Acupuncture For Major Depressive Disorder: A Systematic Review and Meta-Analysis of High-Quality Randomized Control Trials

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Research

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Abstract

**Background:** The effects of acupuncture for major depressive disorder (MDD) uncertain. This review aims to determine the effects of acupuncture for MDD.

**Methods:** Eight database were searched to identify randomized control trials (RCTs) on Acupuncture for MDD. All RCTs with adult participants undergoing acupuncture treatment for MDD were included. The primary outcome measure was the 24-item Hamilton rating scale for depression (HAMD-24). We used random-effects meta-analysis to synthesize the results with mean difference or odds ratio. Furthermore, the potential heterogeneity was tested through meta-regression/subgroup analyses/sensitive analysis. The quality of evidence for each outcome was assessed by the Grading of Recommendations Assessment, Development and Evaluation approach.

**Results:** Forty-three studies were included: 9 acupuncture versus sham-acupuncture (n=920), 26 acupuncture versus antidepressants (n=2169), 9 acupuncture plus antidepressants versus antidepressants (n=667). Of the 43 high-quality articles, 24 and 8 were determined to have a low and moderate risk of bias, respectively. The pooled results for HAMD-24 and SDS revealed the clinical benefits of Acupuncture or Acupuncture plus antidepressants compared to sham-acupuncture or antidepressants, with high quality evidence. Furthermore, high quality of evidence showed that acupuncture led to fewer adverse effects compared to antidepressants.

**Conclusions:** Acupuncture or acupuncture plus antidepressants were significantly associated with reduced HAMD-24 scores, with high-quality evidence. More rigorous trials are needed to identify the optimal frequency of Acupuncture for MDD and integrate such evidence into clinical care to reduce antidepressant use.

**Strengths And Limitations Of This Study**

1. The Jadad scores of the original studies included in this study were all greater than or equal to 4, ensuring the credibility and high quality of the study results.

2. This study used the GRADE Guidelines to assess the quality of evidence of the meta-analysis with high quality.

3. The results of this study will be useful to physicians in clinical decision-making and will clarify the effectiveness and safety of acupuncture in treating MDD.

**1. Background**

Major depressive disorder (MDD) is a common psychological condition with an estimated lifetime prevalence of 16%, affecting more than 320 million people across the globe. As of April 2017, depression has been recognized by the World Health Organization (WHO) as the leading cause of health-related disability, accounting for approximately 4.4% of all disabilities and premature deaths worldwide.

Antidepressants such as selective serotonin reuptake inhibitors or selective serotonin-norepinephrine reuptake inhibitors are commonly used to treat MDD. Most evidence-based guidelines recommend antidepressants to be the first-line therapy because of their favorable outcomes and superior characteristics, including broad-spectrum effectiveness, safety, tolerability, simplicity of use, and low cost. Nevertheless, pharmacological interventions also have undesirable side effects, including central nervous system and gastrointestinal disorders, weight gain, sexual dysfunction, and adverse emotional effects. In addition, long-term use may also cause drug tolerance, withdrawal symptoms when discontinued and increased suicidal ideation in certain patient populations.

As an essential component of traditional Chinese medicine, acupuncture therapy has been practiced in China for thousands of years in disease prevention and treatment, functional improvement, longevity enhancement, and regulating emotions. As early as 1979, the WHO held a symposium on Acupuncture and created a list of 43 diseases suitable for Acupuncture. In 2002, the WHO recommended Acupuncture as a treatment for depression (including depressive neurosis and depression following stroke). However, significant heterogeneity has been reported in findings of several randomized control trials (RCTs).

Clinical trials have demonstrated that the effect of acupuncture therapy was partly induced via the autonomic nervous system. In this regard, manual acupuncture leads to a wide range of central nervous system responses involving the amygdala, hippocampus, hypothalamus, cerebellum and other limbic structures, documented by functional magnetic resonance imaging and EEG. Moreover, animal studies have shown that acupuncture therapy exerts its effects via multi-receptor and multi-pathway regulation related to amino acid metabolism and inflammatory pathways, especially the Toll-like receptor signaling pathway, tumor necrosis factor signaling pathway and the nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB) signaling pathway. Besides, acupuncture therapy has been reported to influence the neurotransmitter levels of serotonin and noradrenaline and the adenylate cyclase cyclic adenosine monophosphate-protein kinase A cascade within the central nervous system via mechanisms similar to antidepressant medication.

Although several systematic reviews and meta-analyses suggested that acupuncture therapy effectively treated MDD, some review of these studies found some quality issues, and the original studies did not yield consistent results. Therefore, we conducted this meta-analysis, including only high-quality studies.
quality RCTs, to determine the effectiveness and safety of acupuncture in treating MDD.

2. Methods

2.1 Study registering and reporting

This protocol was registered on INPLASY International Prospective Register of Systematic Reviews (INPLASY2021100073). It was conducted in accordance with the Measure Tool to Assess Systematic Reviews (AMSTAR 2)\(^2\), and the final report was presented following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements\(^2\)\(^4\)\(^5\).

2.2 Selection criteria

Study design

We included all RCTs with eligible intervention(s) and outcome(s) for MDD published in Chinese and English. For the crossover trials with the randomized control design, the first stage consisted of data collection for this meta-analysis. Furthermore, we only included RCTs with a Jadad score $\geq 4$ since the previously published systematic review could not obtain accurate conclusions due to the low quality of RCTs included.

Population

Patients (aged $\geq 18$ years) were diagnosed with MDD according to the third edition of Chinese Classification of Mental Disorders (CCMD-2/3)\(^2\)\(^6\), the International Statistical Classification of Diseases and Related Health Problems (ICD-10/11)\(^2\)\(^7\), or the Diagnostic and Statistical Manual of Mental Disorders (DSM-II/III/III-R/IV/IV-TR/V)\(^2\)\(^8\)\(^2\)\(^9\).

Interventions/Comparators

The experimental group consisted of patients that received Acupuncture or Acupuncture plus antidepressants. The acupoint numbers, retaining time and frequency, treatment sessions were not limited.

The control group included non-acupuncture techniques, such as placebo control or other active therapies.

Outcome measures

The primary outcome was the Hamilton Depression Rating Scale for Depression (HAMD17/24). The secondary outcomes included changes in the Zung Self-rating Depression Scale (SDS) and the incidence of adverse effects.

The data at each time point was extracted from the original trials to be analyzed in this study.

2.3 Literature search

The following online databases were searched: EMBASE, The Cochrane Library, PubMed, The Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, The China National Knowledge Infrastructure (CNKI), The Wanfang database, The VIP Database for Chinese Technical Periodicals, The China Doctoral Dissertations Full-text Database (CDFD). All RCTs were published from inception to 10th September 2021. The Cochrane library database search strategy is shown in Appendix 1.

2.4 Data collection and analysis

2.4.1 Selection of studies

The process of data screening and study selection is displayed in Figure 1. First, studies were imported into Endnote X9 to remove duplicates, including duplications from different publications and multilingual publications and reports on different aspects of the same research. Two investigators (XGX and HBQ) independently assessed the titles and abstracts of the articles to select eligible studies based on the inclusion criteria. Subsequently, two other investigators (HLY and XQW) performed full-text assessments to exclude articles according to the exclusion criteria. Points of disagreement were resolved through consensus or by consulting a fifth investigator (LFR).

2.4.2 Risk of bias and quality assessment

The risk of bias of eligible trials was measured by the Risk of Bias (ROB) Tool in Cochrane Handbook (5.1.0)\(^3\)\(^0\) by two independent researchers (HFY and LYL). Each criterion was graded as "low" risk of bias, "high" risk of bias and "unclear" risk of bias. The methodology quality was assessed by two independent investigators (XQW and HBQ) with the Jadad scale. Any dissent occurred in the assessment procedures was judged by a third investigator (SMS).

2.4.3 Data extraction

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First, a standard table for electronic data extraction was established during a general meeting. After crosschecking for duplicates, the data were extracted by two authors (ZZ and TH) independently. The collected data included: basic information of studies (Study ID, the published date, author information, title, publication); characteristic of trials (study design, sample size, grouping method, blinding, assessment of outcomes, objectives of the study, etc.); the participants (age, gender, ethnicity, country, diagnosis, duration); method of intervention/control (number of treatment, frequency, duration of a session, additional treatment, etc.); outcome measurements (primary outcome, secondary outcome, assessment timeline, length of follow-up, etc.); results (mean, SD, adverse event, etc.). In addition, the extracted data was saved in an Excel format, and a third researcher (XQW) crosschecked the data input to ensure consistency and validity.

2.4.4 Unification of data and dealing with missing data

Before statistical analysis, the unit and time of extracted data were unified to ensure the accuracy of the data analysis. For studies with incomplete data, our researchers invested time and effort to contact the first author or corresponding author to collect the incomplete data as far as possible. If the data was not obtained, a systematic review will be conducted for these data instead of statistical synthesis.

2.4.5 Data synthesis

Meta-analysis of RCTs with available data was performed by calculating the effect size and 95% CI using the random-effects model. Heterogeneity among trials was identified by the $\chi^2$ test and reported as $I^2$. Statistical analyses were performed with RevMan 5.2 and Stata 15.0. Two-sided P-value < 0.05 was considered statistically significant.

Studies were grouped according to the type of intervention (acupuncture, Acupuncture plus antidepressants) and the controls (sham-acupuncture, antidepressants, and sham-acupuncture plus antidepressants). For studies with more than 1 control group, such as Acupuncture versus sham acupuncture versus antidepressants, the results were split into pairwise comparisons by the different comparators.

Given the reported strong correlation between HAMD-17 and HAMD-24, the HAMD-17 scores were converted to the corresponding HAMD-24 scores.

Meta-regression and sensitivity analyses were conducted to explore potential sources of heterogeneity. Meta-regression was used to explore whether the age of patients, baseline HAMD-24, course of MDD, and acupuncture session affect the effectiveness of Acupuncture. Sensitivity analysis was used to identify studies that significantly affected the overall effect.

Publication bias was assessed by funnel plots for asymmetry when at least ten trials were included.

Evidence quality evaluation: The quality of evidence for the outcomes was assessed with the Grading of Recommendations Assessment, Development, and Evaluations (GRADE) system and rated as high, moderate, low, and very low. A summary of findings is presented in Table 1.

| Intervention                                    | Outcome indicators | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Large effect | Dose-response | All plausible confounding | Quality of evidence |
|-------------------------------------------------|--------------------|--------------|---------------|--------------|-------------|-----------------|--------------|---------------|--------------------------|--------------------|
| acupuncture versus sham-acupuncture             | HAMD-24            | 0            | -1$^b$        | 0            | 0           | 0               | 0            | 0             | 0                        | High               |
|                                                 | SDS                | 0            | -1$^b$        | 0            | -1$^c$      | 0               | 0            | 0             | 0                        | Moderate           |
|                                                 | Side effect        | 0            | -1$^b$        | 0            | -1$^c$      | -1$^d$          | 0            | 0             | 0                        | Low                |
| acupuncture versus antidepressants              | HAMD-24            | 0            | -1$^b$        | 0            | 0           | 0               | 0            | 0             | 0                        | High               |
|                                                 | SDS                | 0            | -1$^b$        | 0            | -1$^c$      | -1$^d$          | 0            | 0             | 0                        | High               |
|                                                 | Side effect        | 0            | 0             | 0            | 0           | -1$^d$          | 0            | 0             | 0                        | High               |
| acupuncture plus antidepressants versus antidepressants | HAMD-24 in follow-up | -1$^a$        | 0            | 0            | 0           | -1$^d$          | 0            | 0             | 0                        | Moderate           |
|                                                 | SDS                | 0            | -1$^b$        | 0            | -1$^c$      | -1$^d$          | 0            | 0             | 0                        | Low                |
|                                                 | HAMD-24            | -1$^a$       | 0            | 0            | 0           | -1$^d$          | 0            | 0             | 0                        | Moderate           |
|                                                 | Side effect        | 0            | -1$^b$        | 0            | -1$^c$      | -1$^d$          | 0            | 0             | 0                        | Low                |

Note: GRADE, the Grading of Recommendations Assessment, Development and Evaluation; HAMD-24, 24-item Hamilton rating scale for depression; SDS, Zung Self-Rating Depression Scale; $^a$ included studies have risk of bias; $^b$ heterogeneity of meta-analysis; $^c$ small sample size; $^d$ potential publication bias.

3. Results
3.1 Description of included studies

The initial electronic search yielded 9943 unique records. 296 RCTs on Acupuncture for MDD were selected. Screening and full-text article analysis identified 43 high-quality RCTs with Jadad score ≥4, including 4037 patients (Figure 1, appendix 2) comparing acupuncture/acyupuncture plus antidepressants versus sham-acupuncture/antidepressants. Appendix 3 shows the Jadad score in included trials (Jadad≥4), while Appendix 4 presents the Jadad score in excluded trials (Jadad<4). The sample size in the included trials ranged from 20 to 176, with a mean age of 41.46 (range 30-52.33) and included 1466 men. At the baseline, the mean HAMD-24 score was 32.27 (range 18.2-58.14). Eligible RCTs included one study from India and forty-two from China. Qualitative synthesis was conducted in two studies due to lack of raw data, and quantitative synthesis in forty-one studies.

3.2 Risk of bias assessment

Appendix 5 presents the risk of bias in each trial. One major limitations of this study was low levels of blinding reported for participants, investigators, and outcome assessors. Forty-three (100%) trials had low risk of bias in random sequence generation while 22 (51.2%) had low risk of bias in allocation concealment. Ten RCTs out of 43 (23.3%) reported blinding for participants and investigators, and 9 RCTs (20.9%) reported blinding for outcome assessment. Thirty-eight trials (88.4%) were adjudicated as being at low risk of attrition bias, 15 trials had low risk of bias from selective outcome reporting, and 4 trials were at low risk of bias from other bias.

3.3 Outcomes

3.3.1 HAMD-24

Meta-analysis of 6 trials yielded a significant difference in favor of acupuncture (MD: -4.49 [95% CI: -6.41 to -2.55]; I²=76%) compared with sham acupuncture, with high-quality evidence (Figure 2 and Table 1). Pooled results from 24 RCTs showed that acupuncture (MD: -2.17 [95% CI: -3.31 to -1.03]; I²=65%) was more effective than antidepressants, while the funnel plot showed no publication bias, with high-quality evidence (Figure 3, Figure 4, and Table 1). High-quality evidence from 9 studies showed that acupuncture plus antidepressants (MD: -5.34 [95% CI: -6.68 to -4.00]; I²=38%) had more benefits in improving MDD (Figure 5 and Table 1). Analysis of follow-up outcomes showed that treatment with acupuncture plus antidepressants was more effective than with antidepressants alone, with moderate-quality evidence (Table 1 and Appendix 6).

During the meta-regression analysis of acupuncture versus sham-acupuncture, we found that the disease course of MDD could significantly reduce the heterogeneity (adjusted R² = 51.87%, I²resid = 60.27%, P=0.039, Figure 6). Meta-regression for age (adjusted R²= -15.65%, I²resid: 79.01%, P= 0.906), baseline HAMD-24 (adjusted R²= 17.05%, I²resid: 72.66%, P= 0.181), and acupuncture session (adjusted R²= 34.67%, I²resid: 66.62%, P= 0.095) were not statistically significant (Appendix 7). During the comparison between acupuncture versus antidepressants, the baseline HAMD-24 could reduce the heterogeneity (adjusted R² = 41.96%, I²resid = 75.13%, P=0.001) (Figure 7). Furthermore, meta-regression for age (adjusted R²= 4.56%, I²resid: 82.02%, P= 0.157), disease course (adjusted R²= -3.28%, I²resid: 82.64%, P= 0.531), and acupuncture session (adjusted R²= -1.73%, I²resid: 83.52%, P= 0.386) were not statistically significant (Appendix 8).

During the sensitivity analyses of Acupuncture versus sham acupuncture and Acupuncture versus antidepressants, no studies with significant differences were found (Appendix 9 and Appendix 10). However, for acupuncture plus antidepressants versus antidepressants, the heterogeneity significantly decreased (MD: -5.34 [95% CI: -6.68 to -4.00]; I²=38%) to (MD: -4.83 [95% CI: -5.89 to -3.77]; I²=0%) (Figure 8).

3.3.2 SDS

Pooled analysis of four studies showed that Acupuncture (MD: -8.54 [95% CI: -13.01 to -4.06]; I²=81%) was more effective than sham acupuncture, with moderate quality of evidence (Table 1 and Appendix 11). Furthermore, high-quality evidence from 10 RCTs showed that Acupuncture and antidepressants were of equal effectiveness for MDD but was potentially influenced by publication bias (Table 1, Appendix 12 and Appendix 13). Moreover, pooled results from 4 RCTs provided low-quality evidence that Acupuncture plus antidepressants were not as beneficial as antidepressants for MDD treatment (Table 1 and Appendix 14).

During the meta-regression analysis of acupuncture versus sham-acupuncture, the disease course (adjusted R²= -4.28%, I²resid: 90.81%, P= 0.458), age (adjusted R²= -11.08%, I²resid: 90.84%, P= 0.86), baseline HAMD-24 (adjusted R²= -9.92%, I²resid: 90.80%, P= 0.35), and acupuncture session (adjusted R²= -8.81%, I²resid: 91.01%, P= 0.643) were not statistically significant (Appendix 15).

No studies with significant differences were found in the sensitivity analyses of Acupuncture versus sham acupuncture (Appendix 16).

3.3.3 Adverse Events

Pooled data from 9 studies provided high-quality evidence that acupuncture (OR: 0.27 [95% CI: 0.12 to 0.61]; I²=34%) led to fewer adverse events compared to antidepressants (Table 1 and Figure 9) and low-quality evidence that acupuncture was not statistically different from sham-acupuncture (Table 1 and Appendix 17). Furthermore, low-quality evidence showed that acupuncture plus antidepressants were not statistically different from antidepressants (Table 1 and Appendix 18).
4. Discussion

The systematic review included 43 high-quality RCTs involving 4037 MDD patients, while the meta-analysis included 41 RCTs with 3387 patients. The high quality evidence demonstrated an association between acupuncture with or without antidepressants and significant reduction in HAMD-24 scores. Importantly, relatively few adverse events were associated with acupuncture, consistent with previous studies and reviews.\(^8\-\!\!^{11}\,^{45}\). Our study provided the latest combined evidence for acupuncture alone or in combination with antidepressants in the treatment of MDD and identified research gaps that remain to be addressed.

Unlike previous systematic reviews, only high-quality RCTs were included in this study, ensuring that high-quality results were produced.\(^20\-\!\!^{22}\,^{67}\). Furthermore, the interventions in this study were restricted to acupuncture or acupuncture plus antidepressants, which greatly reduced the impact of diversiform acupuncture therapies.\(^71\-\!\!^{74}\) Accordingly, the present meta-analysis found that acupuncture and acupuncture plus antidepressants were associated with significantly reduced HAMD-24 scores than sham acupuncture or antidepressants, which was not documented in previous reviews.\(^22\,^{67}\) which could be accounted for by our strict inclusion of high-quality RCTs.\(^8\-\!\!^{13}\,^{32\-\!\!^{68}}\). In addition, more stringent inclusion criteria were used to ensure the quality of the source of the included randomized controlled trials.

Positive results from sham acupuncture RCTs suggested that acupuncture in combination with antidepressants had more beneficial effects than sham acupuncture plus antidepressants. Importantly, sham acupuncture helped to exclude the placebo effect of acupuncture.\(^8\). Insufficient blinding in included studies also increased the risk of bias of this meta-analysis. However, in recent years, pragmatic unblinded trials have been recommended to obtain clinically relevant results since they emphasized practical applicability in the real world and extrapolation (increased external validity) rather than treatment effects.\(^75\). This design of our study was well suited to complex and flexible interventions despite the inability to blind acupuncturists.\(^75\-\!\!^{77}\). Interestingly, it has also been suggested that placebo could play a role in the effects of acupuncture.\(^78\-\!\!^{81}\), and pragmatic nonblinded trials could provide more useful evidence for clinical guidelines of acupuncture.\(^82\). However, a gap still exists between the findings of RCTs of Acupuncture and our observations during clinical practice.

Clinically, acupuncture is often used to treat pain and plays an adjunctive treatment role in depression. The intended meaning is not clear. Did the author mean “The evidence from our study substantiated that acupuncture could be used as a major treatment approach for depression; however, the results of the heterogeneity analysis suggested that the results of data synthesis were not robust. Indeed, heterogeneity is an issue that cannot be avoided in meta-analysis, and in the present study, greater heterogeneity was found after data pooling. Importantly, a meta-regression analysis found an association between baseline HAMD scores and acupuncture treatment effectiveness, consistent with some previous studies.”

Therefore, we do not believe that Acupuncture is suitable as the sole treatment for depression. However, the latest clinical evidence suggests that acupuncture has good clinical effectiveness in improving HAMD scores and improving 5-HT and GABA levels.\(^32\,^{41\,\!\!^{48\,\!\!^{68}}\). However, these studies had small sample sizes, emphasizing the need for high-quality studies with large samples to corroborate these findings.

Limitations

There were several limitations to this study. Significant heterogeneity was found in the results of this study, which lowered the level of evidence, while the subgroup analysis did not reduce heterogeneity. There are many similar treatment modalities for Acupuncture, and this study was unable to determine whether Acupuncture was the best treatment modality. The number of acupuncture treatments varied considerably in the included studies, but no association with effectiveness was found after meta-regression analysis. Accordingly, it was not possible to clarify the optimal number of acupuncture sessions for MDD. Funnel plots were not feasible for most outcomes due to the limited number of trials included while assessing each outcome in the meta-analysis, explaining why publication bias could not be fully assessed. Only one of the studies included in this review was not done in China; accordingly, the fact that Chinese people tend to believe in the therapeutic effects of acupuncture may be another source of bias.

Conclusions

The findings of this systematic review and meta-analysis provided high-quality evidence that acupuncture or acupuncture in combination with antidepressants significantly reduced HAMD-24 scores.

Declarations

Patient and Public Involvement

No patient was involved.

Author contribution

Conceptualization: Guixing Xu, Qiwei Xiao, Hanzhou Lei, Ling Zhao, Fanrong Liang.

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**Writing - review & editing:** Guixing Xu, Qiwei Xiao.

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**Availability of data and materials**

The findings of this meta-analysis and systematic review will be published in peer-reviewed publications or conference presentations, and all of the data will be reported.

**Competing interests**

None.

**Consent for publication**

Not applicable.

**Ethics approval and consent to participate**

Ethics approval and patient consent were not required since this is secondary research without patient involvement.

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**Patient consent**

Not required.
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Figures

20835 of records identified through database searching (PubMed: 747; Embase: 1034; Cochrane library: 1383; WOS: 1015; CNKI: 6469; WF: 2831; VIP: 2938; CBM: 4418.)

9943 of records after duplicates removed

9943 records screened

296 RCTs of acupuncture for depression need screen the full-text

296 of full-text articles assessed for eligibility

253 of full-text articles excluded (Jadad score <4)

43 of studies included in qualitative synthesis

41 of studies included in quantitative synthesis (meta-analysis)

Figure 1

Flowchart of study selection

| Study or Subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|-------------------|------------------|----|--------|--------------|----|--------|--------|-------------------------------------|-------------------------------------|
| Fan_2005a         | -9.49            | 6.19| 28     | -5.28        | 5.45| 25     | 8.8%   | -4.21 [-7.34, -1.08]               | -4.21 [-7.34, -1.08]               |
| Fan_2015a         | -13.44           | 5.07| 47     | -6.24        | 4.28| 48     | 11.9%  | -7.20 [-9.09, -5.31]               | -7.20 [-9.09, -5.31]               |
| Fan_2015b         | -13.44           | 5.07| 47     | -11.04       | 4.91| 48     | 11.6%  | -2.40 [-4.41, -0.39]               | -2.40 [-4.41, -0.39]               |
| Fu_2006a          | -16.76           | 4.38| 78     | -8.83        | 6.95| 41     | 10.7%  | -7.93 [-10.27, -5.59]              | -7.93 [-10.27, -5.59]              |
| Fu_2008a          | -13.62           | 5.25| 176    | -7.77        | 5.82| 88     | 13.0%  | -5.85 [-7.29, -4.41]               | -5.85 [-7.29, -4.41]               |
| Jiang_2012a       | -12.55           | 4.06| 38     | -10.7        | 5.68| 34     | 10.8%  | -1.85 [-4.15, 0.45]                | -1.85 [-4.15, 0.45]                |
| Jiang_2012b       | -12.55           | 4.06| 38     | -8.38        | 6.42| 36     | 10.4%  | -4.17 [-6.63, -1.71]               | -4.17 [-6.63, -1.71]               |
| Jiang_2016a       | -11.31           | 5.25| 36     | -9.13        | 3.81| 39     | 11.4%  | -2.18 [-4.27, -0.09]               | -2.18 [-4.27, -0.09]               |
| Jiang_2016b       | -11.31           | 5.25| 36     | -7.03        | 3.91| 37     | 11.3%  | -4.28 [-6.41, -2.15]               | -4.28 [-6.41, -2.15]               |

Total (95% CI) 524 396 100.0% -4.49 [-5.93, -3.04]

Heterogeneity: $\tau^2 = 3.63$; $\chi^2 = 33.41$, df = 8 ($P < 0.0001$); $I^2 = 76$

Test for overall effect: $Z = 6.09$ ($P < 0.00001$)

Figure 2

Forest plot of HAMD-24 for Acupuncture versus sham-acupuncture
| Study or Subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|-------------------|------------------|----|-------|--------------|----|-------|--------|------------------------------------|------------------------------------|
| Cai_2014          | -11              | 10.27 | 28    | -12.85       | 10.67 | 31    | Not estimable                      |                                   |
| Cai_2018          | -12.37           | 5.52  | 30    | -13.81       | 6.06  | 30    | 6.2% 1.44 [-1.49, 4.37]             |                                   |
| Chen_2007         | -18.44           | 5.52  | 30    | -15.96       | 4.94  | 30    | 6.4% -2.48 [-5.13, 0.17]            |                                   |
| Chen_2020a        | -14.82           | 6.36  | 30    | -15.96       | 4.94  | 30    | Not estimable                      |                                   |
| Chen_2020b        | -14.3            | 6     | 49    | -12.44       | 6.03  | 25    | Not estimable                      |                                   |
| Du_2005a          | -8.62            | 6.64  | 29    | -12.44       | 6.03  | 25    | 5.9% 3.82 [0.44, 7.20]              |                                   |
| Du_2005b          | -9.49            | 6.19  | 28    | -9.66        | 5.9   | 24    | 6.0% 0.17 [-3.12, 3.46]            |                                   |
| Fan_2005b         | -16.76           | 4.38  | 78    | -13.05       | 5.84  | 82    | Not estimable                      |                                   |
| Fu_2006b          | -13.62           | 5.25  | 176   | -11.21       | 6.01  | 176   | Not estimable                      |                                   |
| Fu_2008b          | -7.22            | 4.43  | 30    | -6.6         | 2.14  | 30    | Not estimable                      |                                   |
| Li Haixing_2019   | -17.05           | 6.58  | 36    | -10.66       | 7.4   | 36    | Not estimable                      |                                   |
| Li Qiaojun_2019   | -9.92            | 4.65  | 29    | -5.55        | 5.49  | 29    | 6.4% -4.37 [-6.99, -1.75]          |                                   |
| Liu_2011          | -10.34           | 4.44  | 32    | -9.96        | 3.78  | 32    | Not estimable                      |                                   |
| Liu_2015          | -17.04           | 4.43  | 30    | -13.78       | 4.94  | 31    | 6.6% -3.26 [-5.61, -0.91]          |                                   |
| Liu_2016          | -9.4             | 5.39  | 30    | -10.25       | 4.59  | 30    | 6.5% 0.85 [-1.68, 3.38]            |                                   |
| Lu_2015           | -12.88           | 4.53  | 33    | -16.23       | 2.92  | 34    | 6.9% 3.35 [1.52, 5.18]             |                                   |
| Miao_2015         | -24.77           | 9.59  | 30    | -18.08       | 8.08  | 30    | 5.1% -6.69 [-11.18, -2.20]         |                                   |
| Shi_2015a         | -20.73           | 9.16  | 30    | -18.08       | 8.08  | 30    | Not estimable                      |                                   |
| Shi_2015b         | -12.04           | 5.66  | 30    | 7.3          | 5.95  | 30    | Not estimable                      |                                   |
| Shou_2020         | -17.71           | 6.84  | 30    | -17.39       | 7     | 30    | 5.8% -0.32 [-3.82, 3.18]           |                                   |
| Wang_2007         | -18.84           | 4.42  | 33    | -12.25       | 3.83  | 32    | 6.8% -6.59 [-8.60, -4.58]          |                                   |
| Wei_2021          | -6               | 5.3   | 16    | -5.53        | 4.71  | 15    | 5.8% -0.47 [-3.99, 3.05]           |                                   |
| Xiang_2016        | -17.5            | 4.58  | 120   | -16.14       | 4.76  | 120   | 7.2% -1.36 [-2.54, -0.18]          |                                   |
| Xing_2011         | -20.03           | 4.48  | 30    | -16          | 5.52  | 30    | 6.5% -4.03 [-6.57, -1.49]          |                                   |
| Zhang_2015        | -14.84           | 6     | 28    | -14.06       | 7.12  | 27    | 5.8% -0.78 [-4.27, 2.71]           |                                   |
| Zhou_2021         | -32.5            | 8.04  | 53    | -21.4        | 9.41  | 52    | 5.9% -11.10 [-14.45, -7.75]        |                                   |
| Zou_2010          | -18.84           | 4.42  | 33    | -12.25       | 3.83  | 32    | Not estimable                      |                                   |
| Total (95% CI)    |                  | 579  |       | 569          |      | 100.0% | -1.94 [-3.73, -0.16]               |                                   |

Heterogeneity: Tau² = 11.09; Chi² = 117.64, df = 15 (P < 0.00001); I² = 87%
Test for overall effect: Z = 2.13 (P = 0.03)

Figure 3

Forest plot of HAMD-24 for Acupuncture versus antidepressants
Figure 4

Funnel plot of HAMD-24 for Acupuncture versus antidepressants

| Study or Subgroup | Experimental Mean | SD | Total | Control Mean | SD | Total | Weight | Mean Difference [IV, Random, 95% CI] |
|-------------------|------------------|----|-------|--------------|----|-------|--------|-------------------------------------|
| Aimi_2018         | -26.93           | 5.66| 25    | -21.87       | 5.82| 23    | 10.9%  | -5.06 [-8.29, -1.83]                |
| Cal_2018          | -9.22            | 7.36| 41    | -6.85        | 6.04| 41    | 12.4%  | -2.37 [-5.28, 0.54]                 |
| Chen_2011         | -30.93           | 6.26| 64    | -26.52       | 7.23| 63    | 15.6%  | -4.41 [-6.76, -2.06]                |
| Chen_2014         | -32.18           | 9   | 38    | -21.87       | 8.41| 32    | 7.9%   | -10.31 [-14.39, -6.23]              |
| Huang_2010        | -34.06           | 4.85| 30    | -28.92       | 4.42| 30    | 15.6%  | -5.14 [-7.49, -2.79]                |
| Lin_2012a         | -26.39           | 10.49| 34    | -18.37       | 9.2 | 34    | 6.4%   | -8.02 [-12.71, -3.33]               |
| Lin_2012b         | -31.49           | 7.1 | 44    | -25.07       | 9.39| 54    | 10.8%  | -6.42 [-9.69, -3.15]                |
| Lin_2014          | -21.62           | 6.51| 30    | -17.9        | 6.59| 30    | 10.6%  | -3.72 [-7.03, -0.41]                |
| Zhou_2021         | -20.01           | 5.9 | 27    | -14.06       | 7.12| 27    | 9.9%   | -5.95 [-9.44, -2.46]                |
| Total (95% CI)    | 333              | 334 | 100.0%| 333          | 334 | 100.0%| 5.34 [-6.68, -4.00]                |

Heterogeneity: Tau² = 1.56; Chi² = 12.94, df = 8 (P = 0.11); I² = 38%
Test for overall effect: Z = 7.81 (P < 0.00001)

Figure 5

Forest plot of HAMD-24 for Acupuncture + antidepressants versus antidepressants
Figure 6

Meta-regression with baseline disease course as a single continuous covariate
Figure 7

Meta-regression with baseline HAMD-24 as single continuous covariate

| Study or Subgroup | Experimental | Control | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | Mean Difference | IV, Random, 95% CI |
|-------------------|--------------|---------|------|----|-------|------|----|-------|--------|-------------------|-----------------|-------------------|
| Almi_2018         | -26.93       | 5.56    | 25   | -21.87 | 5.82 | 23   | 10.8% | -5.06 [-8.29, -1.83] |
| Cal_2018          | -9.22        | 7.36    | 41   | -6.85 | 8.04 | 41   | 13.3% | -2.37 [-5.28, 0.54]  |
| Chen_2011         | -30.93       | 6.26    | 64   | -26.52 | 7.23 | 63   | 20.3% | -4.41 [-6.76, -2.06] |
| Chen_2014         | -32.18       | 9       | 38   | -21.87 | 8.41 | 32   | 0.0%  | -10.31 [-14.39, -6.23] |
| Huang_2010        | -34.06       | 4.85    | 30   | -28.92 | 4.42 | 30   | 20.4% | -5.14 [-7.49, -2.79]  |
| Lin_2012a         | -26.39       | 10.49   | 34   | -18.37 | 9.2  | 34   | 5.1%  | -8.02 [-12.71, -3.33] |
| Lin_2012b         | -31.49       | 7.1     | 44   | -25.07 | 9.39 | 54   | 10.5% | -6.42 [-9.69, -3.15]  |
| Lin_2014          | -21.62       | 6.51    | 30   | -17.9 | 6.59 | 30   | 10.2% | -3.72 [-7.03, -0.41]  |
| Zhou_2021         | -20.01       | 5.9     | 27   | -14.06 | 7.12 | 27   | 9.3%  | -5.95 [-9.44, -2.46]  |

Total (95% CI) 295 302 100.0% -4.83 [-5.89, -3.77]

Heterogeneity: Tau² = 0.00; Chi² = 6.48, df = 7 (P = 0.49); I² = 0%
Test for overall effect: Z = 8.92 (P < 0.00001)

Figure 8

Forest plot of HAMD-24 for Acupuncture versus antidepressants with Chen_2014 removed
### Forest Plot of Adverse Events for Acupuncture versus Antidepressants

| Study or Subgroup | Experimental | Control | Weight | Odds Ratio M-H, Random, 95% CI | Odds Ratio M-H, Random, 95% CI |
|-------------------|-------------|---------|--------|-------------------------------|-------------------------------|
| Chen_2007         | 3           | 10      | 16.0%  | 0.22 [0.05, 0.91]             |                               |
| Du_2005a          | 0           | 2       | 5.6%   | 0.09 [0.00, 2.06]             |                               |
| Du_2005b          | 0           | 2       | 5.6%   | 0.16 [0.01, 3.48]             |                               |
| Fan_2005a         | 0           | 4       | 5.9%   | 0.08 [0.00, 1.57]             |                               |
| Lu_2015           | 1           | 7       | 9.6%   | 0.11 [0.01, 0.99]             |                               |
| Miao_2015         | 2           | 3       | 12.5%  | 0.48 [0.08, 2.84]             |                               |
| Wang_2007         | 6           | 20      | 18.9%  | 0.13 [0.04, 0.40]             |                               |
| Wei_2021          | 2           | 3       | 11.7%  | 0.67 [0.10, 4.28]             |                               |
| Xiang_2016        | 6           | 0       | 5.9%   | 21.21 [1.07, 420.80]          |                               |
| Xiang_2016b       | 1           | 3       | 8.3%   | 0.27 [0.02, 2.90]             |                               |
| **Total (95% CI)**| **292**     | **261** | **100.0%** | **0.27 [0.12, 0.61]**         |                               |
| **Total events**  | **21**      | **55**  |        |                               |                               |

Heterogeneity: $\text{I}^2 = 34\%$, $\chi^2 = 13.61$, df = 9 ($P = 0.14$)

Test for overall effect: $Z = 3.16$ ($P = 0.002$)

Figure 9

Forest plot of adverse events for Acupuncture versus antidepressants

### Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- AppendixV1.0.docx
- PRISMAChecklist.doc