



## Review

# Is acupuncture beneficial in depression: A meta-analysis of 8 randomized controlled trials?

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## Abstract

**Background:** Depression is one of the most common mental health disorders. Acupuncture is a popular complementary and alternative medicine intervention suggested in the treatment of depression, but its effectiveness is uncertain. This updated meta-analysis was conducted to more precisely assess the beneficial effect of acupuncture in depression therapy.

**Methods:** The following databases were searched: MEDLINE, EMBASE, BIOSIS, Cochrane Central Register of Controlled Trials, and Chinese Scientific Journal Database. The following terms were used: acupuncture, acupressure, depression, depressive disorder, clinical trial, and randomized controlled trial.

**Results:** Eight small-randomized controlled trials comparing 477 subjects were included in the meta-analysis. Our results confirmed that acupuncture could significantly reduce the severity of depression, which was indicated by decreased scores of Hamilton rating scale for depression (HAM-D) or Beck Depression Inventory (BDI). The pooled standardized mean difference of the 'Improvement of depression' was  $-0.65$  (95% CI  $-1.18, -0.11$ ;  $P=0.02$ ) by random effect model. However, no significant effect of active acupuncture was found on the response rate (RR 1.32, 95% CI 0.83 to 2.10;  $P=0.25$ ) and remission rate (RR 1.30, 95% CI 0.57 to 2.95;  $P=0.53$ ).

**Conclusion:** Although this meta-analysis might be discounted due to the low quality of individual trials, it supported that acupuncture was an effective treatment that could significantly reduce the severity of disease in the patients with depression. More full-scale randomized clinical trials with reliable designs are recommended to further warrant the effectiveness of acupuncture.

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**Keywords:** Depression; Acupuncture; Meta-analysis; Randomized clinical trial

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## 1. Introduction

Depressive disorders are one of the more common psychiatric disorders in adults (Prince et al., 2007). Symptoms associated with depression generally include fatigue, depressed mood and a decrease of interest in people or activities. Other symptoms may include sleep difficulties, anxiety, irritability, poor concentration and poor appetite. The most common conventional treatments for depression, such as antidepressant medication and psychotherapy, are well researched and known to be efficacious. However, their effectiveness is always reduced by lack of effect in some individuals, intolerable adverse effects, and high rates of dropout. This reality drives patients and also researchers to search for other modalities of treatment in an attempt to further improve outcomes (Pilkington et al., 2006).

In recent years, acupuncture, which was long used for emotional, psychological and spiritual disorders including anxiety, stress, insomnia and depression in China, Japan and Korea, has become a subject of major interest and one of the most popular complementary therapies in the West. On human body, there are more than 2000 acupuncture points connecting with 12 main and 8 secondary pathways called meridians, which conduct energy - qi - between the surface of the body and the internal organs. Qi regulates spiritual, emotional, and physical balance. The opposing forces of yin and yang influence qi. According to traditional Chinese medicine, when yin and yang are balanced, they work together with the natural flow of qi to help the body achieve and maintain health. Acupuncture is believed to balance yin and yang, keep the normal flow of energy unblocked, and restore health to the body and mind. Present interpretation of the treatment effect of acu-

puncture on depression is that acupuncture stimulates afferent Group III nerve fibers that transmit impulses to various parts of the central nervous system and induce the release of serotonin, norepinephrine, substance P, dopamine, b-endorphin, enkephalin, and dynorphins, primarily in the hypothalamus. This suggests a direct influence on the pathogenic mechanisms of depression (Ulett et al., 1998; Colbert, 2000; Zhang et al., 2006; Shi et al., 2006; Siedentopf et al., 2005). Otherwise, building evidence implicates a role for the plasticity of specific neuro-circuitry in both the pathophysiology and treatment of depression. Electro-acupuncture could reverse the decreased level of cyclic AMP responsive element binding protein (CREB), a molecule playing an important role in neuronal plasticity, in cortex, hippocampus and hypothalamus regions in rat depression model, which may contribute to the treatment effect of acupuncture (Husseini et al., 2001; Nair and Vaidya, 2006; Lu et al., 2006).

Compared to conventional treatment, several potential advantages are associated with acupuncture, such as its low cost, relatively few complications, and possibility of a personalized treatment. Complications of acupuncture can arise from inadequate sterilization of needles and improper delivery of treatments, which cause infections and punctured organs, and can be avoided and rectified easily by using it properly. Thus, researchers started to design and conduct randomized controlled trials to assess the efficacy of acupuncture in depression from 1990s. Although several randomized clinical trials have reported a benefit from acupuncture in the treatment of depression, generally results appear contradictory, suggesting both beneficial and detrimental effects. For example, the first randomized controlled trial, which recruited a small sample of woman with major depression, has reported that

after 8-week treatment there was a significant difference in symptom reduction between acupuncture (Mean = -11.7, SD = 7.3) and placebo groups (Mean = -2.9, SD = 7.9) on HAMDS, indicating a beneficial effect of acupuncture on symptom relief in depression (Allen et al., 1998). However, in a larger scale clinical trial published in 2006, the same authors failed to support the efficacy of acupuncture as a monotherapy for major depression. Compared with the waitlist group, greater decreases in severity were exhibited by both acupuncture ( $z = 3.5$ ,  $P < 0.001$ ) and sham acupuncture ( $z = 4.3$ ,  $P < 0.001$ ) groups, but the two groups did not differ in the rate of change from one another ( $z = 1.1$ ,  $P > 0.2$ ) (Allen et al., 2006).

Thus, with the aim of detecting moderate treatment effects, which are unlikely to be reliably detected in small studies, and objectively assessing the sources of the conflicting results achieved in different trials, we conducted this updated meta-analysis with the results from all relevant randomized clinical trials that had compared acupuncture with sham acupuncture in depression patients.

## 2. Methods

### 2.1. Search strategy

All prospective randomized controlled trials of acupuncture vs sham acupuncture enrolling patients with depression were identified using a 2-level search strategy. First, public domain databases including MEDLINE, EMBASE, BIOSIS, Cochrane Central Register of Controlled Trials, and Chinese Medical Literature Database were searched using web-based search engines with the last computerized search undertaken in March 2007. Second, relevant studies were identified through a manual search of secondary sources including references of initially identified articles and a search of reviews, commentaries, and proceedings from meetings. The following terms were used: “acupuncture”, “acupressure”, “depression”, “depressive disorder”, “clinical trial”, and “randomized controlled trial”. The search was not restricted to specific languages or years of publication.

### 2.2. Inclusion criteria

Two reviewers for the literature independently reviewed the trials for inclusion. Any disagreement on inclusion was resolved through discussion. The inclusion criteria were the following: (1) the studies had to be a randomized clinical trial, published or unpublished, comparing acupuncture with sham acupuncture

in subjects with major depression or depressive neurosis. Major depression is characterized by a combination of symptoms that interfere with a person's ability to work, study, sleep, eat, and enjoy once-pleasurable activities. Depressive neurosis is characterized by long-term (two years or longer) but less severe depressive symptoms that may not disable a person but can prevent one from functioning normally or feeling well; (2) patients were included in the studies depending on the diagnostic criteria of depression, such as Diagnostic and Statistical Manual of Mental Disorders (DSM), International Classification of Disease (ICD) or Chinese Classification of Mental Disorders (CCMD). Definitions of depressive disorder in these systems have several symptoms in common including: depressed mood, loss of interest, decrease in energy or increased fatigue, sleep disturbance, appetite disturbance, recurrent thoughts of death, inability to concentrate or indecisiveness, psychomotor agitation or retardation, and ideas of guilt and unworthiness. The criterion sets differ in that CCMD has two additional items: reduced self-esteem or self-confidence and loss of interest on sex, while ICD-10 combines reduced self-esteem or self-confidence only; (3) all types of acupuncture were included: manual acupuncture, electroacupuncture or laser acupuncture. Traditional manual acupuncture relies on the manual stimulation exerted on needles after they have been inserted into specific points, i.e. rotating needle slowly or quickly. Electroacupuncture is concerned with electrical stimulation applied by attaching electrodes to traditional needles. Laser acupuncture is involved with the use of a low-level laser beam instead of an acupuncture needle to stimulate an acupuncture point.

### 2.3. Data extraction

Data were extracted by 2 reviewers independently. Once completed, any disagreement on data extraction and evaluation was resolved through discussion. Recorded data included study characteristics, patient characteristics, and outcomes.

Jadad scale was used to measure the quality of the included studies (Jadad et al., 1996). This validated scale included the following criteria: method of randomization, double blinding, and reporting of withdrawal and dropouts. Because quality scales have their limitations, we also examined the individual components of study quality for each included randomized controlled trial, including, in particular, concealment of treatment allocation, assessor blinding, intention-to-treat analysis, dropouts, and sample size.

#### 2.4. Data synthesis

Outcome data at the end of active treatment in each study were employed for meta-analysis. The primary outcome of interest was ‘Improvement in Depression’, calculated as the difference of the baseline minus the follow-up levels of depression for the intervention and control groups. Net change in depression was calculated as the mean difference (active treatment minus placebo) of the change (follow-up minus baseline). Since there was not a single scale of depression used in the trials, the standardized mean differences were calculated for each trial. To calculate the pooled effects, each study was assigned weights consisting of the reciprocal of the total variance for the net change in depression. For the trials, in which variance for paired differences during the trial was reported separately for each arms, we calculated a total variance for net depression change using the function as:

$$\text{var}(X_2 - X_1) = \text{var}(X_2) + \text{var}(X_1) - 2\rho\sqrt{\text{var}(X_1)\text{var}(X_2)}$$

where  $\text{var}(X_1)$ ,  $\text{var}(X_2)$ , and  $\text{var}(X_2 - X_1)$  were variance of ‘initial depression level’, ‘final depression level’, and ‘Improvement in Depression’ respectively,  $\rho$  was the correlation coefficient between initial and final depression levels. Correlation coefficient  $\rho$  of 0.43 was calculated with the HAMD scores reported in clinical trial of Allen et al. (1998) using the above function.

Secondary outcomes were response rate and remission rate. Response is generally defined as a 50% decrease in scores on depression scales, that is a “significant” reduction of symptoms or a global impression of at least moderate benefit. Remission is an indicator of wellness. An HAMD score of less than 7 is often used as a definition of remission. Treatment effect of the categorical outcomes was analyzed by relative risk (RR) with associated 95% CIs.

For both continuous and dichotomous outcomes, the test of statistical homogeneity of effects across studies was performed using the  $\chi^2$  distributed Cochran  $Q$  test, with  $P \leq 0.10$  indicating significant, and formally quantified by  $I^2$  statistic, with value less than 25% indicating low, 25% to 50% indicating moderate, and greater than 50% indicating high heterogeneity. If there was statistical difference among the trials, the random effect model was applied. Causes of heterogeneity were examined by subgroup analysis and sensitivity analysis. Subgroup analysis was planned to examine the effects of acupuncture in patients with different diagnoses, that is major depression and depressive neurosis.

A 1-way sensitivity analysis was performed to assess the effect of each selected study on the overall results of the meta-analysis. Potential publication bias was explored by funnel plot and the test of Egger (Egger et al., 1997). All analyses were conducted using RevMan 4.2 application.

### 3. Results

#### 3.1. Included trials

Over 200 possible trials were identified but only eight studies satisfied the inclusion criteria. The reasons for excluding reports were as follows: comparative trial that was not randomized, reports of uncontrolled or open studies; foreign language versions of included studies also reported in English (Röschke et al., 1998); second report of an included study but provided some additional data of extended follow-up (Gallagher et al., 2001); report of the results of a small part of participants (Fan et al., 2005). Two articles from Chinese database met our inclusion criteria. The descriptive information for each of the eight trials was shown in Table 1 (Allen et al., 1998; Eich et al., 2000; Röschke et al., 2000; Luo et al., 2003; Manber et al., 2004; Quah-Smith et al., 2005; Allen et al., 2006; Fu et al., 2006).

The eight randomized trials included in this study enrolled 477 patients with depression, of whom 256 received active acupuncture. Patients from three studies were recruited through newspaper advertisements (Allen et al., 1998; Quah-Smith et al., 2005; Allen et al., 2006), while other patients were in- or out-patients from hospital care. The diagnosis of depression was satisfied with DSM-III, or DSM-IV by six studies (Allen et al., 1998; Röschke et al., 2000; Luo et al., 2003; Manber et al., 2004; Quah-Smith et al., 2005; Allen et al., 2006), and other two used ICD (Eich et al., 2000) and CCMD-2-R (Fu et al., 2006) respectively. Seven studies targeted patients suffering from major depression and one study recruited subjects with depressive neurosis (Fu et al., 2006).

Patients from seven studies received manual acupuncture (or plus electric acupuncture), while those from the other one study received laser acupuncture (Quah-Smith et al., 2005). In four studies, acupuncture sites were individually selected following the principles of traditional Chinese medicine (Allen et al., 1998; Manber et al., 2004; Quah-Smith et al., 2005; Allen et al., 2006). While in other four trials, acupuncture was performed on a fixed set of points. Six studies described the acupuncture points in detail, but the selected points varied significantly (Eich et al., 2000; Röschke et al., 2000; Luo et al., 2003; Quah-

Table 1  
Characteristics of included studies comparing acupuncture with sham acupuncture in the treatment of depression

Author	Diagnosis criteria	Subject (M/F)		Primary variable	Acup sessions	Randomization detail	Blindness	Intention to treat	Withdrawal		Jadad score
		Acup	Sham acup						Acup	Sham acup	
Allen et al. (1998)	DSM-IV	12 (0M /12F)	11 (0M /11F)	HAMD	12	NR	DB	No	2	2	3
Eich et al. (2000)	ICD	28 (9M/19F)	28 (15M/13F)	HAMD	10	Block randomization	DB	Yes	8	4	5
Röschke et al. (2000)	DSM-III-R	22 (3M/19F)	24 (9M/15F)	HAMD	12	NR	SB	Yes	6	8	3
Luo et al. (2003)	DSM-IV	31	32	HAMD	30	Block randomization	DB	Yes	1	3	5
Manber et al. (2004)	DSM-IV	20 (0M/20F)	21 (0M/21F)	HAMD	20–29	NR	DB	No	4	2	3
Quah-Smith et al. (2005)	DSM-IV	16 (3M/13F)	14 (4M/10F)	BDI	12	Simple randomization	DB	No	2	3	3
Allen et al. (2006)	DSM-IV	49 (16M/33F)	50 (16M/34F)	HAMD	12	Stratified randomization	DB	Yes	8	4	5
Fu et al. (2006)	CCMD-2-R	78 (26M/52F)	41 (19M/22F)	HAMD	24	Simple randomization	DB	No	NR	NR	3

Acup: acupuncture; M: male; F: female; DB: double blind; SB: single blind. NR: not reported.

Smith et al., 2005; Allen et al., 2006; Fu et al., 2006). The sham acupuncture was designed differently to set up the standard of placebo. Five studies chose non-specific locations in the neighborhood of the special loci and merely pricked the skin superficially (Eich et al., 2000; Röschke et al., 2000; Luo et al., 2003; Manber et al., 2004; Fu et al., 2006). Two studies designed a control acupuncture treating a disharmony that did not specifically address depression symptoms (Allen et al., 1998; Allen et al., 2006). The study of laser acupuncture used non-simulation as control, but the beep and flash of instrument still functioned during ‘treatment’ (Quah-Smith et al., 2005). The duration of treatment varied significantly, more than 16 weeks in one study (41 patients) (Manber et al., 2004), 6 to 12 weeks in five studies (334 patients) (Allen et al., 1998; Luo et al., 2003; Quah-Smith et al., 2005; Allen et al., 2006; Fu et al., 2006), and 2 to 4 weeks in two studies (102 patients) (Eich et al., 2000; Röschke et al., 2000). Total acupuncture sessions ranged from 10 to 30. In one study, mianserin (90–120 mg/day) was given to all participants in treatment and control groups as standardized antidepressant medication (Röschke et al., 2000). While in the other trials, no concomitant medications were given.

### 3.2. Methodological quality

Five of the eight randomized controlled trials reported how the randomization was performed in detail: one study used stratified randomization (Allen et al., 2006), two

trials utilized block randomization (Eich et al., 2000; Luo et al., 2003), and two studies mentioned simple randomization procedure (Quah-Smith et al., 2005; Fu et al., 2006). Seven of the eight studies used double-blinded design, including subject, acupuncturist, and evaluator blinding; the other study was single-blinded, involving patient- but not therapist-blinding (Röschke et al., 2000). The rates of dropout were 13% (Allen et al., 1998), 21% (Eich et al., 2000), 33% (Röschke et al., 2000), 6% (Luo et al., 2003), 15% (Manber et al., 2004), 13% (Quah-Smith et al., 2005), 13% (Allen et al., 2006), and 12% (Fu et al., 2006) respectively. Five studies described the detailed reasons for withdrawal of subjects (Allen et al., 1998; Luo et al., 2003; Manber et al., 2004; Quah-Smith et al., 2005; Allen et al., 2006). Intention-to-treat analysis was carried out in four studies (Eich et al., 2000; Röschke et al., 2000; Luo et al., 2003; Allen et al., 2006). Among them, two trials used the last observation carried forward method (LOCF) for imputing missing values (Luo et al., 2003; Allen et al., 2006), while the other two trials did not mention how to handle the missing data. Per protocol analysis was used in the other four trials (Allen et al., 1998; Manber et al., 2004; Quah-Smith et al., 2005; Fu et al., 2006).

### 3.3. Synthesis

#### 3.3.1. Improvement in depression

Seven trials, involving 421 participants, reported patients’ depressive condition using HAMD scale (Allen et al., 1998; Eich et al., 2000; Luo et al., 2003;



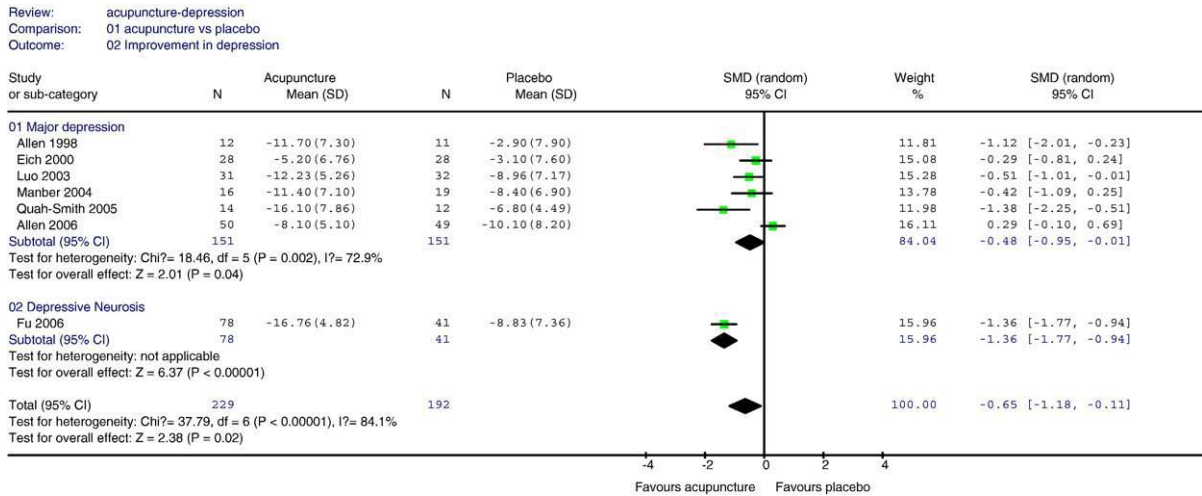


Fig. 1. The meta-analysis of the primary outcome of interest ‘Improvement in depression’ (net change in depression) by random effect model. Net change was calculated as the difference of the baseline minus the follow-up levels of depression for acupuncture and sham-acupuncture groups. The size of the square corresponds to the weight of the study. CI indicates confidence interval. Negative values indicate lower depression level in acupuncture group than in control.

Manber et al., 2004; Allen et al., 2006; Fu et al., 2006) or BDI scale (Quah-Smith et al., 2005). The results from four trials (Allen et al., 1998; Luo et al., 2003; Quah-Smith et al., 2005; Fu et al., 2006) suggested significant effect of acupuncture on symptom relief in depression, while those from other three studies could not detect any difference between active and sham acupuncture (Fig. 1). The values of ‘Improvement of depression’

could be obtained directly in Allen et al. (1998), Quah-Smith et al. (2005) and Allen et al. (2006) studies, but was calculated from the depression scores of before and after treatment in other four trials following the method mentioned above. Significant difference was detected between acupuncture and sham acupuncture groups at the end of intervention (SMD  $-0.65$ , 95% CI  $-1.18$  to  $-0.11$ ,  $P=0.02$ ).

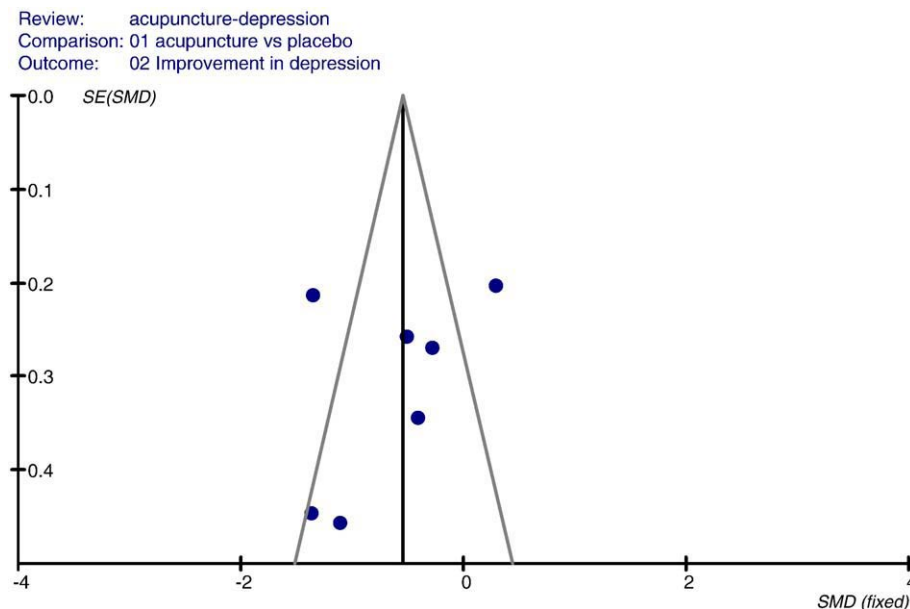


Fig. 2. Funnel plot of the primary outcome of interest ‘Improvement in depression’ (net change in depression) for all seven trials in the meta-analysis. The effect size (SMD) was plotted against study sample size (SE).

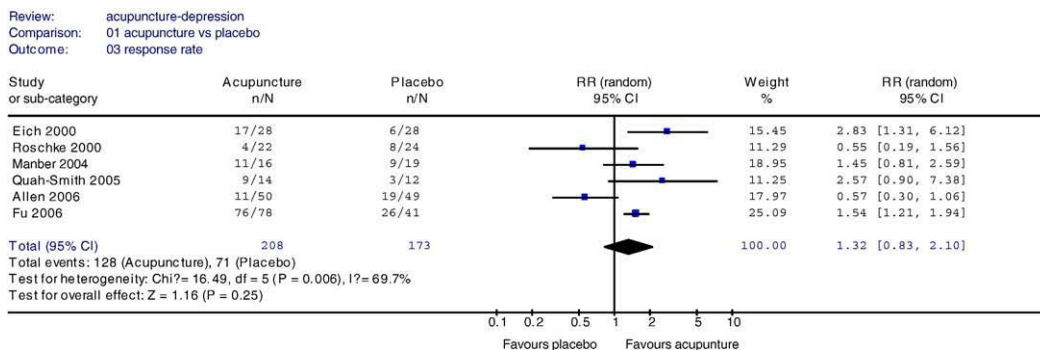


Fig. 3. Difference in responder rate for the included studies comparing acupuncture with sham acupuncture in the treatment of depression. The size of the square corresponds to the weight of the study. CI indicates confidence interval.

The test of heterogeneity showed Cochran  $Q=37.79$ ,  $P<0.00001$ ;  $I^2=84.1\%$ , indicating significant evidence of heterogeneity in seven studies. In the subgroup analysis between major depression and depressive neurosis, significant difference was found between acupuncture and placebo groups in the six trials recruiting subjects with major depression (SMD  $-0.48$ , 95% CI  $-0.95$  to  $-0.01$ ). Similarly, significant difference was detected in the only trial of depressive disorder (SMD  $-1.36$ , 95% CI  $-1.77$  to  $-0.94$ ).

One-way sensitivity analysis demonstrated that the overall effect size and its statistical significance were not altered by omitting any single study from meta-analysis. The  $I^2$  value ranged from 66.8% to 86.8%, also indicating high heterogeneity among studies. A funnel plot of effect size vs. precision (SE) seemed symmetrical (Fig. 2). Formal statistical test for publication bias, the test of Egger was not significant (Intercept=1.03; 90% CI,  $-8.53$  to  $10.58$ ;  $P=0.84$ ).

### 3.3.2. Response rate

Response rate was a short-term measure of the effectiveness of antidepressant treatment. Six trials

presented this outcome. Significant difference was found between treatment and placebo groups in two studies (Eich et al., 2000; Fu et al., 2006), while no difference was found in other four (Röschke et al., 2000; Manber et al., 2004; Quah-Smith et al., 2005; Allen et al., 2006). Pooled results (RR 1.32, 95% CI 0.83 to 2.10) indicated non-beneficial effect of intervention with acupuncture on the response rate (Fig. 3). Heterogeneity was identified in the meta-analysis (Cochran  $Q=16.49$ ,  $P=0.006$ ;  $I^2=69.7\%$ ).

### 3.3.3. Remission rate

Recently, increased focus has led many researchers to suggest that remission, i.e. a virtual elimination of depressive symptoms and restoration of psychosocial functioning, should be the primary goal of the initial phase of therapy (Thase et al., 2001; Thase, 2003). Patients who undergo remission will experience less likelihood of relapse after remission is achieved. Only four studies mentioned this outcome in the articles. No significant difference was found between groups (RR 1.30, 95% CI 0.57 to 2.95) (Fig. 4). Heterogeneity was identified in the meta-analysis (Cochran  $Q=9.34$ ,  $P=0.03$ ;  $I^2=67.9\%$ ).

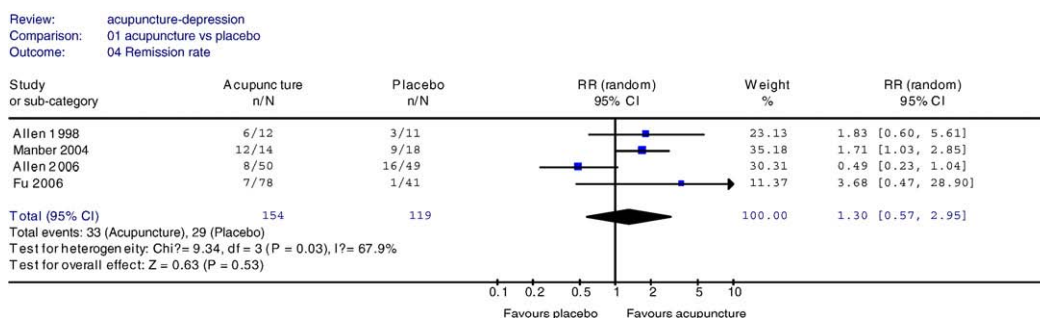


Fig. 4. Difference in remission rate for the included studies comparing acupuncture with sham acupuncture in the treatment of depression. The size of the square corresponds to the weight of the study. CI indicates confidence interval.

#### 4. Discussion

Depression is a significant cause of morbidity and mortality worldwide. At present, major problems are that much of depression is under-diagnosed and under-treated, and compliance with antidepressants is often low. Thus, complementary and alternative medicine, such as acupuncture, is gradually utilized by those who are depressed (Thachil et al., 2007). It has served as adjuncts to or substitutes for existing treatments, or as maintenance or preventive treatments following remission.

A previous systematic review of seven trials involving 517 patients (Smith and Hay, 2005) included quantitative summaries of only one trial of 23 participants comparing acupuncture with sham acupuncture (Allen et al., 1998). A greater mean reduction in depression scores was found among participants in the acupuncture group (WMD  $-8.80$ , 95% CI  $-15.03$  to  $2.57$ ). However, no significant difference was found in the numbers reporting full remission between two groups (RR  $4.58$ , 95% CI  $0.63$  to  $33.36$ ). Results from 5 trials (409 participants), which compared acupuncture with medication, showed no difference in the reduction in the severity of depression (WMD  $0.53$ , 95% CI  $-1.42$  to  $2.47$ ). Evidence was insufficient to determine the efficacy of acupuncture vs. sham acupuncture, or medication seems due to the poor methodological quality and reporting of these trials. A recent systematic review, which compared acupuncture with control conditions within 9 randomized controlled trials, suggested some evidence for the utility of acupuncture in depression. Acupuncture modalities were as effective as antidepressants, while sham acupuncture was often no different from intended verum acupuncture (Leo and Ligot, 2007).

Several types of comparisons had been made in these systematic reviews. But very small number of study was included for the comparison of acupuncture with sham acupuncture. Evidence was insufficient to conclude the effect of acupuncture on depression. In our study, we merely compared the efficacy of acupuncture with placebo condition. Eight randomized controlled trials, including two high quality Chinese trials, satisfied the inclusion criteria. The study, which comparing 477 depression patients, did find evidences of an effect of acupuncture in ameliorating the clinical global impression of depression patients, indicated by the significant reduce of depression level at the end of treatment (SMD  $-0.65$ , 95% CI  $-1.18$  to  $-0.11$ ). But statistical heterogeneity was high ( $I^2=84.1\%$ ). The results of subgroup analysis showed that there was no difference between major depression and depressive neurosis re-

garding their response to acupuncture. Different diagnoses of participants could not explain the heterogeneity.

We did not determine the effect of acupuncture on two dichotomous outcomes, which were response rate (RR  $1.32$ , 95% CI  $0.83$  to  $2.10$ ) and remission rate (RR  $1.30$ , 95% CI  $0.57$  to  $2.95$ ). In addition, the adverse effects of acupuncture seemed fable. In the study of Quah-Smith, author assessed the side effects of acupuncture with Adverse Effect Questionnaire. Although 29% patients in the active laser group experienced adverse effects, 60% of these were fatigue; the effects were transient and persisted for less than 24 h (Quah-Smith et al., 2005). Compared to adverse effects from pharmacotherapy that may persist and affect patient compliance, these transient adverse effects were better tolerated.

Even though beneficial effects of acupuncture were detected for the treatment of depression in our study, the results of this meta-analysis should be utilized prudently. For the acupuncture trials satisfied including criteria, they varied in virtually every conceivable way. Firstly, the application of randomized controlled trial model to acupuncture was potentially fraught with difficulties. The insertion of a needle for placebo group was necessary to produce the blindness of participants and acupuncturists. But the design of sham acupuncture varied quite differently among trials. Some utilized non-specific locations in the neighborhood, while some chose points treating a disharmony not addressing depression symptoms. These kinds of non-specific treatment were no a real placebo because it might be an active treatment which could have more impact than a truly inert placebo treatment. In some trials, the sham acupuncture appeared some beneficial effect on depression. In addition, it remained possible that acupuncturists developed some awareness of the differences between the treatments, causing the failure of blindness. Secondly, the type of acupuncture (e.g. manual or electrical stimulation, traditional or formular) and the treatment schedule (e.g. number of acupuncture points treated, frequency of sessions, and length of treatment period) differed vastly. From the point of view of traditional Chinese medicine, it appears suitable to choose individual acupuncture protocol depending on each patient's depression condition and not to perform a standardized acupuncture design for all subjects. Thirdly, even when considering only depressive disorder as indication, the severity of patient's depressive condition was far from uniform. In the meta-analysis, one trial recruited patients with depressive neurosis, while seven trials enrolled participants with major depression. Otherwise, the operationally defined depressive episodes according to western diagnosis criteria



were not subject to the proposals of traditional Chinese medicine in the treatment of mood disorder (MacPherson and Schroer, 2007). How to match the intervention of traditional Chinese medicine to western medicine system is a question needed further study.

The results of this meta-analysis were limited by the shortcomings of individual trials. There is an obvious need to conduct a full-scale randomized clinical trial addressing these limitations and comparing the efficacy of acupuncture with placebo and pharmacotherapy in the same study. In the study of Luo et al. (2003), except electro-acupuncture and placebo groups, authors had set up a third group taking fluoxetine. At the end of the 6-week treatment period, there was better improvement in electro-acupuncture group compared to controls, while no significant difference was detected between electro-acupuncture and fluoxetine groups, indicating that electro-acupuncture was as efficacious as fluoxetine for the treatment of major depressive disorders.

In conclusion, in this meta-analysis including eight randomized controlled trials comparing acupuncture with sham acupuncture, results supported acupuncture as an effective treatment that could significantly reduce the severity of disease in the patients with major depression and depressive neurosis. More full-scale randomized clinical trials with reliable designs are recommended to further evaluate the clinical benefit and long-term effectiveness of acupuncture for the treatment of depression.

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#### Conflicts of interest

All authors declare that they have no conflicts of interest for the publication of this work.

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