Therapeutic effect of acupuncture combined with antidepressants on changes in the HAMD-17 score in major depressive disorder

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Therapeutic effect of acupuncture combined with antidepressants on changes in the HAMD-17 score in major depressive disorder

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Abstract. The effectiveness of antidepressant medications ranges from 60%–70%, and serious side effects can occur; therefore, various therapeutic modalities have been developed, including acupuncture. This study aimed to compare the effectiveness of acupuncture and antidepressant with that of sham acupuncture and antidepressant in patients with major depressive disorder assessed using the Hamilton Rating Scale for Depression (HAMD-17). A single-blind randomized clinical trial was conducted in 48 patients with major depressive disorder allocated to the intervention (acupuncture and antidepressant) and control (sham acupuncture and antidepressant) groups. The mean HAMD-17 scores in the intervention group before and after treatment were 22.2 ± 3.38 and 7.3 ± 2.64, respectively, whereas those in the control group before and after treatment were 21.4 ± 3.10 and 9.3 ± 3.33, respectively. A significant decrease in the mean HAMD-17 scores was observed between the intervention and control groups before and after 12 therapy sessions (14.9 ± 2.45 to 12.2 ± 4.30; p < 0.005). Thus, acupuncture and antidepressant was more effective in reducing the symptoms of major depressive disorder than was sham acupuncture and antidepressant.

1. Introduction
Depression is a form of psychiatric disorder that affects an individual’s mood (affective or mood disorder) marked by gloomy feelings, decreased passion for life, and feelings of uselessness and despair [1,2]. According to the Diagnostic and Statistical Manual of Mental Disorders-IV Text Revision (DSM-IV TR), major depressive disorder (heavy or unipolar) is a psychiatric disorder that is characterized by the appearance of at least four of the following symptoms: loss of weight and appetite, sleep disturbance, loss of interest in activity, low energy, guilt, difficulty in concentrating and making decisions, and recurrent death or suicidal thoughts, without a history of manic (mixed or hypomanic) episodes, persisting since ≥2 weeks [3,4].
The prevalence of depression worldwide is approximately 8%–20%, and depression is estimated to affect 350 million individuals [5-7]. The World Health Organization (WHO) predicted that the burden of depression is expected to be second only to heart diseases by 2020, with a prevalence rate of approximately 5%–13% for women and 2%–8% for men and an estimated lifetime prevalence of 16.2% [2-8]. Based on the Global Burden of Disease data on 2000, depression is ranked fourth as the main cause of disability [9]. The most common depressive disorder is major depressive disorder [3,10,11], the prevalence of which is 10%–25% in women and 5%–10% in men and approximately 2% in students and 5% in teenagers in the developed countries [11,12]. Depression is a major reason for suicide, with approximately 15% of depressed patients committing suicide, and ranks sixth in the USA among the reasons for suicide [2-12]. The World Mental Health Survey conducted in 17 countries found that approximately 1 in 20 individuals on average has an episode of depression every year and almost 1 million lives are lost every year because of suicide [6].

In Indonesia, no research has been conducted on depression, concealed depression, and anxiety sufferers. However, periodic observations have suggested that psychiatric disorders, such as depression and anxiety, are continually increasing [2]. Indonesian health research (Riskesdas) in 2013 has shown that the national prevalence of mental–emotional disorders among 37,728 subjects, such as anxiety and depression, was 6.0%. The province with the highest prevalence was Central Sulawesi (11.6%), and the prevalence was higher in cities than in rural areas [13]. A morbidity survey of the Family Health Survey in 1995 found that the prevalence of mental–emotional disorder symptoms in Indonesia was 140 per 1000 citizens [14]. Cipto Mangunkusumo Hospital data from 1996 showed that referrals to the psychiatric ward mostly came from internists (39.1%), surgeons (18.1%), neurologists (17.4%), and orthopedists (9.4%) [11].

Although psychological and psychopharmacological therapies are the main treatments for depressive disorder, some patients do not completely respond and experience relapses or side effects [5,15]. The effectiveness of antidepressant medications is only 60%–70%, and serious side effects can occur, so alternative therapy is needed. Acupuncture has been applied for the treatment of mental illness for a long time, particularly for heavy depression [12-16]. Recent studies have shown that acupuncture is a safe and effective therapy for neuropsychiatric disorders [5].

Several single-blind controlled clinical trials have proved the effectiveness of acupuncture therapy on depression, particularly major depressive disorder. In 2002, the WHO released an official report on diseases or medical conditions, including depressive disorder, treated using acupuncture therapy; however, further evidence is required [17]. Que et al studied the effect of acupuncture combined with paroxetine (PRX) on patients with major depressive disorder. Treatment outcomes were measured by using the 17-item Hamilton Depression Rating Scale (HAMD-17), Self-rating Depression Scale (SDS), and clinical response, which revealed greater clinical response in the manual acupuncture (MA) and electroacupuncture (EA) (69.8%) groups than in the group treated with PRX alone (41.7%) [5]. Zang et al conducted a study on the safety and efficacy of acupuncture combined with fluoxetine as an intervention for major depressive disorder. A total of 80 patients were divided into two groups, namely the combination of acupuncture with 10 mg/day fluoxetine and the sham acupuncture with 20–30 mg/day fluoxetine groups. They found no statistically significant difference in the therapeutic responses after the treatment between the acupuncture with 10 mg/day fluoxetine group (80%) and the sham acupuncture with 20–30 mg/day fluoxetine group (77.5%) or in the HAMD-17 scores, but improvement in the symptoms of anxiety and side effects was better in patients in the acupuncture with 10 mg/day fluoxetine group [18].

On the basis of these studies, we assumed that acupuncture is effective for the treatment of depressive disorder. In Indonesia, there is no study has proven the effectiveness of acupuncture in reducing depression symptoms, particularly those of major depressive disorder. The aim of this study was to compare the effectiveness of acupuncture+antidepressant with that of sham acupuncture+antidepressant in patients with major depressive disorder assessed using the HAMD-17 [19].
2. Methods
The study design was a single-blind randomized clinical trial. The study was conducted at the Psychiatric Clinic and Medical Acupuncture Clinic of Cipto Mangunkusumo Hospital, Jakarta, from October 2014 to February 2015. The study population comprised patients with major depressive disorder who came to the RSCM psychiatric clinic. The inclusion criteria were patients aged 18–65 years, those with major depressive disorder according to the Mini International Neuropsychiatric Interview (MINI) screening and diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders-IV, those with early HAMD-17 score ≥17, those receiving selective serotonin reuptake inhibitor (SSRI) antidepressant therapy related to major depressive disorder, those willing to participate in the study until completion, and those signed the informed consent. The exclusion criteria were patients who were pregnant, those with a history of other mental illness (according to the MINI screening), those with fever > 38 °C, those with normal sugar levels of ≥200 mg% determined via glucometry, and those with a tumor or wound at the acupuncture point. Patients were eliminated if they skipped >2 sessions.

The sample number was calculated using an unpaired numerical analytical method. A total of 48 subjects were included and randomly allocated to two groups using a randomization table to avoid selection bias. The treatment group received a combination of acupuncture and antidepressant (n = 25) and the control group received a combination of sham acupuncture and antidepressant (n = 23). Acupuncture was performed at the acupuncture points of GV20 Baihi, EX-HN1 Sishenchong, EX-HN3 Yintang, LI4 Hegu bilateral, and LR3 Taichong bilaterally thrice a week for 12 sessions using a 0.25 × 25-mm Dombang disposable needle. In the acupuncture treatment group, a pre-holed plaster was assembled and the needle was then inserted into the hole until a puncture sensation was felt. In the control group, a plaster with no hole was assembled and the needle was then inserted into the pad with the plaster not touching the subject’s skin. The needle was left in place for 30 min and then extracted. The primary outcome measure was the HAMD-17 score, which was assessed before the first therapy session and after the 3rd, 6th, 9th, and 12th sessions.

Comprehensive unpaired numerical data analysis was performed using the unpaired t test for normally distributed data and the Mann–Whitney test for non-normally distributed data in both groups. Differences between groups were considered statistically significant for p < 0.05. This study was conducted after receiving approval from the Health Research Ethics Committee of Faculty of Medicine, Universitas Indonesia-Cipto Mangunkusumo Hospital (Ethics review no: 718/UN2.F1/ETIK/2014). The subjects signed informed consent forms, and the privacy of their data was guaranteed.

3. Results
No subject was eliminated during the study. Demographic data and characteristics of subjects are presented in Table 1.

No statistically significant differences were observed between the treatment and control groups (p > 0.05) for all characteristics.

In both groups, the HAMD-17 scores decreased from the beginning of the session until the 12th session (treatment group: from 22.2 ± 3.38 to 7.3 ± 2.64; control group: from 21.4 ± 3.10 to 9.3 ± 3.33), but the decrease was greater in the treatment group (Table 2).

As seen in Table 3, significant differences were observed in the decreased HAMD-17 scores from before therapy to after the 3rd, 6th, 9th, and 12th sessions between the treatment and control groups. The score decrease after the 1st week (3x therapy) was 6.0 ± 2.62 in the treatment group and 4.1 ± 1.77 in the control group (p < 0.005) and that decrease after the 4th week was 14.9 ± 2.45 in the treatment group and 12.2 ± 4.30 in the control group (p < 0.005).

The largest HAMD-17 score decreases occurred for the 4th–6th questions that were regarding early, middle, and late insomnia (Table 4). Most patients in the treatment group experienced improvement in their sleep patterns.
Table 1. Demographic data and basic characteristic of subjects

| Information        | Treatment group (n = 25) | Control group (n = 23) | p     |
|--------------------|--------------------------|------------------------|-------|
| Sex                | Male         | 4 (16%)                | 3 (13%)| 1.00* |
|                    | Female       | 21 (84%)               | 20 (87%)|       |
| Age (years)        | Mean (SD)     | 49.9 (11.66)           | 48.2 (13.05)| 0.635**|
|                    | Median       | 50.0                   | 51.0   |       |
|                    | Range        | 25–65                  | 19–65  |       |
| Occupation         | Domestic     | 15 (60.0%)             | 14 (60.9%)|       |
|                    | Government/private employees | 9 (36.0%)                | 6 (26.1%)|       |
|                    | Entrepreneur | 1 (4.0%)               | 1 (4.3%)| 0.465* |
|                    | College student | -                     | 2 (8.7%)|       |
| Latest education   | Primary school | 3 (16.0%)              | 3 (13.0%)|       |
|                    | Middle school | 2 (8.0%)               | 6 (26.1%)|       |
|                    | High school   | 13 (52.0%)             | 7 (30.4%)|       |
|                    | Diploma       | 2 (8.0%)               | 4 (17.4%)|       |
|                    | Bachelor      | 3 (13.0%)              |        |       |
| Marital status     | Single        | 4 (16.0%)              | 7 (30.4%)|       |
|                    | Married       | 12 (48.0%)             | 9 (39.1%)| 0.493* |
|                    | Widow/widower | 9 (36.0%)              | 7 (30.4%)|       |

*chi square test; **t test

Table 2. Mean HAMD-17 scores before therapy and after 3rd, 6th, 9th, and 12th therapy sessions.

|                      | Treatment Mean | SD  | Control Mean | SD  | p      |
|----------------------|----------------|-----|--------------|-----|--------|
| HAMD-17 score before therapy | 22.2           | 3.38| 21.4         | 3.10| 0.42*  |
| HAMD-17 score after 3rd session | 16.2           | 4.13| 17.3         | 2.95| 0.31*  |
| HAMD-17 score after 6th session | 12.6           | 4.45| 13.6         | 3.39| 0.41*  |
| HAMD-17 score after 9th session | 8.7            | 2.66| 11.4         | 3.08| 0.002***|
| HAMD-17 score after 12th session | 7.3            | 2.64| 9.3          | 3.33| 0.003***|

(*) independent t test (t) for normal distributions; (**) Mann–Whitney test (Z) for non-normal distributions; X: p<0.05

Table 3. Decrease in mean HAMD-17 scores before therapy and after 3rd, 6th, 9th, and 12th therapy sessions

| Score decrease after therapy | Treatment Mean | SD  | Control Mean | SD  | p      |
|------------------------------|----------------|-----|--------------|-----|--------|
| HAMD-17 score decrease after 3x therapy (1st week) | 6.0            | 2.62| 4.1          | 1.77| 0.006***|
| HAMD-17 score decrease after 6x therapy (2nd week) | 9.6            | 3.58| 7.8          | 2.48| 0.012***|
| HAMD-17 score decrease after 9x therapy (3rd week) | 13.5           | 2.37| 10.1         | 2.47| <0.001**|
| HAMD-17 score decrease after 12x therapy (4th week) | 14.9           | 2.45| 12.2         | 4.30| <0.001**|

(*) independent t test (t) for normal distribution; (**) Mann–Whitney test (Z) for non-normal distribution; X: p<0.05
| Question | HAMD-17 score | Before therapy | After therapy |
|----------|---------------|----------------|---------------|
| 0        | 0             | 0              | 10            |
| 1        | 2             | 13             | 2             |
| 2        | 11            | 2              | 0             |
| 3        | 12            | 0              | 19            |
| 4        | 0             | 0              | 11            |
| 0        | 1             | 11             | 5             |
| 1        | 11            | 0              | 0             |
| 2        | 11            | 1              | 0             |
| 3        | 1             | 0              | 0             |
| 4        | 1             | 0              | 0             |
| 0        | 2             | 18             | 7             |
| 1        | 3             | 7              | 0             |
| 2        | 20            | 0              | 1             |
| 0        | 3             | 21             | 11            |
| 5        | 0             | 1              | 0             |
| 1        | 5             | 4              | 0             |
| 2        | 17            | 0              | 3             |
| 0        | 3             | 20             | 0             |
| 6        | 0             | 4              | 1             |
| 1        | 3             | 21             | 1             |
| 2        | 19            | 1              | 1             |
| 0        | 1             | 3              | 5             |
| 1        | 5             | 15             | 0             |
| 7        | 2             | 7              | 0             |
| 3        | 11            | 0              | 4             |
| 0        | 0             | 22             | 0             |
| 1        | 3             | 22             | 3             |
| 8        | 2             | 0              | 3             |
| 3        | 0             | 0              | 0             |
| 4        | 0             | 0              | 0             |
| 0        | 2             | 0              | 12            |
| 1        | 13            | 14             | 0             |
| 9        | 2             | 1              | 0             |
| 3        | 2             | 0              | 3             |
| 4        | 0             | 3              | 2             |
| 0        | 1             | 5              | 0             |
| 1        | 2             | 14             | 0             |
| 10       | 2             | 14             | 17            |
| 3        | 8             | 0              | 0             |
| 4        | 0             | 0              | 0             |
| 0        | 0             | 8              | 0             |
| 1        | 4             | 14             | 0             |
| 11       | 2             | 16             | 3             |
| 3        | 5             | 0              | 0             |
| 4        | 0             | 0              | 0             |
| 0        | 12            | 0              | 12            |
| 12       | 1             | 13             | 4             |
| 2        | 0             | 0              | 0             |
Table 4. Continue

| Question | HAMD-17 score | Before therapy | After therapy |
|----------|---------------|----------------|---------------|
| 0        | 0             | 0              | 9             |
| 13       | 1             | 4              | 16            |
|          | 2             | 21             | 0             |
|          | 0             | 23             | 23            |
| 14       | 1             | 2              | 2             |
|          | 2             | 0              | 0             |
|          | 0             | 12             | 24            |
|          | 1             | 2              | 1             |
| 16       | 2             | 11             | 0             |
|          | 3             | 0              | 0             |
|          | 4             | 0              | 0             |
|          | 5             | 0              | 0             |
|          | 0             | 24             | 25            |
| 17       | 1             | 1              | 0             |
|          | 2             | 0              | 0             |

Table 5. Treatment-related side effects observed during the study

| Side effects | Treatment group (n = 25) | Control group (n = 23) |
|--------------|--------------------------|------------------------|
| o None       | 14 (56%)                 | 23 (100%)              |
| o Present    | 11 (44%)                 | 0 (0%)                 |
| o Pain       | 8 (16.67%)               | 0 (0%)                 |
| o Hematoma   | 3 (6.25%)                | 0 (0%)                 |

In the treatment group, 14 (56%) subjects did not experience side effects during the therapy, whereas in the control group, all (100%) subjects experienced side effects of pain and 11 (22.9%) experienced side effects of pain and hematoma.

4. Discussion
This single-blind randomized clinical trial was conducted in 48 patients with major depressive disorder using HAMD-17 scores as measures of therapeutic outcomes. The aim of this study was to compare the effectiveness of acupuncture combined with antidepressant with that of sham acupuncture combined with antidepressant by assessing the decreases in the HAMD-17 scores after therapy for major depressive disorder. All subjects were randomly divided into the acupuncture combined with antidepressant group (treatment group) and the sham acupuncture combined with antidepressant (control group). The subjects were unaware of the therapy that they were going to receive and were willing to participate in the study for thrice a week until 12 sessions of therapy were completed. To maintain the compliance of patients, the researchers stayed in contact with the subjects during the therapy and always reminded them 1 day prior to the therapy and control sessions.

In both groups, the HAMD-17 scores decreased relative to the scores before therapy after the 3rd, 6th, 9th, and 12th sessions, but the decreases were greater in the treatment group than in the control group and all were statistically significant. The mean difference in the HAMD-17 scores was 6.0 ± 2.62 after the 1st week (three sessions) and 14.9 ± 2.45 after the 4th week (12 sessions) in the treatment group and 4.1 ± 1.77 after the 1st week (three sessions) and 12.2 ± 4.30 after the 4th week (12 sessions) in the control group. Similar results were also obtained by Wang et al. in their study on 76 patients.
diagnosed as having depression. Their patients were randomly divided into two groups as the treatment (acupuncture combined with SSRI) and control (SSRI only) groups. The HAMD-17 was used to quantitatively assess the patients after the 1st, 2nd, 4th, and 6th weeks of treatment. The mean (SD) baseline HAMD-17 scores were 22.2 (0.60) for the treatment group and 22.1 (0.33) for the control group. After the 1st week of treatment, the HAMD-17 score in the treatment group decreased to 15.6 (0.81), which was significantly different from that of 18.3 (0.55) in the control group (p < 0.05). This significant difference was maintained to the end of the treatment period [20].

The results of our study and those of Wang et al. demonstrated that acupuncture can provide an antidepressant effect and can synergistically work with antidepressant medications to improve the symptoms experienced by patients with major depressive disorder, as shown by the decreased HAMD-17 scores.

The mechanism underlying how acupuncture moderates depression remains unclear. Acupuncture has been associated with increases in monoamine neurotransmitters, particularly serotonin and norepinephrine that facilitate serotonin production in the brain stem and stimulate serotonin release at the terminal nerve. Acupuncture also modulates norepinephrine activity at the locus coeruleus (LC) and other parts of the brain, such as the hypothalamus, amygdala, and prefrontal cortex that regulate mood. Acupuncture can increase neurotransmitter availability in the neuronal synapse and, thereby, increase the interactions between postsynaptic cells, leading to various complex intracellular mechanisms [7,12,21,22]. These previous findings are strengthened by the study by Surijadi S of the EA effect on blood serotonin concentrations in patients with anxiety symptoms in which 84% of patients in the treatment group experienced increased serotonin concentrations and 67% of those in the control group experienced decreased serotonin concentrations [23].

Forehead acupuncture points innervated by the trigeminal sensory pathway have intimate connections with the brainstem reticular formation, particularly the dorsal raphe nucleus (DRN) and LC. The DRN and LC are major sources of 5-HT and NA neuronal antibodies that reach the subcortical and cortical areas, including the prefrontal cortex and amygdala, which are heavily involved in the pathogenesis of depression. Neuroimaging studies have shown that EA stimulation can directly modulate the activity of the emotion processing-related brain regions [24]. Acupuncture also induces dysregulation in the hypothalamic–pituitary–adrenal (HPA) axis through neuropeptide Y (NPY) and corticotropin-releasing factor (CRF). NPY is a neuropeptide in the central nervous system, particularly in the hypothalamus, which has an important role in depressive disorders. Increasing NPY expression in the periventricular nucleus modulates the nervous activity in the hypothalamus and hippocampus, which lowers the synthesis and release of CRF [25,26]. A feedback reaction then occurs along the HPA axis, which can inhibit stress reactions and normalize emotional functions. A study by Wang et al has demonstrated that acupuncture inhibited an overexpression of CRH and resolved stress via the regulation of the HPA function [27].

In addition to the above findings, acupuncture can also increase the expression of the adenyllylcyclase–cyclic adenosine monophosphate–protein kinase A cascade that has an important role in neuronal plasticity in the brain, particularly in the cortex, hippocampus, and hypothalamus, triggered by depression disorders [12]. A study by Lu et al has shown that acupuncture could activate extracellular signal–regulated kinase–cAMP response element-binding protein that influences brain-derived neurotrophic factor (BDNF) and neuronal function [10]. Additionally, the study by Sun et al revealed higher serum levels of BDNF after acupuncture [28]. Several other studies have also shown that acupuncture, either manual or EA, could increase neurotropin factors, such as nerve growth factor and BDNF. These factors could lead to the proliferation of nerve stem cells and protect nerves from damage [29,30].

Medications used for the treatment of depressive disorders must be able to correct neurotransmitter disturbances in the central nervous system [2]. SSRI antidepressants selectively inhibit serotonin resorption, monoamine oxidase inhibitors downregulate the adrenergic and serotonergic receptors, and tricyclics inhibit serotonin resorption and noradrenal in the synaptic clef at the nerve terminal. Serotonin has an important role in regulating the HPA axis because there is a direct relationship between synapses and corticotrophin-releasing hormone levels in the paraventricular nucleus from the
nucleus raphe dorsalis, which controls cortisol causing depression [25,31]. Therefore, acupuncture can synergistically work with antidepressants, particularly those from the SSRI class. Acupuncture can enhance serotonin release, and SSRIs selectively inhibit serotonin reuptake.

In a systematic review and meta-analysis by Stub et al of 26 randomized controlled trials involving 2,173 subjects with depression, 12 trials with 892 subjects showed that MA improved the symptoms, as measured by the HAMD score. There was no significant difference in the effects between the MA and EA groups [32]. Additionally, Qu et al conducted a study on the effect of acupuncture combined with paroxetine (PRX) on patients with major depressive disorder. They assigned 160 patients to PRX alone (n = 48), PRX combined with MA (PRX + MA, n = 54), and PRX combined with EA (PRX + EA, n = 58) therapy, but only 143 completed the study. Treatment outcomes were mainly measured using the HAMD-17, SDS, and clinical responses. The PRX + MA and PRX + EA groups showed significantly lower HAMD-17 scores than the PRX alone group through the 6th week (p = 0.000), but there were no significant differences in the scores between the PRX alone group and the PRX + MA and PRX + EA groups [5].

Most subjects experienced changes in their sleep patterns before and after the acupuncture therapy. As shown in Table 4, the answers to question 4 regarding early insomnia, question 5 regarding middle insomnia, and question 6 regarding late insomnia indicated that most patients in the acupuncture with antidepressant group showed improvement in their sleeping patterns and experienced more comfortable sleep after the acupuncture therapy. This result corresponded with those of a study by Feisal B on the effect of acupuncture on the reduction of The Pittsburgh Sleep Quality Index (PSQI) score in depression patients with insomnia, which showed a reduction in the PSQI mean score from 14.50 ± 2.14 to 5.70 ± 2.25 (p < 0.005) in the treatment group and from 13.62 ± 1.43 to 16.66 ± 1.83 (p < 0.05) in the control group [33]. The underlying mechanism of the relationship between insomnia and mental disorder is complex. Researchers have found that patients with heavy insomnia are six times more prone to psychiatric disorders. Additionally, 14 studies have found that psychiatric diagnoses are 5.04 times more prevalent in patients with insomnia than in those without insomnia [34]. Jaussent I et al have revealed that the symptoms of insomnia increase the risk of depression (OR, 1.23; 95% CI, 1.01–1.09 and OR, 2.05; 95% CI, 1.30–3.23) [35].

Our study on the effect of acupuncture combined with antidepressants assessed using the HAMD-17 was the first to be conducted in Indonesia. The reason for conducting this research was the high incidence of depression, which is associated with high treatment costs and long treatment times as well as side effects from antidepressants. Acupuncture has similar effects as those of antidepressants and have a synergistic effect [7]. A meta-analysis by Zang et al comparing between acupuncture and an antidepressant found that the effect of acupuncture was stronger than that of the antidepressant alone [36].

Acupuncture does not have any serious side effect, except the pain caused by needle insertion and small hematomas that disappear after 1–3 days. In this study, 11 (22.9%) subjects complained of side effects, 8 (16.67%) complained of pain, and 3 (6.25%) complained of hematomas at the insertion sites. The incidence of the side effect of pain was higher in this study than in that by Witt et al on acupuncture safety in 220,230 subjects in which 19,726 (8.6%) experienced side effects. Hematomas occurred in 6.1%, pain occurred in 1.7%, and vegetative symptoms occurred in 0.7% of the patients. On the insertion of the needle, a tingling or numb sensation may occur. When the visual analog scale assessment was performed, the pain experienced by the subjects did not exceed 3 or was ranged from 1 to 3. Therefore, it can be concluded that the pain at the time of needle insertion was mild.

However, acupuncture is much safer than medications [37]. A study by Mischoulon et al examined the efficacy and safety of acupuncture as monotherapy for major depressive disorder. They found that acupuncture was safer and more effective for major depressive disorder [9]. Wu et al also found that acupuncture was safer and more effective and had better tolerance as monotherapy for depression, particularly in subjects who did not respond to antidepressant medication. Furthermore, acupuncture was shown to reduce the side effects of antidepressants, but they did not find that acupuncture enhanced the efficacy of antidepressant medication [38]. Major depressive disorder is a chronic disease with a multifactorial pathogenesis, and patients with this disorder often undergo relapse. Because the treatment outcomes of depression are better evaluated gradually and acupuncture therapy
in this study was only performed thrice per week for 1 month for a total of 12 sessions of therapy, further study is required to evaluate the long-term effects of acupuncture combined with antidepressants regarding how long the effect lasts after treatment and how long acupuncture can be continued in depressive patients. Additionally, various types of SSRI antidepressants were used in this study; therefore, future studies using the same kind of medication and dose should be conducted.

5. Conclusions
This study showed that a combination of acupuncture with an antidepressant was effective in reducing the depression symptoms, as assessed by the change in the HAMD-17 scores.

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