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Review Article

Meta-analysis of acupuncture combined with paroxetine in the treatment of depression

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Abstract: Objective: To systematically evaluate the clinical efficacy of acupuncture combined with paroxetine in the treatment of depression. Methods: The research literature on the treatment of depression with acupuncture and moxibustion combined with paroxetine was collected using keywords in PubMed, Embase, Web of Science, Cochrane Library, CNKI, World Wide Web, Chinese Biomedical Literature and other public publication databases. Collaborative screening of literature was performed according to pre-established inclusion and exclusion criteria. The data in the literature were extracted, the quality of the literature was evaluated, and the RevMan software was used for statistical analysis. Results: This study finally included 21 research papers involving 1733 clinical patients. The main evaluation indicators for clinical patients were Hamilton Depression Rating Scale (HAMD), total clinical response rate, Rating Scale for Side Effects (SERS) and Treatment Emergent Symptom Scale (TESS). SERS was developed by Asberg. The Chinese version was revised by Zhang Mingyuan (Chairman of the Chinese Medical Association Mental Health Society) et al. The SERS is divided into 14 items, all of which use a 4-point scoring method (none, mild, moderate and severe, respectively). This scale is mainly used to assess the side effects of antidepressants. TESS was compiled by the NIMH of the United States in 1973. It has the most comprehensive items and the widest coverage among the scales of its kind, including not only common adverse symptoms and signs, but also several laboratory test results. Meta-analysis of the above results showed that compared with the control group, the acupuncture combined with paroxetine treatment group showed lower HAMD score (WMD=-4.18 [-5.04, -3.31], P<0.001), higher total response rate (OR=4.01 [3.01, 5.33], P<0.001), lower SERS score (WMD=-2.54 [-4.58, -0.51], P<0.001) and lower TESS score (WMD=-4.39 [-5.15, -3.62], P<0.001), and the differences were statistically significant. Conclusion: The therapeutic effect of acupuncture combined with paroxetine on depression is better than that of conventional drug treatment, and its safety is comparable to that of conventional treatment.

Keywords: Paroxetine, acupuncture/electroacupuncture, depression, meta

Introduction

Depression is a common mental illness. It is mainly characterized by persistent low mood, indifference and resistance to the surrounding environment and people. Patients with severe conditions can have suicidal tendencies [1]. At present, the treatment for depression is mainly based on drugs. Among them, paroxetine is listed in the guidelines for the prevention and treatment of depression as a first-line treatment drug, and it is widely used in clinical practice. Several research reports have shown that paroxetine has a good clinical effect on patients with depression, but long-term use will lead to dose dependency in patients, and symptoms will recur if treatment is terminated [2, 3]. In clinical practice, paroxetine is usually combined with drug or non-drug therapy to improve treatment effect and reduce adverse reactions, but there is a lack of systematic evidence. In this meta-analysis, paroxetine combined with acupuncture or electroacupuncture was analyzed to evaluate the clinical efficacy and adverse reactions in the treatment of depression, so as to provide systematic evidence for the treatment of depression.

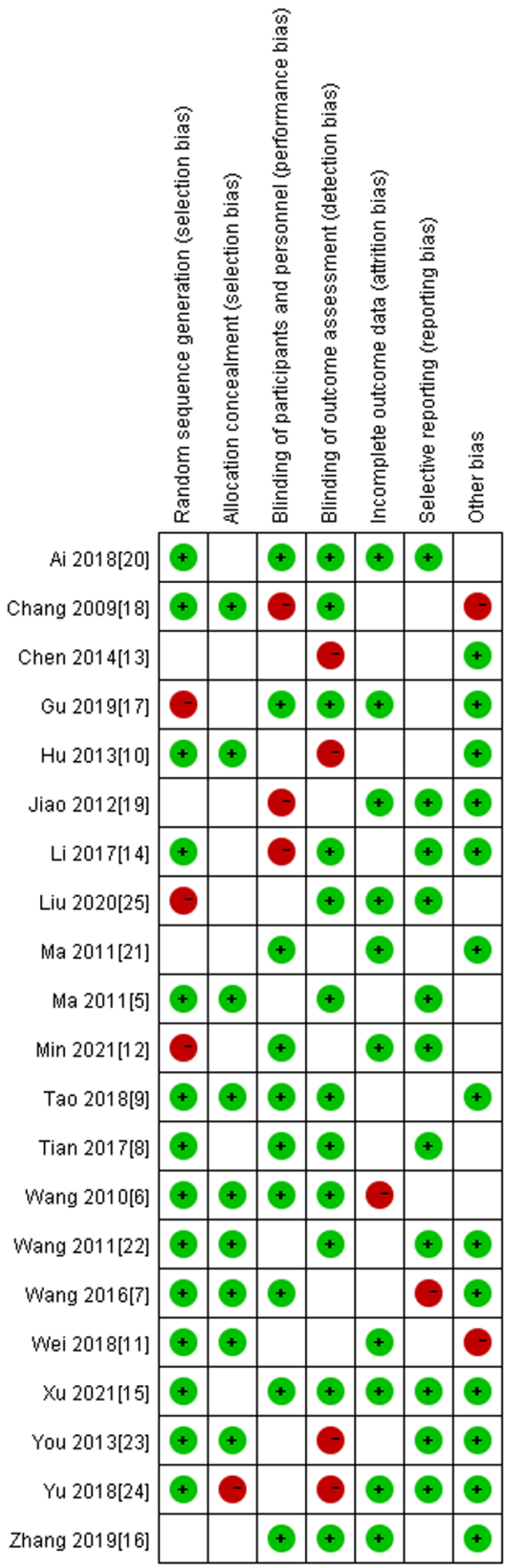

Figure 1. The quality assessment of all the 21 included literature.

Materials and methods

Document retrieval

The related literature in PubMed, Embase, Web of Science, Cochrane Library, Chinese Biomedical Literature, CNKI, Wanfang Database, etc. were manually searched, and the search time range was from the establishment of the database to March 2022. The search strategy was to combine subject keywords with free words. The keywords were acupuncture, electroacupuncture, paroxetine and depression. Example combinations were as follows, Paroxetine combined Acupuncture or electroacupuncture in Depression, Paroxetine and Acupuncture in Depression, Paroxetine and Electroacupuncture and Depression.

Inclusion and exclusion criteria

Inclusion criteria: Following the PICO principles, the included studies were all randomized controlled trials composed of patients, interventions, comparisons, outcomes and trial designs.

Exclusion criteria: Duplicate published literature, reviews, conference reports, books, case reports, letters were excluded. Literature with data parameters could not be extracted or insufficient data was also excluded.

Literature screening and data extraction

Firstly, two independent researchers, according to the pre-established inclusion and exclusion criteria, read the title and abstract of the retrieved literature to initially obtain the research. Secondly, the full text was read to further screen the included literature. If there was any ambiguity, a third researcher was involved in the screening process to discuss and resolve the ambiguity. Data extraction was independently conducted and cross-checked by two researchers, then reviewed by a third researcher. The data of the included studies should include year of publication, author, country, patient sample size, study location, intervention measures and outcome measures.

Quality assessment of literature

Two investigators independently assessed the quality of the included literature according to the New castle-Ottawa Scale (NOS) score. If there was disagreement, group discussion was intervened for determination (**Figure 1**).

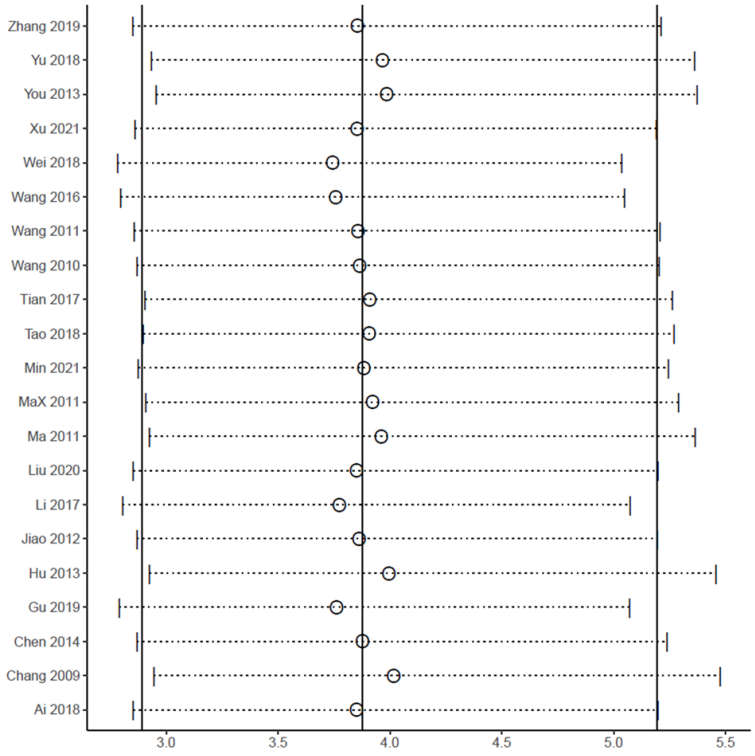

Figure 2. Sensitivity analysis.

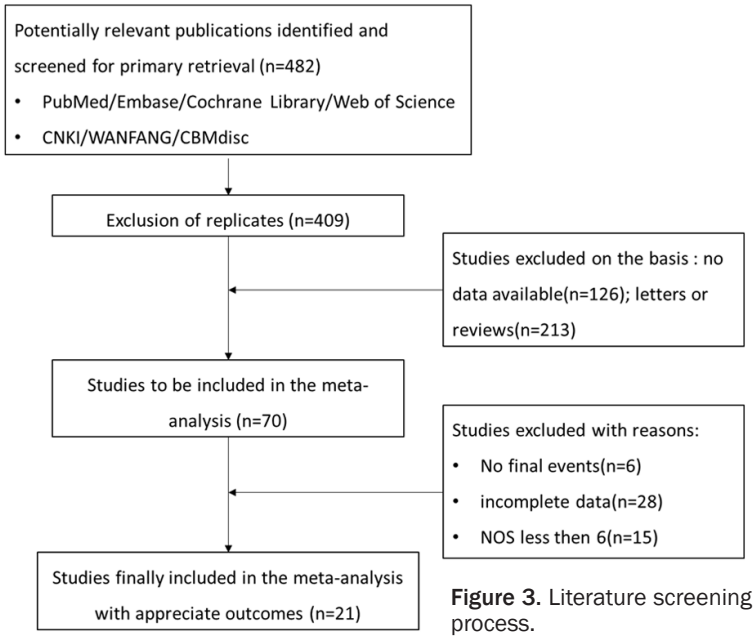

Figure 3. Literature screening process.

Sensitivity analysis

Sensitivity analysis was implemented by Stata software, and the data of each study were eliminated in turn to observe their impact on the final results. The analysis showed that the final results did not change significantly after excluding any study, suggesting that the differences between the included literatures were small, and the results of this study were stable and reliable. See **Figure 2**.

Statistical processing

RevMan software was used for systematic analysis. Enumeration data were expressed by OR value and its confidence interval. Measurement data were expressed by weighted mean difference (WMD) and confidence interval. A difference of $P<0.05$ was considered to be statistically significant. The heterogeneity among the studies was assessed by the I^2 test and *P* value, that is, $I^2>50$ or $P<0.1$, indicating that there was a significant heterogeneity among the studies. In this case, a random effect model was used for the study results. Otherwise, a fixed effect model was used. The funnel plot test was used to evaluate the publication bias between different studies, and the test level was $\alpha=0.05$.

Results

Literature search results

Through database search, we obtained a total of 482 literatures and removed 73 duplicate literatures. After reading the titles and abstracts of the articles, 339 items did not meet the inclusion criteria. Among them, 126 studies were unavailable for clinical data, and 213 were reviews, case reports, conference abstracts or monographs. We reviewed the full text of the remaining 70 articles, 6 articles had no study endpoint, 28 articles were excluded due to

Table 1. General characteristics of included studies

Research	Country	Number of patients in each group		Course	Intervention Program		Observation Indicator	NOS
		Treatment	Control		Treatment	Control		
Ma 2011 [5]	China	26	29	6w	Paroxetine	Electroacupuncture + Paroxetine	A, B	7
Wang 2010 [6]	China	30	30	6w	Paroxetine	Electroacupuncture + Paroxetine	A, B	6
Wang 2016 [7]	China	60	60	2m	Paroxetine	Electroacupuncture + Paroxetine	A	7
Tian 2017 [8]	China	25	25	6w	Paroxetine	Electroacupuncture + Paroxetine	A, C	7
Tao 2018 [9]	China	32	32	6w	Paroxetine	Electroacupuncture + Paroxetine	A, B	8
Hu 2013 [10]	China	45	45	3w	Paroxetine	Electroacupuncture + Paroxetine	A, C	8
Wei 2018 [11]	China	60	60	6w	Paroxetine	Electroacupuncture + Paroxetine	A, C	7
Min 2021 [12]	China	30	30	6w	Paroxetine	Electroacupuncture + Paroxetine	A	6
Chen 2014 [13]	China	38	32	6w	Paroxetine	Electroacupuncture + Paroxetine	A, B	8
Li 2017 [14]	China	29	28	8w	Paroxetine	Electroacupuncture + Paroxetine	A	7
Xu 2021 [15]	China	52	52	8w	Paroxetine	Electroacupuncture + Paroxetine	A, C	6
Zhang 2019 [16]	China	42	42	6w	Paroxetine	Electroacupuncture + Paroxetine	A	6
Gu 2019 [17]	China	50	50	8w	Paroxetine	Electroacupuncture + Paroxetine	A, C	7
Chang 2009 [18]	China	75	75	6w	Paroxetine	Electroacupuncture + Paroxetine	A	6
Jiao 2012 [19]	China	17	16	4w	Paroxetine	Electroacupuncture + Paroxetine	A, B	7
Ai 2018 [20]	China	50	50	6w	Paroxetine	Electroacupuncture + Paroxetine	A	8
Ma 2011 [21]	China	55	50	6w	Paroxetine	Electroacupuncture + Paroxetine	A, C	7
Wang 2011 [22]	China	25	25	2w	Paroxetine	Electroacupuncture + Paroxetine	A	8
You 2013 [23]	China	30	30	4w	Paroxetine	Electroacupuncture + Paroxetine	A, B	8
Yu 2018 [24]	China	51	50	4w	Paroxetine	Electroacupuncture + Paroxetine	A	6
Liu 2020 [25]	China	50	50	6w	Paroxetine	Electroacupuncture + Paroxetine	A	6

Note: For observation indicators, A refers to Hamilton Depression Rating Scale (HAMD); B refers to Rating Scale for Side Effects (SERS); C refers to Treatment Emergent Symptom Scale (TESS). NOS: New castle-Ottawa Scale.

insufficient data, 15 articles had NOS scores below 6 points, and finally 21 articles were included in the study, including a total of 1733 patients. All included studies had a NOS score of ≥6 points. The literature screening process and results are shown in **Figure 3**, the basic characteristics of the included literature are shown in **Table 1**.

Hamilton depression rating scale (HAMD)

The 21 studies provided the results of HAMD scale analysis to evaluate the therapeutic effect of acupuncture combined with paroxetine. Meta-analysis found that there was a heterogeneity among the studies (I^2=87%, P< 0.001), so a random-effects model was used for joint analysis. The results showed that the HAMD score of the experimental group was significantly lower than that of the control group, and the difference was statistically significant (WMD=-4.18 [-5.04, -3.31], P<0.001). The results are shown in **Figure 4**.

Overall efficiency

In each study, the clinical efficacy of the subjects was accessed according to the HAMD score. Meta-analysis of overall response rates found no significant heterogeneity among the studies (I^2=0%, P=0.85). Therefore, a fixed-effects model was used. The analysis results showed that the overall response rate of patients in the experimental group was significantly higher than that in the control group, and the difference was statistically significant (OR=4.01 [3.01, 5.33], P<0.001). The results are shown in **Figure 5**.

SERS scale

A total of 6 studies evaluated the SERE in patients. Meta-analysis found that there was a heterogeneity among the studies (I^2=98%, P<0.001), so a random effect model was used for joint analysis. The results showed that the side effects of antidepressants in the experimental group were significantly fewer than

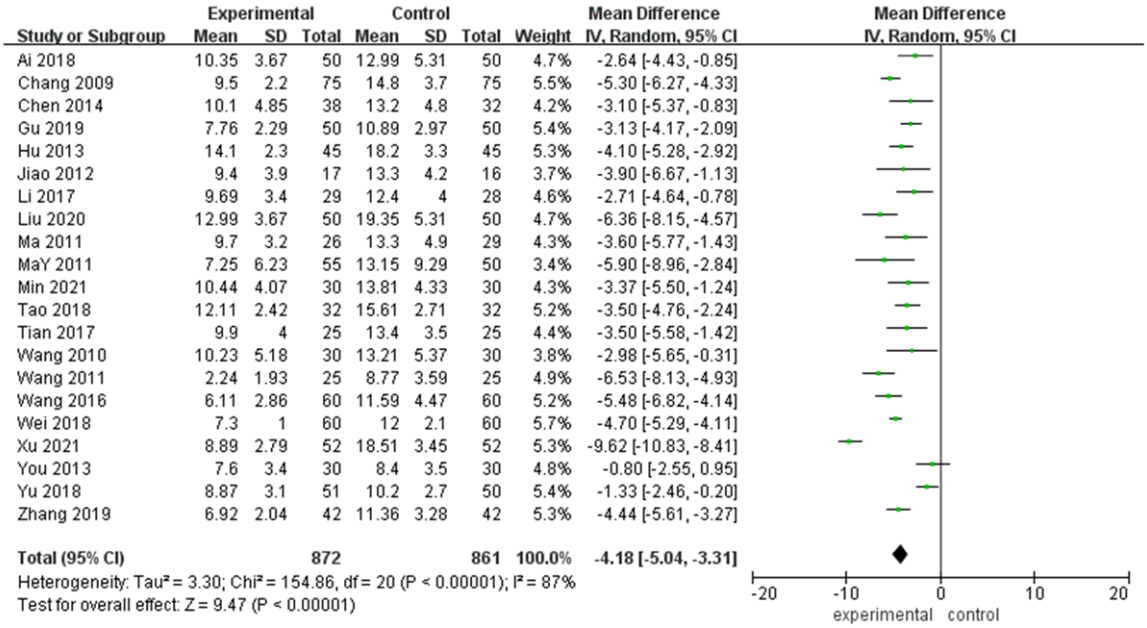

Figure 4. Meta-analysis of the HAMD scale in the experimental group and the control group. HAMD: Hamilton Depression Rating Scale.

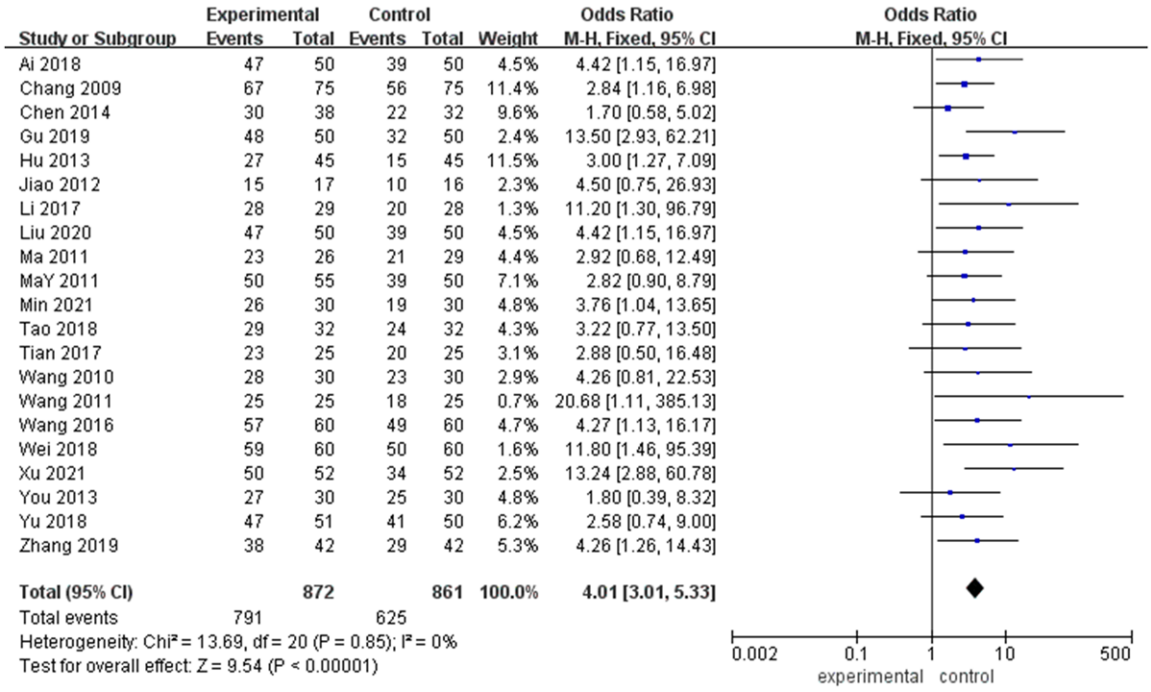

Figure 5. Meta-analysis of the overall response rate of patients in the experimental group and the control group.

those in the control group, and the difference was statistically significant (WMD=-2.54 [-4.58, -0.51], P<0.001). The results are shown in **Figure 6**.

TESS scale

A total of 6 studies evaluated TESS in patients. Meta-analysis found that there was a heteroge-

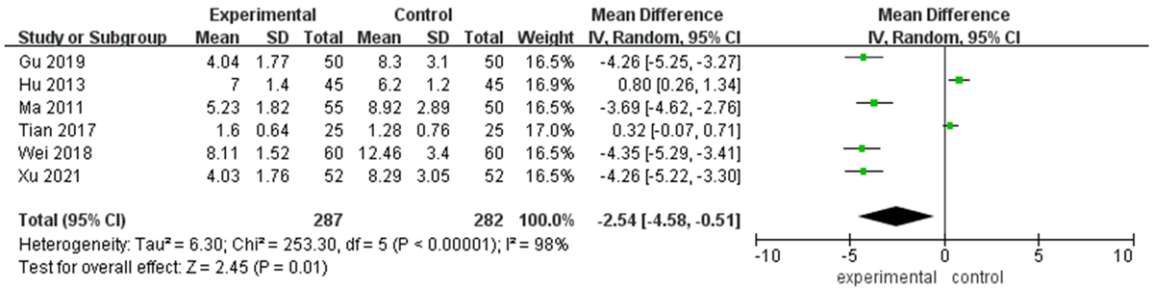

Figure 6. Meta-analysis of side effects of patients in the experimental group and the control group.

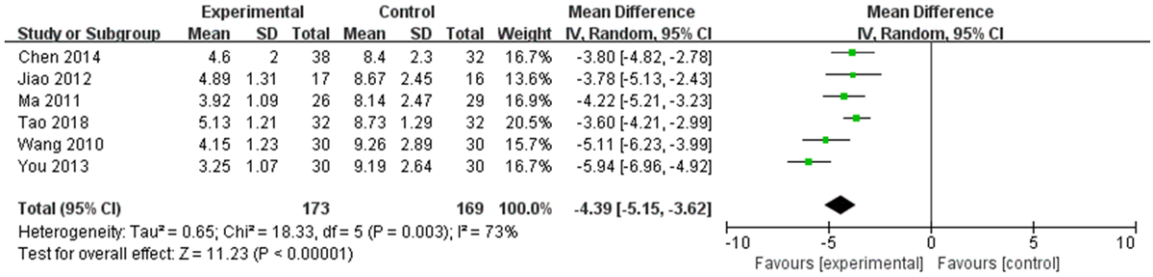

Figure 7. Meta-analysis of adverse reactions in the experimental group and the control group.

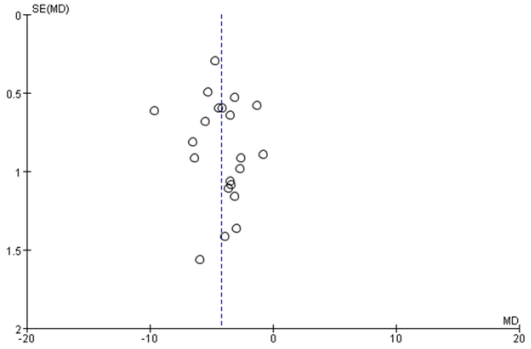

Figure 8. Published offset analysis.

neity among the studies (I^2=73%, P<0.001), so a random effect model was used for joint analysis. The results showed that the adverse reactions in the experimental group were significantly fewer than those in the control group, and the difference was statistically significant (WMD=-4.39 [-5.15, -3.62], P<0.001). The results are shown in **Figure 7**.

Post offset

A funnel plot analysis was performed on the research literatures included in the analysis, and it was found that the scattered points in the figure were basically symmetrically distributed, indicating that the included studies had no obvious publication bias. See **Figure 8**.

Discussion

Depression is a common clinical mental disease with an increasing incidence in recent years. Effective and safe treatment for depression has always been an important direction of clinical research. According to the theory of traditional Chinese medicine, depression is a "stagnation disease", which is caused by a combination of stagnation of qi and emotional disturbance. For such diseases, traditional Chinese medicine theory believes that the main acupuncture points should be dredging. Acupuncture at Dumai, Dazhui, Baihui can improve the neurological function of the patient's brain and correct the spirit of the depressed patient [26]. The basic research conducted by Shi et al. found that acupuncture intervention on Baihui acupuncture point can affect the neuroendocrine and neurotransmitter transmission in the brain, and regulate related nerve signal conduction (hypothalamic-pituitary-adrenal axis) [27]. From a perspective of cell signal transduction and hippocampal neurogenesis, it is stated that acupuncture and moxibustion are effective in antidepressant

treatment through multilevel and multiple targets [28]. As a first-line drug treatment for depression, paroxetine can inhibit the occurrence of depression by selectively inhibiting the reuptake of 5-hydroxytryptamine (5-HT) by brain tonic neurons and increasing the concentration of 5-HT between synapses. In recent years, a number of studies have reported that acupuncture combined with paroxetine has a synergistic effect on the treatment efficacy of depression, which can not only improve the depressive symptoms of patients, but also improve the quality of life of patients [2, 3]. In this study, according to the established search strategy, the literature was screened through inclusion and exclusion criteria, and relevant data were extracted. Meta-analysis was used to quantitatively evaluate the included studies and to objectively and systematically evaluate the effectiveness of acupuncture combined with paroxetine in the clinical treatment of patients with depression, so as to provide reliable systematic medical evidence for clinic.

It is worth noting that all the studies included in this article are From China, because they are about acupuncture, which is a traditional Chinese treatment method. Although we have tried to search a variety of databases, both in Chinese and English, all the studies met the inclusion and exclusion are Chinese studies.

This study found that in the acupuncture combined with paroxetine treatment group, the HAMD score was significantly lower and the overall response rate was significantly higher than those of the control group. The side effects and adverse reactions of depressants in the acupuncture combined with paroxetine treatment group were significantly lower than those in the control group, indicating that acupuncture combined therapy can reduce the side effects and adverse reactions caused by the drug, showing safety and reliability. However, this study also has certain limitations. Firstly, some data were calculated from the article, which may be different from the original data. Secondly, the included published literature is only Chinese literature, so the generality of the results may be limited to a certain extent. Thirdly, this systematic review is limited by the defects and possible biases of the original research, and there are not many available data, so the reliability of the results still needs to be verified by a large sample of related clinical studies. Nonetheless, from the preliminary results of this study, acupuncture combined with paroxetine in the treatment of depression is superior to conventional treatment, and has lower side effects and adverse reactions, but higher safety, with certain clinical application value.

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Disclosure of conflict of interest

None.

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