202H) and EA was delivered using continuous waves at alternating 2/100Hz frequency (each lasting for 3 s) with a variable pulse width, as reported previously.[21] The intensity of stimulation was adjusted to a level at which patients felt most comfortable, which ranged from 5 to 10 mA. Stimulation lasted for 30 min. EA was performed in treatment rooms by experienced acupuncturists who had each completed a 5-year undergraduate degree in Chinese medicine and had been practising for over 3 years. To ensure consistency in the EA procedure, acupuncturists participated in a training workshop to standardise the acupuncture protocol before the study began.

CBT was based on ABC (activating events-belief-consequence) theory[22] and consisted of six weekly sessions, each lasting 1.5–2 h. The interventions, led by a therapist with a psychology counselling certificate who was trained in the approach, were conducted in a treatment room with groups of 6–10 subjects. The procedure was developed by Koshikawa Fusako and Ishii Yasutomo and is documented in a previous report.[23] Briefly, subjects were required to submit weekly homework recording their negative experiences, beliefs, emotions and behaviour. A cognitive restructuring technique was taught, aiming to identify and challenge irrational, unrealistic or overly negative

thoughts with a special focus on adverse events recorded through homework.

Subjects in the combination therapy group received exactly the same EA and CBT procedures as conducted in the other two groups. No intervention was performed in the untreated control group.

Clinical assessment

The primary outcome measure was change from baseline in the total HAMD-17 score. Secondary outcome measures included clinical remission rate (remission being defined as an endpoint HAMD-17 score of <7) and change in CES-D score. Factor scores of HAMD-17 were analysed to determine the therapeutic targets of different therapies.[24] Quality of life was assessed using WHOQOL-BREF scores. Endpoint assessments were conducted immediately after the last treatment (or equivalent). To ensure the consistency of assessments across the study, a training workshop was conducted for clinical assessors, led by an experienced psychiatrist.

Data collection and statistical analysis

A case report form listing demographic characteristics and symptom spectrum was completed by the outcome assessors for each enrolled participant. EpiData Software V.3.02 (EpiData Association, Odense, Denmark) was used for data management. Raw data were entered and stored by two staff members; a double entry method was used to ensure the accuracy of data entry.

An intention-to-treat (ITT) analysis was performed, with imputation of baseline data as outcome data for subjects who had dropped out. Intra-group differences between pre- and post-treatment values were examined using the paired Student t test. One-way analysis of variance (ANOVA) was applied to detect inter-group differences between the four groups for the HAMD-17, CES-D, and WHOQOL-BREF scores, followed by the post-hoc test of least significant difference. Categorical variables, including relevant baseline variables and clinical remission rate, were analysed using the χ^2 test. Statistical significance was defined as a two-tailed $p<0.05$. All analyses were performed with the Statistical Package for the Social Sciences (SPSS) V.17 (SPSS Inc, Chicago, Illinois, USA).

RESULTS

Disposition and characteristics of subjects

In total, 33 undergraduates were recruited. A total of three subjects were lost to follow-up; however, all 33 participants were included in the ITT analysis (figure 1). Baseline characteristics are summarised in table 1. No significant differences were found in any demographic variables (including gender and age) between the four groups. The severity of depression (HAMD-17 and CES-D scores) and subjective quality of life (WHOQOL-BREF score) at baseline were comparable with no statistically significant differences ($p>0.05$).

HAMD-17 scores and remission rate

As shown in table 2, after 6 weeks of intervention, the HAMD-17 scores in the EA, CBT, and EA+CBT groups were greatly reduced relative to baseline ($p<0.01$) while no significant changes were observed within the control group ($p>0.05$). Inter-group comparisons showed that the post-treatment HAMD-17 scores in all three intervention groups were significantly lower than that in the control group ($p<0.01$); however, there were no statistically significant differences between the three intervention groups ($p>0.05$). χ^2 tests revealed a significantly lower remission rate in the control group relative to the other three groups (18.2% vs 66.7–83.3%; table 3).

CES-D scores

After 6 weeks of intervention, the CES-D scores in the EA, CBT, and EA+CBT groups were all greatly reduced compared with baseline values ($p<0.01$) while no significant change occurred in the control group ($p>0.05$; table 2). Inter-group comparisons showed that post-treatment CES-D scores in all three intervention groups were significantly lower than those in the control group ($p<0.01$); however, there were no statistically significant differences between the three intervention groups ($p>0.05$).

HAMD-17 factor score comparisons

After the 6-week treatment regime, the HAMD-17 factor scores including anxiety/somatisation, sleep disturbance, retardation, and cognitive impairment were each attenuated in the three intervention groups compared with the control group ($p<0.05$; table 2). Post-hoc comparisons demonstrated that the anxiety/somatisation score improved to a significantly greater degree in the EA+CBT group compared with the other two intervention groups (EA and CBT alone, $p<0.05$ each). Sleep disturbance scores decreased more in the EA group than in the CBT and EA+CBT groups ($p<0.05$ each), while retardation scores in the two CBT-treated groups (CBT alone and EA+CBT) were both significantly lower than the EA group ($p<0.01$ and $p<0.05$, respectively). By contrast, there were no significant differences in cognitive impairment scores between the three intervention groups ($p>0.05$).

WHOQOL-BREF scores

As shown in table 4, following 6 weeks of treatment, the general health, physical health, psychological health, and social relationship domain scores were greater in the three intervention groups compared with the control group ($p<0.05$), while overall quality of life and environment domain scores did not differ between the four groups ($p>0.05$).

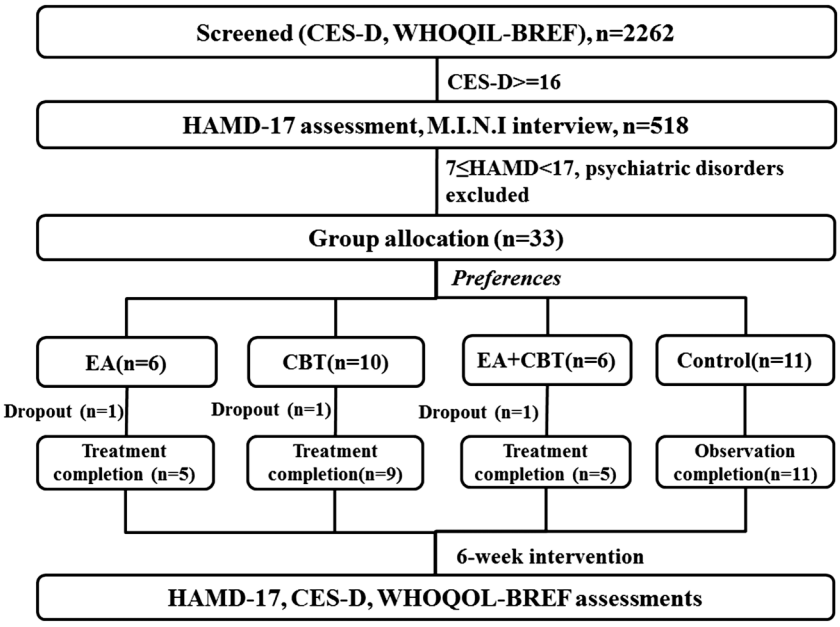

Figure 1 Flowchart detailing the screening and recruitment of participants. CBT, cognitive behavioural therapy; EA, electroacupuncture; HAMD-17, Hamilton Rating Scale for Depression. M.I.N.I., Mini International Neuropsychiatric Interview; CES-D, Center for Epidemiologic Studies Depression scale. WHOQOL-BREF, WHO Quality of Life-Brief version.

Furthermore there were no significant differences between the EA, CBT, and EA+CBT groups in any of the five domains.

DISCUSSION

In the current study, we provided EA and CBT (both alone and in combination) as interventions for SSD. The effectiveness of the three treatment regimens were evaluated based on pre- and post-intervention comparisons in 'subjective' (HAMD-17) and 'objective' (CES-D) measures. We found significant improvements in both scores following all three treatments compared to untreated controls, but no evidence that one approach was better than the other in terms of either HAMD-17 or CES-D. Similar results were observed in an earlier clinical study of the therapeutic effects of EA, CBT and combination therapy as early interventions for mild depression.[23] Based on the analysis of HAMD factor scores (secondary outcomes), some potential advantages of one treatment modality over another were identified. Specifically, EA was associated with a greater alleviation of sleep disturbance when used in the absence of CBT, while the group receiving CBT alone demonstrated a greater reduction in retardation scores compared with the EA group. Furthermore, combination therapy resulted in a greater reduction in anxiety/somatisation and retardation compared to EA and/or CBT alone. We also

Table 1 Baseline characteristics of participants

Variables	EA (n=6)	CBT (n=10)	EA+CBT (n=6)	Control (n=11)	p Value (F or χ^2 test)
Female, n (%)	4 (66.7%)	6 (60%)	3 (50%)	7 (63.6%)	0.962
Age (years)	22.0±0.9	21.6±1.4	21.3±1.4	21.5±1.0	0.805
HAMD-17 score	11.5±1.4	11.9±2.3	11.0±2.7	11.7±1.9	0.867
CES-D score	30.0±7.4	29.5±8.7	27.7±5.0	28.8±3.3	0.249
WHOQOL-BREF score					
Overall quality of life	2.5±0.5	2.7±0.9	2.8±0.7	2.8±0.6	0.395
General health	2.7±0.5	3.0±0.7	2.8±1.3	3.1±0.8	0.413
Physical health	19.6±2.6	18.2±4.1	19.7±3.3	20.7±4.4	0.184
Psychological health	18.2±1.8	16.2±2.1	17.7±2.4	17.6±3.4	0.043
Social relationship	8.2±1.8	8.9±1.9	8.1±1.6	9.3±1.4	0.218
Environment	22.7±3.3	22.8±4.6	24.8±4.3	22.7±5.1	0.383

Continuous data are expressed as mean±SD.
CBT, cognitive behavioural therapy; CES-D, Center for Epidemiologic Studies Depression scale; EA, electroacupuncture; HAMD-17, Hamilton Rating Scale for Depression; WHOQOL-BREF, WHO Quality of Life-Brief scale.

Table 2 HAMD-17 scores, factor scores and CES-D scores at baseline and 6 weeks

	EA (n=6)		CBT (n=10)		EA+CBT (n=6)		Control (n=11)		Inter-group comparison at 6 weeks
	Baseline	6 weeks	Baseline	6 weeks	Baseline	6 weeks	Baseline	6 weeks	p Value
HAMD-17	11.60±1.52	5.60±2.51**##	11.44±1.94	4.44±2.00**##	10.20±2.16	3.20±1.64**##	11.72±1.90	10.54±2.50	<0.001
Anxiety/somatisation	4.40±0.54	1.50±0.57**##	4.22±1.30	1.78±0.83**##	3.80±0.83	1.00±0.65**##△$	3.97±0.75	3.67±0.51	<0.001
Cognitive disturbance	0.90±0.44	0.40±0.50**#	1.33±0.50	0.22±0.23**##	1.00±0.60	0.20±0.24**##	1.01±0.64	1.17±0.65	0.03
Retardation	3.60±1.14	2.05±1.01**##	3.11±0.93	1.11±0.33**##△△	2.80±0.84	1.40±0.55**##△	3.67±0.82	2.83±1.16	<0.001
Sleep disturbance	2.00±0.71	0.25±0.50**##$§	1.89±0.78	1.01±0.51**##	1.80±1.09	0.60±0.54**##	2.29±0.54	2.17±0.75	<0.001
CES-D	27.20±5.44	12.80±2.95**##	27.89±5.46	13.11±3.68**##	27.20±5.63	12.00±4.64**##	27.50±1.64	26.30±1.63	<0.001

**p<0.01=intra-group comparisons (baseline vs 6 weeks). Far right hand-column shows overall ANOVA p values for inter-group comparisons at 6 weeks with post-hoc comparisons denoted by symbols, as follows: #p<0.05, ##p<0.01: versus control group; △p<0.05, △△p<0.01: versus EA group; $p<0.05: versus CBT group. §p<0.05: versus EA+CBT group.
ANOVA, analysis of variance; CBT, cognitive behavioural therapy; CES-D, Center for Epidemiologic Studies Depression scale; EA, electroacupuncture; HAMD-17, Hamilton Rating Scale for Depression.

Table 3 Clinical remission rates at 6 weeks

Group	n	HAMD <7 Cases (%)	HAMD ≥7 Cases (%)	p Value
EA	6	4 (66.7)	2 (33.3)	0.012
CBT	10	8 (80.0)	2 (20.0)	
EA+CBT	6	5 (83.3)	1 (16.7)	
Control	11	2 (18.2)	9 (81.8)	

Proportions compared using χ^2 test.
CBT, cognitive behavioural therapy; EA, electroacupuncture; HAMD-17, Hamilton Rating Scale for Depression.

found that quality of life in terms of general health, physical health, psychological health, and social relationship domains was significantly improved relative to untreated controls after the 6-week treatment, although no statistically significant differences were found between the three intervention groups.

Our finding that EA appeared to be better at improving sleep disturbance (a somatic symptom) is partly consistent with previous studies demonstrating the beneficial effect of EA on depressive symptoms,[25 26] in which EA (alone or in combination) resulted in relatively lower sleep disturbance scores compared to CBT. Previous research has suggested that acupuncture may help regulate circadian rhythm and melatonin levels, which are reported to be intimately linked to sleep-related problems and depressive disorders.[27–30]

Cognitive behavioural interventions are based on the notion that cognition plays a central role in the aetiology and maintenance of depressive disorders. In the present study, we employed the ABC theory, which is based on the premise that it is belief about (activating) events, rather than the events per se, that determines how one feels, thinks or behaves. The alleviation of depressive symptoms seen herein is in keeping with a previous study reporting that depression risk could be substantially lessened following a brief group CBT programme.[31]

Although we failed to detect any significant differences in overall effectiveness of combination therapy, it was associated with greater mitigation of anxiety/somatisation and retardation scores, which comprise both physical and psychological symptoms, such as depressed mood, loss of interests, psychic and somatic anxiety, and general and gastrointestinal symptoms. A recent study indicated that acupuncture and psychological counselling reduced depression symptoms to a comparable degree in primary care.[32] Neuroimaging studies also suggest that EA and CBT modulate complementary neural structures and brain networks,[33 34] which offers potential for further clinical research to test the hypothesis that combination therapy can be used to augment the effects of either treatment for depressive symptoms.

In regard to quality of life, no significant differences were found relative to the untreated control group in

Table 4 WHOQOL-BREF scores at baseline and 6 weeks

	EA (n=6)		CBT (n=10)		EA+CBT (n=6)		Control (n=11)		Inter-group comparison at 6 weeks
	Baseline	6 weeks	Baseline	6 weeks	Baseline	6 weeks	Baseline	6 weeks	p Value
Overall quality of life	2.60±0.55	2.80±0.45	2.67±0.60	3.22±0.44	2.80±0.84	3.40±0.89	2.59±0.54	2.67±0.81	0.21
General health	2.40±0.51	3.00±0.71**#	2.48±0.74	3.11±0.52**#	2.20±0.84	3.56±0.60**##	2.33±0.82	2.50±0.58	0.03
Physical health	17.00±2.34	22.60±2.30**##	16.67±2.82	19.78±3.11*#	17.40±1.67	20.80±2.38**##	17.33±0.82	17.00±1.41	0.01
Psychological health	16.40±2.60	18.40±2.53*#	16.56±1.87	20.77±2.54**##	17.10±1.10	20.20±1.30**##	17.17±2.56	16.83±2.40	<0.001
Social relationship	7.60±1.86	8.90±3.19*#	8.10±1.92	10.89±2.71**##	7.80±1.63	10.00±1.22**##	8.17±1.45	7.33±1.21	0.01
Environment	21.20±3.11	23.60±1.51	21.67±3.27	23.33±2.12	22.20±2.68	23.80±2.49	22.67±5.12	22.17±5.23	0.09

*p<0.05, **p<0.01=intra-group comparisons (baseline vs 6 weeks). Far right hand-column shows overall ANOVA p values for inter-group comparisons at 6 weeks with post-hoc comparisons denoted by symbols, as follows: #p<0.05, ##p<0.01: versus control group.
ANOVA, analysis of variance; CBT, cognitive behavioural therapy; EA, electroacupuncture; WHOQOL-BREF, WHO Quality of Life-Brief scale.

overall scores or environment domain scores. One possible explanation might be that overall quality of life is such a complex and comprehensive assessment that it would be difficult to influence within a 6-week period. Furthermore, the environmental domain includes factors such as the natural environment and economic status, which are unlikely to be improved by short-term inventions.

In the current study, we allocated subjects according to their preferences. Despite screening 2262 undergraduates and performing 518 HAMD assessments, only 33 subjects finally agreed to participate in the study (figure 1) and one third of these chose to receive no intervention. The low recruitment rate and stated preference for treatment might relate to limited knowledge of SSD and potential stigma associated with psychological disorders, which is an important public health issue. In addition, although overall effectiveness of the different treatments was similar, EA and EA+CBT appeared to be less acceptable therapies, which could be ascribed to insufficient understanding of acupuncture among undergraduates.

There are several major limitations to our study. Firstly, the sample size is small, therefore the findings must be interpreted with great caution. Only tentative conclusions may be drawn regarding the effectiveness of the various interventions in SSD, and further studies with larger sample sizes are warranted. Secondly, we did not apply randomisation during group allocation. Although preference is an important factor in routine care, lack of randomisation is associated with a high risk of bias due to potential confounding by known or unknown factors. Thirdly, due to the relatively short duration of follow-up in the present study, it remains unclear whether EA and CBT (alone or as combination therapy) will have long-term prophylactic effects with respect to the prevention of major depression, and extended follow-up of patients with SSD treated using EA±CBT is required. Finally, as our study selected undergraduates as subjects, it is possible that our results are not generalisable to other populations that are also at high risk of SSD.[35 36]

In summary, we have produced encouraging preliminary evidence that EA and/or CBT as early interventions are likely to be beneficial for SSD, reflected by significant improvements in depressive symptoms and quality of life after 6 weeks of treatment relative to untreated controls. Although our conclusions are greatly limited by a small sample size, our analysis of secondary outcomes (HAMD-17 factor scores) indicated that EA and CBT appear to target different symptoms, suggesting that combination therapy might potentially represent a better strategy for SSD treatment. Larger-scale, randomised (ideally multicentre) trials are required to evaluate conclusively the effectiveness of EA±CBT for the prevention and treatment of major depressive disorders.

Acknowledgements The authors would like to thank Dr Yutong Fei from Beijing University of Chinese Medicine and Dr Sihong Song from the University of Florida for their suggestions regarding manuscript revision.

Contributors TY, TG and WZ conceived and designed the trial. TG, WZ, WM, JH and XH conducted the questionnaire survey. WZ and XY conducted the HAMD-17 assessments. ZG and XY performed the EA and CBT, respectively. TG and XC analysed the data. TG and TY drafted and revised the manuscript. All authors approved the final version before publication.

Funding This study was supported by an international cooperation project supported by the China Ministry of Science and Technology (reference no. 2007DFA30780).

Competing interests None declared.

Patient consent Obtained.

Ethics approval Medical Ethical Committee of the Third Affiliated Hospital of Beijing University of Chinese Medicine.

Provenance and peer review Not commissioned; externally peer reviewed.

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