Acupuncture for the Treatment of Major Depressive Disorder: A Randomized Controlled Trial

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Background: Over 50% of patients with major depressive disorder (MDD) either do not tolerate or do not respond to antidepressant medications. Several preliminary studies have shown the benefits of acupuncture in the treatment of depression. We sought to determine whether a 2-point electroacupuncture protocol (verum acupuncture) would be beneficial for MDD, in comparison to needling at nonchannel scalp points with sham electrostimulation (control acupuncture).

Method: Fifty-three subjects aged 18–80 years, recruited via advertisement or referral, were included in the primary analysis of our randomized controlled trial, which was conducted from March 2004 through May 2007 at UPMC Shadyside, Center for Complementary Medicine, in Pittsburgh, Pennsylvania. Inclusion criteria were mild or moderate MDD (according to the Structured Clinical Interview for *DSM-IV* Axis I Disorders) and a score of 14 or higher on the Hamilton Depression Rating Scale (HDRS). Exclusion criteria included severe MDD, seizure disorder or risk for seizure disorder, psychosis, bipolar disorder, chronic MDD, treatment-resistent MDD, and history of substance abuse in the prior 6 months. Patients were randomized to receive twelve 30-minute sessions of verum versus control acupuncture over 6 to 8 weeks. The HDRS was the primary outcome measure. The UKU Side Effect Rating Scale was used to assess for adverse effects.

Results: Twenty-eight subjects were randomized to verum electroacupuncture and 25 to control acupuncture. The 2 groups did not differ with regard to gender, age, or baseline severity of depression. Both groups improved, with mean (SD) absolute HDRS score decreases of −6.6 (5.9) in the verum group and −7.6 (6.6) in the control group, corresponding to 37.5% and 41.3% relative decreases from baseline. There were no serious adverse events associated with either intervention, and endorsement of adverse effects was similar in the 2 groups.

Conclusions: We were unable to demonstrate a specific effect of electroacupuncture. Electroacupuncture and control acupuncture were equally well tolerated, and both resulted in similar absolute and relative improvement in depressive symptoms as measured by the HDRS.

Trial Registration: clinicaltrials.gov Identifier: NCT00071110

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Depression is a common problem affecting as much as 20% of the adult population during their lifetime.[1] Depression is associated with reduced quality of life, increased suicide risk, and increased morbidity and mortality of common conditions such as heart disease[1] and is often resistant to treatment, with over 50% of patients either not tolerating or not responding to antidepressant medications.[2,3] In addition, many Americans refuse conventional treatments for depression, or they discontinue them prematurely.[4,5] Other barriers to adequate antidepressant treatment involve perceived stigma associated with mental illness and minimization of the need for somatic treatment.[6]

Thus, a growing number of Americans have been turning to complementary and alternative modalities for the treatment of depression.[7] In a large survey, depression was among the 10 most frequently reported medical conditions for which respondents sought alternative treatments.[8]

These alternatives might be used as adjuncts to, or substitutes for, conventional acute treatments or as maintenance or preventive treatments following remission. A 2005 Cochrane review[9] found 7 published reports[10–16] on controlled studies of the efficacy of acupuncture for major depressive disorder (MDD). Overall, these 7 trials included a total of 547 patients, but they used a variety of designs and acupuncture interventions, and most of them had significant methodological flaws.[9] We identified 2 additional reports[17,18] published since 2004, for a total of 9 published studies: In 5 studies, all conducted in China, acupuncture or electroacupuncture was as efficacious as, or more efficacious than, amitriptyline (150–400 mg/d)[10–13] or maprotiline (75–250 mg/d).[15] By contrast, in the 2 US studies,[14,18] acute response and remission rates did not differ significantly among subjects randomized to depression-specific acupuncture protocols according to the principles of traditional Chinese medicine (TCM), nonspecific ("control") acupuncture, or a wait-list condition.[14,18] Finally, in a small Australian study[17] (N = 30), there was greater improvement in depressive symptoms with active laser acupuncture than with control laser acupuncture.

In a recent meta-analysis,[19] the efficacy of monotherapy acupuncture was comparable to that of an antidepressant alone—and not different from control acupuncture. A recent

update of the Smith et al Cochrane review[20] included all randomized controlled trials comparing acupuncture with control acupuncture, no treatment, pharmacologic and psychotherapeutic treatment, or standard-of-care treatment. On the basis of a total of 30 trials involving over 2,800 participants, the authors concluded that there was insufficient evidence of a consistent beneficial effect of acupuncture.[20] However, a recent randomized controlled trial[21] found depression-specific acupuncture to be more beneficial than nonspecific control acupuncture in depressed pregnant women,[21] supporting the possibility that acupuncture could be a valuable alternative to pharmacotherapy given the risks and side effects of antidepressants during pregnancy.[21,22]

We used a randomized parallel-group design to compare the efficacy and tolerability of electroacupuncture and control ("sham") acupuncture for the treatment of mild or moderate MDD. We hypothesized that (1) depressed subjects randomized to 12 sessions of electroacupuncture would have a significantly higher decrease in their scores on the Hamilton Depression Rating Scale (HDRS)[23] than subjects randomized to control acupuncture, (2) a higher proportion of subjects randomized to electroacupuncture would experience clinical response, (3) a significantly higher proportion of depressed subjects randomized to electroacupuncture than to control acupuncture would experience an improvement in functioning, and (4) there would be no significant difference between subjects randomized to electroacupuncture and control acupuncture with regard to adverse events.

METHOD

Subjects

Patients aged 18–80 years who met the criteria for mild or moderate MDD, according to the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID),[24] and who presented with an HDRS score of 14 or above were recruited via advertisement or referral. Patients with severe MDD (as per SCID criteria) or with acute suicidality were excluded from the study. Other exclusion criteria included (1) a seizure disorder or significant risk factors for a seizure disorder (history of brain trauma, recent stroke, brain tumor); (2) psychosis; (3) bipolar disorder; (4) chronic MDD (as per SCID criteria, ie, duration of 2 years or longer); (5) treatment-resistant MDD, defined as having failed at least 1 prior adequate antidepressant trial according to the criteria of the Antidepressant Treatment History Form[25]; and (6) history of substance abuse in the 6 months prior to enrollment.

The trial was conducted from March 2004 through May 2007 at UPMC Shadyside, Center for Complementary Medicine, in Pittsburgh, Pennsylvania, and was registered at www.clinicaltrials.gov (Identifier: NCT00071110). The protocol was approved by the Institutional Review Board of the University of Pittsburgh, Pittsburgh, Pennsylvania, and all subjects provided written informed consent.

Active and Control Interventions

Treatment regimen. Both the active and control intervention consisted of 12 sessions (2 sessions/wk), with each session lasting 30 minutes.

Cointerventions. All antidepressants and other psychotropic medications were tapered prior to randomization. Subjects remained free of psychotropic medications during the duration of the study. No other cointerventions (eg, herbs, exercises, life-style advice) were used.

Needling procedures. For subjects randomized to the active electroacupuncture intervention, 0.22×30-mm sterile stainless steel needles were inserted at the following 2 points: Du 20 (top of the scalp, located at the intersection of the midsaggital plane and an imaginary line drawn between the apexes of the ears) and Yintang (midpoint between the eyebrows). These points were selected on the basis of the protocol reported by Luo et al.[26] At Du 20, the needle was inserted obliquely in the frontal direction beneath the scalp for 2 cm. At Yintang, the needle was inserted obliquely and downward for 2 cm. An Electro-Stimulator 4-C (Pantheon Research, Venice, California) was connected to the needles with a current of 3–5 mA and a frequency of 2 Hz. At this current intensity, subjects typically felt a slight but not uncomfortable twitching. Current was applied for 30 minutes.

The control intervention consisted of needling at nonchannel scalp points with sham electrostimulation. For subjects randomized to this control acupuncture intervention, the procedures closely followed the procedures used for the active electroacupuncture intervention except that (1) needles were inserted at 2 points that are remote from any classically described meridian or extraordinary acupuncture point and (2) no current was applied to the needles. These 2 points were located as follows: the anterior superior aspect of each ear where the helix meets the temporal region was identified, and the 2 control points were 3 cun (a Chinese word that translates to "anatomical inch") superior bilaterally. These points correspond to the area of the coronal suture and the inferior temporal line. The location of these points on the head enhanced the similarity between the control acupuncture and the electroacupuncture and the believability of the control procedures.[27,28] The needles were inserted obliquely approximately 1 cm, which was the minimum needed to allow a stable connection to the electroacupuncture leads. We used a control electro-stimulator identical to the one used for the electroacupuncture intervention, with the lead modified so that no electrical stimulation was administered when the stimulator was turned on.

Practitioner background. A licensed acupuncturist provided both the active and controlled interventions. The acupuncturist had 4 years of schooling, completing a Masters of Acupuncture and Traditional Chinese Medicine, was certified by the National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM), was a licensed acupuncturist, and had been in the practice of acupuncture and TCM for 5 years prior to the start of the study. His clinical practice included the treatment of anxiety

disorders and depression. He monitored the subjects periodically throughout the session for both active and control conditions, but he did not engage the subjects in conversation.

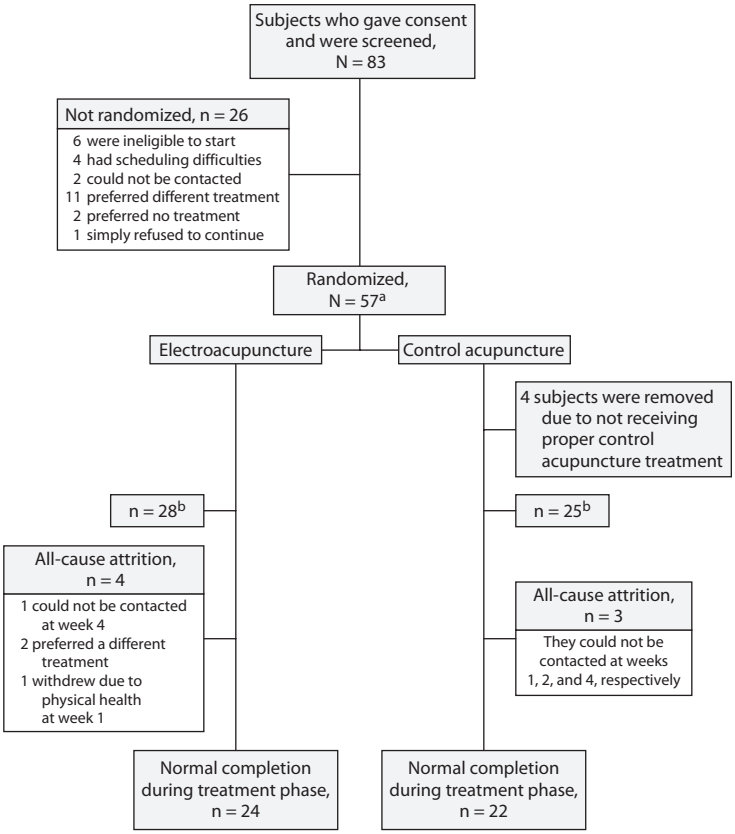
Outcome Measures and Other Assessments

Ratings were performed at the initial screen, at baseline prior to the first intervention session, weekly during the intervention, and 2 weeks postintervention. All ratings were performed by a trained research associate who was blind to the subject's randomized assignment.

The primary outcome measure was defined a priori as the absolute change in HDRS score. In addition, we also compared the proportions of responders in each group, with response defined as both a final HDRS score of 10 or less and a relative decrease of at least 50% from baseline. The UKU Side Effect Rating Scale (UKU)[29] was used weekly to assess tolerability. The Medical Outcomes Study 36-Item Short-Form Health Survey (MOS-SF-36)[30] was used at baseline and completion to assess functional improvement. Response rates, the UKU, and the MOS-SF-36 were a priori–defined secondary outcome measures. The Global Assessment of Functioning[31] was also completed at baseline and 2 weeks postintervention. In addition, an exploratory analysis was conducted to determine whether acupuncture had a meaningful impact on anxiety or sleep symptoms that have been shown to be frequently present with MDD and to respond to antidepressant treatment.[32,33] We assessed the change in scores for 2 HDRS subscales: HDRS anxiety (items 9, 10, 11, and 15 for agitation, psychic anxiety, somatic anxiety, and hypochondriasis, respectively) and HDRS sleep (items 4, 5, and 6 for early, middle, and late insomnia, respectively).[33]

At baseline, the Cumulative Illness Rating Scale[34] was completed to assess for comorbid physical illnesses, and the Mini-Mental State Examination[35] was complete to assess cognitive status.

Figure 1. Flowchart of Recruitment and Retention of Study Subjects



[a]These 57 subjects were included in the sensitivity analysis.
[b]These 53 subjects were included in the primary analysis.

Statistical Analysis

Randomized subjects who completed at least 1 follow-up assessment were included in the intent-to-treat analysis. We used a hierarchical linear model to assess the difference in baseline mean HDRS scores between the 2 groups (electroacupuncture and control acupuncture). The significance of the treatment effect and rate of change was compared using a mixed-effects model with random intercepts to detect time and group-by-time differences that were treated as fixed-effects study factors in the mean-response mixed-model analysis. The dependent variable was the HDRS score at each time point. We assumed an unstructured covariance structure to account for correlation among different intervention assessment points. The significance of the treatment effect was assessed using the likelihood ratio statistic using a type I error of $\alpha = .05$. The analysis was performed using SAS Version 9.2 PROC MIXED.[36] Proportions of responders in each group were compared with χ^2 statistics; tolerability (measured by the UKU) and functional improvement (measured by the MOS-SF-36) were compared using 2-sample *t* tests. Changes in the scores for the HDRS anxiety and sleep subscales were analyzed using a hierarchical linear model as described above.

On the basis of the results of studies that had been published at the time this study was designed,[12,14] we predicted that we would observe a mean (SD) improvement in HDRS scores of approximately 12.2 (5.4) points in the electroacupuncture group and 2.9 (7.9) points in the control acupuncture group. Thus, we estimated that with at least 20 subjects in each group we would have a 91% power to detect a significant difference between the 2 groups.

RESULTS

Figure 1 summarizes the recruitment and retention of study subjects. Of 83 persons screened, 57 subjects who met all eligibility criteria were randomized—28 to electroacupuncture and 29 to control acupuncture. Over the first 4 months of the study, the primary acupuncturist erred in

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Table 1. Demographic and Baseline Clinical Characteristics of Study Subjects (N = 53)[a]

Characteristic	Electroacupuncture Group (n = 28)	Control Acupuncture Group (n = 25)	Statistic (t or χ^2)	P Value
Age at consent, y	46.0 (11.5)	49.1 (14.0)	0.88	.38
Sex, male, n (%)	7 (25.0)	8 (32.0)	0.32	.57
Race, white, n (%)	21 (75.0)	22 (88.0)	1.46	.23
Education, y	15.4 (2.7)	15.3 (2.8)	0.10	.92
Hamilton Depression Rating Scale score	17.7 (3.9)	18.6 (2.9)	0.89	.36
UKU Side Effect Rating Scale score	13.4 (5.0)	15.9 (6.0)	1.74	.09
Mini-Mental State Examination score	29.6 (0.6)	26.7 (0.6)	0.53	.60
Cumulative Illness Rating Scale score	2.6 (2.2)	3.8 (3.0)	1.68	.10
Medical Outcomes Study 36-Item Short-Form Health Survey score				
Physical component	48.8 (9.9)	48.8 (11.8)	0.00	1.00
Mental component	27.1 (9.0)	25.8 (10.9)	−0.45	.66
Bodily pain index	62.5 (24.8)	60.3 (23.7)	−0.31	.75
Global Assessment of Functioning score	60.5 (6.1)	59.2 (5.2)	−0.84	.41
Hamilton Depression Rating Scale sleep subscore	2.5 (1.5)	1.8 (1.7)	−1.58	.12
Hamilton Depression Rating Scale anxiety subscore	4.8 (1.7)	4.5 (1.6)	−0.52	.61

[a]All results are reported as mean (SD) unless otherwise indicated.

Table 2. Score Changes From Baseline to Postintervention Evaluation (N = 45)[a]

Measure	Electroacupuncture Group (n = 23)	Control Acupuncture Group (n = 22)	Statistic (t)	P Value
Hamilton Depression Rating Scale	−7.4 (6.2)	−7.9 (7.4)	0.24	.81
UKU Side Effect Rating Scale	−4.0 (4.6)	−7.0 (6.3)	1.59	.12
Medical Outcomes Study 36-Item Short-Form Health Survey				
Physical component	0.5 (6.9)	−1.7 (8.0)	−1.00	.32
Mental component	6.2 (13.6)	14.1 (17.5)	1.56	.09
Bodily pain index	−1.0 (18.3)	6.8 (19.7)	1.40	.17
Global Assessment of Functioning	10.3 (10.3)	11.4 (8.8)	0.39	.70

[a]All results are reported as mean (SD).

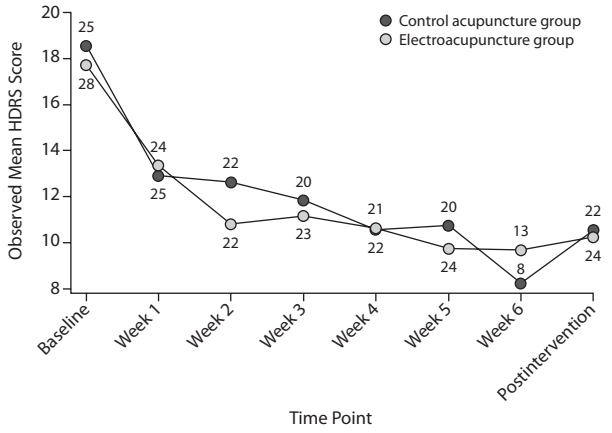
treating the first 4 control acupuncture subjects. Although he correctly used the control electricity procedure (ie, no current was applied to the needles), he placed needles into the verum electroacupuncture points of Du 20 and Yintang for these 4 subjects randomized to control acupuncture. Therefore, we excluded them from the primary analysis, resulting in the inclusion of 28 subjects treated with electroacupuncture and 25 treated with control acupuncture in the intent-to-treat analysis. Of these, 24 subjects in the electroacupuncture group completed the protocol (21 of whom received at least 10 sessions), and 22 in the control acupuncture group completed the protocol (all of whom received at least 10 sessions).

Table 1 presents the demographic and baseline clinical characteristics of the 53 subjects included in the analysis. The 2 groups did not differ with regard to gender, age, education, baseline HDRS scores, and cognitive or functional status.

The absolute and relative decreases in mean (SD) HDRS scores observed in the 2 groups did not differ significantly (Table 2). In the mixed-model analysis including all subjects, the absolute decreases were −6.6 (5.9) for electroacupuncture versus −7.6 (6.6) for control acupuncture ($t_{48} = 0.59$, $P = .56$); the mean relative decreases were 37.5% (32.8) vs 41.3% (34.3), respectively ($t_{48} = 0.41$, $P = .69$). The mixed model revealed no differences between the rates of change (group-by-time interaction estimate = 0.13, SE = 0.23; $P = .47$), and there was no statistically significant difference between the HDRS scores in the 2 groups at end-point or at any evaluation point (Figure 2). Similarly, the proportion of responders did not differ significantly in the 2 groups (40.0% for electroacupuncture vs 44.0% for control acupuncture; $\chi^2_1 = 0.08$, $P = .77$).

We also conducted a sensitivity analysis that included in each study group the 4 subjects who were randomized to control acupuncture but who had the needles inserted into the verum points. Again, the absolute and relative decreases observed in the 2 groups and the proportion of responders did not differ significantly between the groups: (1) When we included these 4 subjects in the control acupuncture group, the mean HDRS absolute decreases were −6.6 (5.9) for electroacupuncture and −8.3 (6.4) for control acupuncture ($t_{52} = -0.96$, $P = .34$); the mean relative decreases were 37.5% (32.8) versus 45.9% (34.4), respectively ($t_{52} = 0.91$, $P = .36$);

Figure 2. Hamilton Depression Rating Scale (HDRS) Weekly Scores (main efficacy findings)[a]



[a]Plot of observed mean depression scores by week, with the frequency at each point labeled.

and the proportions of responders were 40.0% versus 48.3%, respectively ($\chi^2_1 = 0.37$, $P = .54$). (2) When we included these 4 subjects in the electroacupuncture group, the mean absolute decreases were −7.3 (5.9) for electroacupuncture and −7.6 (6.6) for control acupuncture ($t_{52} = -0.19$, $P = .85$); the mean relative decreases were 42.5% (33.6) versus 41.3% (34.3), respectively ($t_{52} = -0.13$, $P = .90$); and the proportions of responders were 44.8% versus 44.0%, respectively ($\chi^2_1 = 0.0037$, $P = .95$).

There were no serious adverse events in either group. Endorsement of adverse effects and endpoint UKU scores did not differ between the 2 groups (see Table 2). Similarly, there was no difference in functional improvement, as measured by the MOS-SF-36 (see Table 2). The 2 groups had similar baseline HDRS sleep subscale scores (see Table 1), and a second mixed model revealed that both groups experienced a significant decrease in their HDRS sleep subscale scores over time ($t_{253} = -2.04$, $P = .04$), with no difference between the groups. The 2 groups had similar baseline HDRS anxiety subscale scores (see Table 1), and both groups also experienced a significant decrease in their HDRS anxiety subscale scores over time ($t_{253} = -4.99$, $P < .001$), with no significant difference between the groups.

DISCUSSION

We conducted a randomized controlled trial to compare the efficacy and tolerability of electroacupuncture and control acupuncture for the treatment of mild or moderate MDD. Electroacupuncture was well tolerated and resulted in close to a 50% reduction in depressive symptoms as measured by the HDRS. However, there was no significant difference between the absolute or relative changes in HDRS score observed in the electroacupuncture and the control acupuncture groups. Similarly, the 2 groups did not differ with regard to functional improvement or improvement in anxiety or sleep symptoms. These results differ from the reports in the Chinese literature[10–12,26] but are similar to reports from other trials conducted in North America.[14,18,37]

Our negative results need to be considered in the context of some potential limitations in the design and conduct of our study: an error in the treatment of 4 subjects, the selection of our control ("sham") condition, and a standardized protocol using only 2 needles.

Inadvertently, the acupuncturist treated the first 4 subjects in the control group with the verum points without electricity. As a result, these subjects did not fit with either group, and they were excluded from the analysis. A sensitivity analysis showed that including them in either group would not appreciably change the study results.

One possible interpretation of our results is that the beneficial effect of electroacupuncture we observed is due solely to a placebo effect. However, there are many complexities in conducting acupuncture research. Similar to research on pharmacotherapy, studies of acupuncture commonly find that a believable control intervention improves clinical outcomes comparably to the active (verum) acupuncture treatment but to a greater extent than no-treatment, wait-list, or other nonneedle controls.[38,39] A placebo is defined as being *inert* and *believable*.[40] Extensive studies and commentaries have indicated problems with both of these assumptions.[41] As with the use of placebo pills, needling at nonacupuncture points can be associated with physiologic effects that can be detected by functional neuroimaging.[42] Even sham or nonpenetrating needles display these properties. For our control condition, the needles were inserted far from any specific acupuncture meridian. However, in both TCM and Japanese approaches, the entire scalp is considered a microsystem, with any point corresponding to an area of the body and having some effect.[38,43] The control points we used are located on the scalp and thus might not offer a viable inert control to the verum points. Therefore, we might have in fact tested 2 potentially effective treatments, explaining why we did not detect any differences between our active and control interventions. Also, care was taken in our study and other studies to maintain the blind; however, given the difference in technique and the fact that the treating acupuncturist cannot be blinded, it is difficult to have the same level of concealment as in a placebo-drug study.

There has been extensive research and discussion in the literature regarding the optimal design of acupuncture trials, including the above issues pertaining to placebo.[40,41,43,44] Considerations include the use of nonpenetrating, telescoping needles; the use of a multigroup design with comparison of verum acupuncture, a needle control, and some other control such as wait-list; and options for providing a more individualized acupuncture intervention.[28,40,43]

Another factor that has an impact on acupuncture trials is the use of a standardized treatment. In clinical practice, an acupuncturist will individualize treatment on the basis of the TCM diagnosis, which includes evaluation of constitutional symptoms, pulses, and the tongue. This evaluation leads to

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the use of specific points for treatment and to modulation of the intensity of stimulation of the needles, all based on the TCM diagnosis. Conversely, most Western-designed randomized controlled trials, including this study, have utilized a standardized protocol for all subjects, which may minimize the treatment efficacy.

Finally, dosage of the treatment may also have contributed to this study's negative results. The use of only 2 acupuncture points reflects a minimalist approach. We selected this approach on the basis of the positive results of previous studies published by Luo et al[11,26] that used the same 2 acupuncture points. However, their study used a much higher dose of electroacupuncture (6 sessions per week for 6 weeks) than our protocol, which consisted of twelve 30-minute sessions—a dosage that has been commonly used in other studies and that is considered adequate to determine an acute effect. A number of other acupoints have been described in the TCM literature as being useful for the treatment of depression, anxiety, and sleep problems. Consequently, one could consider a "dose-finding study" comparing our active protocol, 1 or 2 additional conditions with a greater number of points to be treated, and a control condition. However, such a multigroup design would require a much larger sample size. Moreover, recruitment into our study was hindered by the exclusion of anyone taking any psychotropic medications. To conduct a larger study, investigators could include and stratify subjects who are currently taking a selective serotonin reuptake inhibitor or other antidepressant.

In conclusion, our data support the tolerability of electroacupuncture in the treatment of mild or moderate MDD. Both the subjects treated with electroacupuncture and those who received control acupuncture experienced a significant and comparable decrease in HDRS scores from baseline to end-of-intervention. Thus, we were not able to demonstrate a specific effect of electroacupuncture. Future studies might consider different designs, such as a 3-group design comparing our 2-acupoint protocol, a more extensive TCM-based acupuncture intervention, and a control condition using noninserted placebo needles.

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