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REVIEW

A Meta-Analysis on the Efficacy of Acupuncture as an Adjuvant Therapy for Schizophrenia

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Objective: To systematically evaluate the efficacy of acupuncture in the treatment of schizophrenia.

Methods: We searched China National Knowledge Infrastructure (CNKI), Wanfang Database, Chongqing VIP Chinese Science and Technology Periodical Database (VIP), China Biology Medicine Database (CBM), PubMed, Embase, Web of Science, Cochrane Library for relevant literature on the acupuncture treatment of schizophrenia published from database inception to May 17, 2023. The evaluation criteria included total effective rate, incidence of adverse reactions, TESS scale, PANSS scale, BPRS scale, SANA scale, SAPS scale. Two researchers independently screened the literature, extracted data, and assessed the risk of bias of the included studies. The RevMan 5.4 software was used for meta-analysis, risk of bias (ROB) evaluation tool was used to evaluate the risk of bias of the studies, and the GRADE evaluation tool was used to evaluate the quality of evidence. The study was registered on PROSPERO, CRD42023416438.

Results: A total of 38 RCTs involving 3143 patients were included in the meta-analysis. The results showed that acupuncture can improve the total effective rate [OR=3.43 (95% CI: 2.71, 4.35), moderate credibility], reduce the incidence of adverse reactions [OR=0.45 (95% CI: 0.32, 0.63), moderate credibility], reduce the TESS score (side effect scale) [MD=−1.83 (95% CI: −2.94, −0.71), very low credibility]. Acupuncture also reduced the PANSS total score [MD=−5.75 (95% CI: −8.08, −3.42), very low credibility], SANA score [MD=−2.66 (95% CI: −6.84, 1.51), very low credibility], SAPS score [MD=−1.26 (95% CI: −2.55, −0.02), very low credibility], and BPRS score [MD=−7.02 (95% CI: −10.59, −3.46), very low credibility].

Conclusion: Existing evidence indicates that acupuncture as an adjunctive therapy can improve the total effective rate of SZ patients, reduce the incidence of adverse reactions, improve clinical symptoms, and alleviate depression and anxiety in SZ patients. However, more high-quality clinical research evidence is still needed to support these findings.

Keywords: acupuncture, meta-analysis, schizophrenia

Introduction

Schizophrenia (SZ) is a chronic mental illness characterized by changes in personality, cognitive, thinking, emotional, and behavioral disorders, as well as a lack of coordination between mental activity and the environment. Its main clinical manifestations are delusions, hallucinations, disordered thinking (speech), obvious disordered or abnormal movements and behaviors, and other symptoms. It affects approximately 20 million people worldwide,[1] and the global prevalence of schizophrenia is estimated to be between 0.33% and 0.75%.[1] The disease is more common in young adults or adults.[2] At the same time, schizophrenia seriously affects the daily life of patients, and maintaining daily activities is very difficult for schizophrenia patients.

In terms of mechanisms, the etiology of SZ remains elusive to date. Researchers have been searching for biomarkers to aid in the diagnosis and understanding of the pathogenesis of this disease. In recent years, exosomes as a prominent biomarker have garnered widespread attention in this research field. Studies have shown that metabolites derived from

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exosomes have significant potential to provide diagnostic information for SZ, highlighting the role of exosomal miRNA dysregulation in the pathophysiology of SZ.[3]

In clinical practice, drug therapy and psychotherapy are the main treatments for SZ, but their adverse reactions are obvious. Studies have found that second-generation or "atypical" antipsychotics (SGA) can lead to weight gain and significant metabolic changes in patients, indirectly increasing their risk of developing diabetes and increasing circulating cholesterol levels.[4] In addition, the recurrence rate of this disease is as high as 78–82%.

Acupuncture, as a green therapy, provides another option for SZ without significant side effects. The research findings indicate that acupuncture, by modulating functionally opposing brain networks, enhances the behavior of SZ patients, and this effect is contingent upon psychophysiological responses.[5] While the effectiveness of acupuncture in treating SZ has been confirmed by several Cochrane systematic reviews,[6,7] there are limitations in the methodological quality of some included studies, leading to a lack of high-quality evidence. Furthermore, the potential impact factors underlying acupuncture's therapeutic effects in SZ remain a subject of debate. This study aims to bridge these research gaps, offering more systematic evidence and applying meta-regression to investigate potential factors influencing the efficacy of acupuncture in SZ treatment.

Materials and Methods

The study was registered on PROSPERO (CRD42023416438).

Inclusion and Exclusion Criteria

Inclusion Criteria

(1) Randomized controlled trials (RCTs) of acupuncture treatment(Intervention definition can be found in Appendix 1) for schizophrenia were included in this meta-analysis. (2) Patients with a clinical diagnosis of schizophrenia according to diagnostic criteria such as Chinese Classification of Mental Disorders (CCMD-2,[8] CCMD-3[9]), International Classification of Diseases (ICD-10[10]), or Diagnostic and Statistical Manual of Mental Disorders (DSM-V[11]). (3) The intervention group received acupuncture or acupuncture combined with other therapies, and the control group received other therapies except for acupuncture (when the intervention group received acupuncture combined with other adjunct therapies, the control group should receive the same adjunct therapies). (4) The outcome measures must be one of the following, such as total effective rate, incidence of adverse reactions, score on the Treatment Emergent Symptom Scale (TESS), Positive and Negative Syndrome Scale (PANSS), Brief Psychiatric Rating Scale (BPRS), Scale for the Assessment of Negative Symptoms (SANS), and Scale for the Assessment of Positive Symptoms (SAPS).

Exclusion Criteria

(1) Unclear diagnostic criteria or no diagnostic criteria; (2) Studies that did not include outcome measures; (3) Studies with unextractable data or inaccessible full text; (4) Duplicate publications; (5) Reviews, conference abstracts, before-and -after comparison studies, case reports, cohort studies, and other non-randomized studies.

Search Strategy

We searched the China National Knowledge Infrastructure (CNKI), Wanfang Database, Chongqing VIP Chinese Scientific Journal Full-text Database (VIP), China Biology Medicine disc (CBM), PubMed, Embase, Web of Science, and Cochrane Library for relevant literature on acupuncture treatment for schizophrenia. The search time limit was from the establishment of the databases until May 17, 2023. The search terms used included "acupuncture", "acup*" "moxibustion", "electroacupuncture", "schizophrenia", "schizo*" "psychos*" and other relevant terms. Language restrictions were not applied. The specific search formula can be found in Appendix 2

Literature Screening and Data Extraction

Firstly, two researchers independently screened the retrieved literature based on the inclusion and exclusion criteria. In case of any disputes, a third reviewer cross-checked the articles to reach a consensus. The two researchers extracted relevant information from the included literature, including study identification (first author and year of publication),

general characteristics of patients (gender, age, and sample size), intervention measures, treatment process, and outcome indicators.

Risk of Bias Assessment of Included Studies

The Cochrane risk of bias assessment tool (version 5.4.0) was used to evaluate the risk of bias in the included RCTs. It includes seven items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. The risk of bias for each item was classified into three categories: low risk of bias, high risk of bias, or unclear risk of bias. Two reviewers independently assessed the risk of bias of the studies. In case of inconsistent results, a third reviewer made the final decision.

Outcomes and Measures

Primary Outcome

The primary outcome was the total effective rate, which was assessed using the Positive and Negative Syndrome Scale (PANSS), Scale for the Assessment of Positive Symptoms (SAPS), Scale for the Assessment of Negative Symptoms (SANS), Brief Psychiatric Rating Scale (BPRS), Global Assessment of Functioning (GAF), and Pittsburgh Sleep Quality Index (PSQI). In the study, a reduction rate of ≥30% in PANSS score, ≥20% in BPRS score, ≥25% in SAPS excitation score, ≥25% in SANS score, an increase rate of ≥20% in GAF score, and a reduction rate of ≥25% in PSQI score were considered as effective. The evaluation time points included before and after treatment (usually 1–12 weeks).

Secondary Outcomes

The secondary outcome was the PANSS score, which is a scale for evaluating the positive symptoms, negative symptoms, and general psychological symptoms of patients with schizophrenia. The total score ranges from 30 to 210, and includes subscales such as positive symptoms, negative symptoms, and general psychopathology. A threshold of 60 points was used, with higher scores indicating more severe symptoms. The evaluation time points included before and after treatment (usually 1–12 weeks).

BRPS score: The BRPS score was used to evaluate the severity of illness and treatment efficacy in patients with mental illness, with a range of 1–7 points. A score of 1 indicated extremely worsening condition, while a score of 7 indicates complete remission of symptoms. The evaluation time points included before and after treatment (usually 1–12 weeks).

SAPS score: The SAPS score was used to assess the severity and changes in symptoms of mental illness. The scale was consisted of 4 dimensions, including hallucinations, delusions, thought disorders, and affective flattening. The total score ranged from 0–176, with higher scores indicating more severe symptoms. The evaluation time points included before and after treatment (usually 1–12 weeks).

SANS score: The SANS score was used to assess the severity and changes in symptoms of mental illness. The scale was consisted of 5 dimensions, including hallucinations, delusions, thought disorders, affective flattening, and behavioral symptoms, each with multiple scoring indicators. The score range was 0–95, with higher scores indicating more severe symptoms. The evaluation time points included before and after treatment (usually 1–12 weeks).

Effect Size and Heterogeneity Assessment

Meta-analysis was performed using RevMan 5.4 software. With 95% confidence interval (CI), the odds ratio (OR) was used as the effect size (ES) considering the the total effective rate was a dichotomous variable, and the mean difference (MD) was applied for the continuous variables, involving all secondary outcomes.

Effect model: Fixed or random effect models were chosen based on the heterogeneity test results of the studies. Statistical heterogeneity was assessed using I^2 statistic, Cochran's Q test (reporting its between-study variance component $\tau 2$ and corresponding P-value based on the significance level $\alpha=0.1$), and forest plots. If $P > 0.1$ and $I^2 \leq 50\%$, heterogeneity was considered acceptable, and a fixed effect model was used for the pooled effect size. If $P< 0.1$ or $I^2 \geq 50\%$, statistical heterogeneity was considered unacceptable When the random effects model still could not explain the

heterogeneity well, we attempted to explore the sources of heterogeneity using subgroup analysis, sensitivity analysis, or comparing the specific content of the literature.

Publication Bias

Funnel plots were used to assess potential publication bias when the number of included studies exceeded 10.

Evidence Certainty Assessment

To assess the evidence certainty, we used the GRADEpro online tool (http://gdt.gradepro.org/app#projects) to perform the evaluation and followed the recommended procedures for grading (high, moderate, low, very low).

Results

Literature Search Results

A total of 1761 relevant articles were obtained in the initial screening, and after a series of selection processes, 38 RCTs[12–49] were finally included. The flowchart of literature screening process and results are shown in Figure 1.

Characteristics of Included Studies

A total of 38 randomized controlled trials (RCTs) were included in this review, comprising of 3143 participants. Of these, 1595 were in the treatment group and 1548 were in the control group. The trials were conducted in different countries, including China (37 trials[12–48] with 3112 participants) and Tunisia (1 trial[49] with 31 participants). 36 studies[12–47] were published in Chinese, 1[48] in English, and 1[49] in French. Sample sizes ranged from 31 to 200 participants, with treatment durations ranging from 1 to 12 weeks. The age of participants ranged from 18 to 65 years. The main interventions in the treatment group included electroacupuncture, manual acupuncture, and scalp acupuncture. The control group included sham acupuncture, psychological health education, clozapine, quetiapine, risperidone, aripiprazole, dextropropoxyphene tablets, paliperidone, haloperidol, olanzapine, sulpiride, chlorpromazine, team psychological intervention, cognitive behavior therapy, and sertraline hydrochloride tablets. The main outcome measures included the total effective rate, and secondary outcome measures included PANSS score, BRPS score, SAPS score, and SANS score (Table 1).

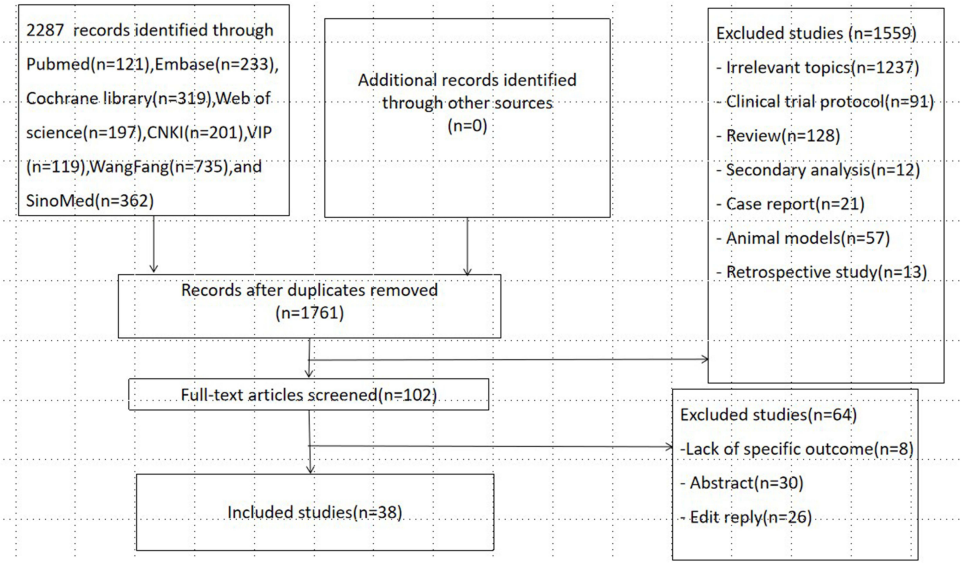

Figure 1 Flowchart of literature search and selection results.

Table 1 Basic Characteristics of the Included Studies

Study	Sample Size	Age (Year, Mean±SD)	Sex (Male/ Female)	Disease course	Methods of Intervention	Comparison	Treatment Duration	Main Outcomes
Yao 2006[12]	T:45	T:31±12	T:28/17	T:8±5m	EA+CI	CI	40d-60d	1,3,5
	C:45	C:29±13	C:22/23	C:9±3m				
Jiang 2011[13]	T=39	T:41.6±9.2	T:21/18	T:12.5±6.8y	EA+QU	QU	8w	1,2,3
	C=39	C:42.2±8.3	C:17/22	C:12.8±7.8y				
Fan 2015[14]	T=42	T:41.2±11.4	T:28/15	T:3.8±2.7y	EA+RI	RI	6w	1
	C=42	C:41.3±11.3	C:29/14	C:3.9±2.5y				
Gong 2015[15]	T=41	T:42±12.58	T:28/13	T:4±1.89y	MA+AR	AR	8w	3,7
	C=37	C:41±13.48	C:25/12	C:3±1.67y				
Liu 2011[16]	T=30	T:40±8	T:18/12	T:15.8±8.55y	EA+CI	CI	4w	4,6,7
	C=32	C:44±10	C:20/12	C:19.53±9.50y				
Huang 2015[17]	T=48	T:41±13	T:25/23	T:15.7±20.3y	MA+PA	DT+PA	6w	1,2,3
	C=48	C:41±12	C:24/24	C:14.9±28.9y				
Gao 2014[18]	T=31	T:36.2±7.2	T:17/14	T:23.6±5.7y	EA+WM+PHE	WM+PHE	4w	3,4
	C=31	C:37.9±8.5	C:16/15	C:24.5±6.3y				
Chen 2015[19]	T=31	T:23.3±7.4	T:18/13	-	EA+CI	CI	7d	3
	C=31	C:25.14±6.7	C:17/14	-				
CJ 2016[20]	T=62	T:26.1±8.2	-	-	EA+RA+HA	RA+HA	7d	3
	C=62	C:27.8±9.1	-	-				
Zhao 2013[21]	T=40	T:27.5±5.6	T:19/21	T:6.08±2.52y	MA+OL	OL	5w	2,3
	C=40	C:27.3±6.2	C:18/22	C:6.06±2.43y				
Xiong 2010[22]	T=40	T:29.4±11.3	T:22/18	T:35.2±12.2m	EA+CI	CI	8W	1,2,3
	C=40	C:28.1±12.2	C:24/16	C:36.3±13.2m				
Du 2011[23]	T=30	T:26.81±7.43	T:18/12	T:6.81±5.42m	EA+SU	SU	2m	3,4,7
	C=30	C:27.47±6.78	C:16/14	C:7.73±5.18m				
LGH 2012[24]	T=59	T:32.30±9.41	T:35/24	T:3.24±1.4y	MA+RI	RI	8w	3,5
	C=58	C:31.30±10.03	C:33/25	C:3.40±1.5y				
LGH 2006[25]	T=64	T:31.30±7.8	T:34/30	T:5.14±2.1y	WM+EA	WM	3w	3
	C=42	C:29.5±5.2	C:28/14	C:4.60±3.2y				
Xu 2010[26]	T=30	T:25.67±8.12	-	T:5.33±4.02m	WM+MA	WM	8w	1,3
	C=30	C:26.33±7.52	-	C:5.04±3.17m				
Cui 2000[27]	T=30	T:35.1±7	T:6/24	T:3.5±2.8y	EA+CH	CH	6w	3,4
	C=30	C:35.1±7	C:6/24	C:3.5±2.8y				
Qu 2014[28]	T=23	T:39±15	T:14/9	T:3.53±2.5y	MA+RI	RI	6W	3
	C=21	C:38±13	C:13/8	C:3.62±2.78y				
Liu 2010[29]	T=47	T:34.05±8.35	T:30/20	T:4.27±3.70y	MA+RI	RI	3m	3,4
	C=49	C:35.12±7.57	C:27/23	C:4.02±3.91y				
Zhao 2018[30]	T=100	T:32.6±2.3	T:53/47	T:5.6±0.9y	MA+RI	RI	3m	3,5
	C=99	C:32.4±2.2	C:50/49	C:5.5±1.1y				
Chen 2017[31]	T=48	T:38.2±7.6	T:20/28	T:4.4±1.9y	MA+AR	AR	8w	1
	C=48	C:39.7±8.1	C:21/27	C:4.5±1.5y				
Dang 2017[32]	T=43	-	-	-	WM+MA	WM	12w	4
	C=26	-	-	-				
Qin 2017[33]	T=40	T:34.5±5.1	-	T:5.4±3.2y	MA+CL	CL	12w	1,2,4
	C=40	C:37.4±5.5	-	C:5.0±2.7y				
Li 2022[34]	T=30	T:28.43±5.36	T:17/13	T:10.43±3.74y	EA+CL	CL	8w	1,3,5
	C=30	C:33.46±5.78	C:18/12	C:9.76±3.41y				
Ji 2022[35]	T=30	T:56.2±8.03	T:16/14	T:2.1±0.79y	EA+CL	CL	6w	1,2,5
	C=30	C:57.1±5.38	C:18/12	C:2.67±1.11y				
Yang 2022[36]	T=31C=32	-	-	-	OL+MA	OL	8w	1,3
Li 2021[37]	T=32	T:37.4±5.3	T:11/21	T:15.3±1.3m	EA+QU	QU	8w	3,4,5
	C=32	C:36.4±5.4	C:12/20	C:16.4±1.1m				

(*Continued*)

Table 1 (Continued).

Study	Sample Size	Age (Year, Mean±SD)	Sex (Male/ Female)	Disease course	Methods of Intervention	Comparison	Treatment Duration	Main Outcomes
Shen 2021[38]	T=41	T:62.2±5.47	T:19/22	T:16.94±6.89y	MA+WM	WM	3m	1
	C=40	C:61.68±8.38	C:18/22	C:19.5±7.18y				
Zhon 2021[39]	T=44	T:37.57±9.73	T:23/21	T:15.68±9.57y	AR+MA	AR	8w	3
	C=44	C:36.92±9.24	C:24/20	C:15.46±9.43y				
Zheng 2020[40]	T=35	T:36±8	T:16/19	T:15.58±5.05y	WM+MA	WM	6w	1
	C=35	C:37±8	C:18/17	C:9.54±4.89y				
LQ 2020[41]	T=30	T:39.2±7.1	T:15/15	-	MA+RI	RI	30d	1
	C=30	C:38.3±6.8	C:14/16	-				
Pan 2020[42]	T=50	T:37.56±9.72	T:28/22	T:15.67±9.56y	MA+WM	WM	12w	1,3,5
	C=51	C:36.91±9.23	C:27/24	C:15.45±9.42y				
LH 2020[43]	T=40	T:27.25±1.15	T:28/12	-	MA+RI	RI	3m	1,4,7
	C=40	C:27.35±1.28	C:27/13	-				
Chen 2020[44]	T=100	T:51.3±7.0	-	T:1.2±2.2y	EA+RI+HA	RI+HA	9d	3
	C=100	C:52.1±7.3	-	C:1.3±2.1y				
LJ 2020[45]	T=59	T:30±9.1	T:29/30	T:9.2±1.5y	MA+RI	RI	6w	1,2,3
	C=58	C:27±8.6	C:30/28	C:8.8±1.6y				
Liao 2019[46]	T=35	T:23~53	T:21/14	T:3~12y	MA+CL	CL	12w	1,3,4,5
	C=30	C:24~52	C:15/15	C:4~13y				
Lin 2018[47]	T=30	T:37.4±5.8	-	T:2.3±0.7y	OL+EA	OL	6w	1,3,5
	C=30	C:37.4±5.8	-	C:2.3±0.7y				
Cheng 2009[48]	T=30	T:31.20±5.79	T:13/17C:15/15	T:10.13±2.89y	EA	SA	6w	1,3
	C=30	C:28.97±5.49	-	C:9.03±2.94y				
Bouhlel 2011[49]	T=15	T:36.6	19/12	T:12.58y	MA+WM	SA+WM	23d	1,6,7
	C=16	C:36.6	-	C:12.58y				

Notes: (1)PANSS (Positive and Negative Syndrome Scale), (2) TESS (Treatment Emergent Symptom Scale), (3) Effectiveness rate, (4) BPRS (Brief Psychiatric Rating Scale), (5) Incidence of adverse reactions, (6) SAPS (Scale for Assessment of Positive Symptoms), and (7) SANS (Scale for Assessment of Negative Symptoms).

Abbreviations: T, treatment; C, control; m, month; w, week; d, day; y, year; MA, Manual acupuncture; SA, sham acupuncture; EA, electro acupuncture; SH, Shallow needling; WM, Western medicine; PHE, psychological health education; CI, Clozapine; QU, Quiclopine; RI, Risperidone; AR, Aripiprazole; DT, Dextropiclone tablet; PA, paliperidone; HA, haloperiaol; OL, olanzapine; SU, sulpiride; SA, scalp acupuncture; CH, chlorpromazine; TPI, Team psychological intervention; CBT, cognitive behavior therapy; SHT, sertraline hydrochloride tablets.

Diagnostic Criteria

Among the 38 studies, three[34,37,46] did not mention the specific version of the diagnostic criteria, while 35 studies had clear versions of the diagnostic criteria. One study[27] used the Chinese Classification of Mental Disorders 2nd edition (CCMD-2), 18 studies[12,13,15,16,18,21–26,28–30,36,43,44,47] used CCMD-3, 9 studies[14,17,31,33,35,39–42] used the International Classification of Diseases 10th edition (ICD-10), and 7 studies[19,20,32,38,45,48,49] used DSM-V.

3.4 Among the 38 studies included in this study, 17 provided sufficient information on randomization and were assessed as having a low risk of selection bias. The randomization methods included random number tables (13),[14,17–19,23–25,29,30,32,36,39,42] digit tables (1),[40] drawing lots (1),[12] random allocation tables (1),[26] and computer-generated random number sequences (1).[48] One study[48] mentioned allocation concealment using sealed opaque envelopes. Two studies[48,49] mentioned blinding of patients and evaluators. Regarding completeness, two studies[24,29] out of the 38 did not address the handling of missing data, and we did not find any sources of selective reporting or other bias in all included studies (Figure 2A and B).

Meta-Analysis Results

Primary Results

Overall Effectiveness

A total of 27 RCTs[12,13,15,17–30,34,36,37,39,42,44–48] with 2367 patients were included. Heterogeneity testing was conducted on the results of the 27 studies. Based on a fixed-effect model, the Meta-analysis showed a statistically significant

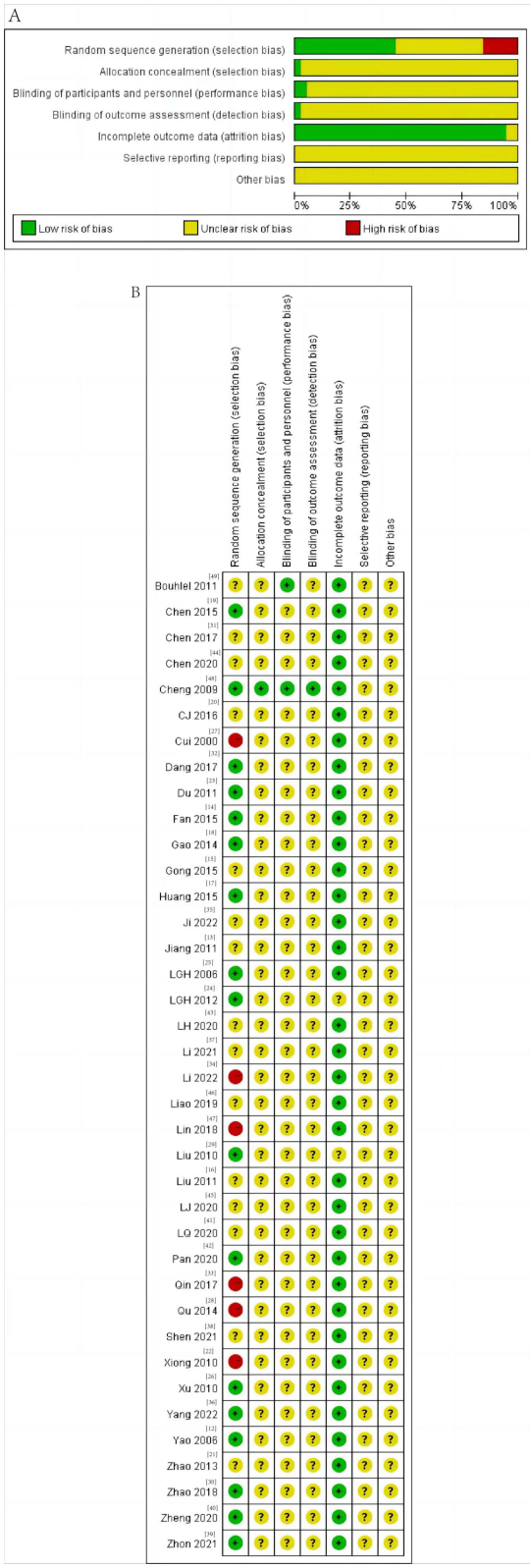

Figure 2 Risk of Bias assessment results.

Notes: (**A**) Graphical representation of the overall risk of bias in the 7 domains. (**B**) Summary of the risk of bias in 7 domains in the 38 studies. Green (+), yellow (?) and red (-) represent low, unclear and high risk of bias respectively. Length of the rectangles (green, yellow or red) show the percentage of studies with low, unclear, or high risk of bias for the 7 domains analyzed.

advantage in total effectiveness of acupuncture compared to the control group (OR=3.43, 95% CI (2.71, 4.35), $P<0.00001$), with low statistical heterogeneity ($Chi^2=26.71$, df=26, $P=0.42>0.1$, $I^2=3\%<50\%$) (Figure 3).

Subgroup Analysis

Different Assessment Measures for Overall Response Rate

PANSS

12 studies[12,13,21,22,26,34,36,39,42,45,47,48] utilized the PANSS scale to evaluate the overall response to acupuncture. The analysis revealed that acupuncture had a significantly greater influence on PANSS scores in comparison to the control group [MD=2.77 (95% CI: 1.93, 3.98), $P<0.00001$, $I^2=34\%$]. (Figure 4)

BPRS

8 studies[18,24,25,27,29,30,37,46] used the BPRS scale to assess the overall response rate of acupuncture. The analysis showed that acupuncture had a greater impact on BPRS scores compared to the control group [MD=3.57 (95% CI: 2.32, 5.51), $P<0.00001$, $I^2=0\%$]. (Figure 4)

SAPS

3 studies[19,20,44] employed the SAPS scale to evaluate the overall response to acupuncture. The analysis demonstrated that acupuncture had a greater effect on SAPS scores compared to the control group [MD=5.59 (95% CI: 3.05, 10.26), $P<0.00001$, $I^2=0\%$]. (Figure 4)

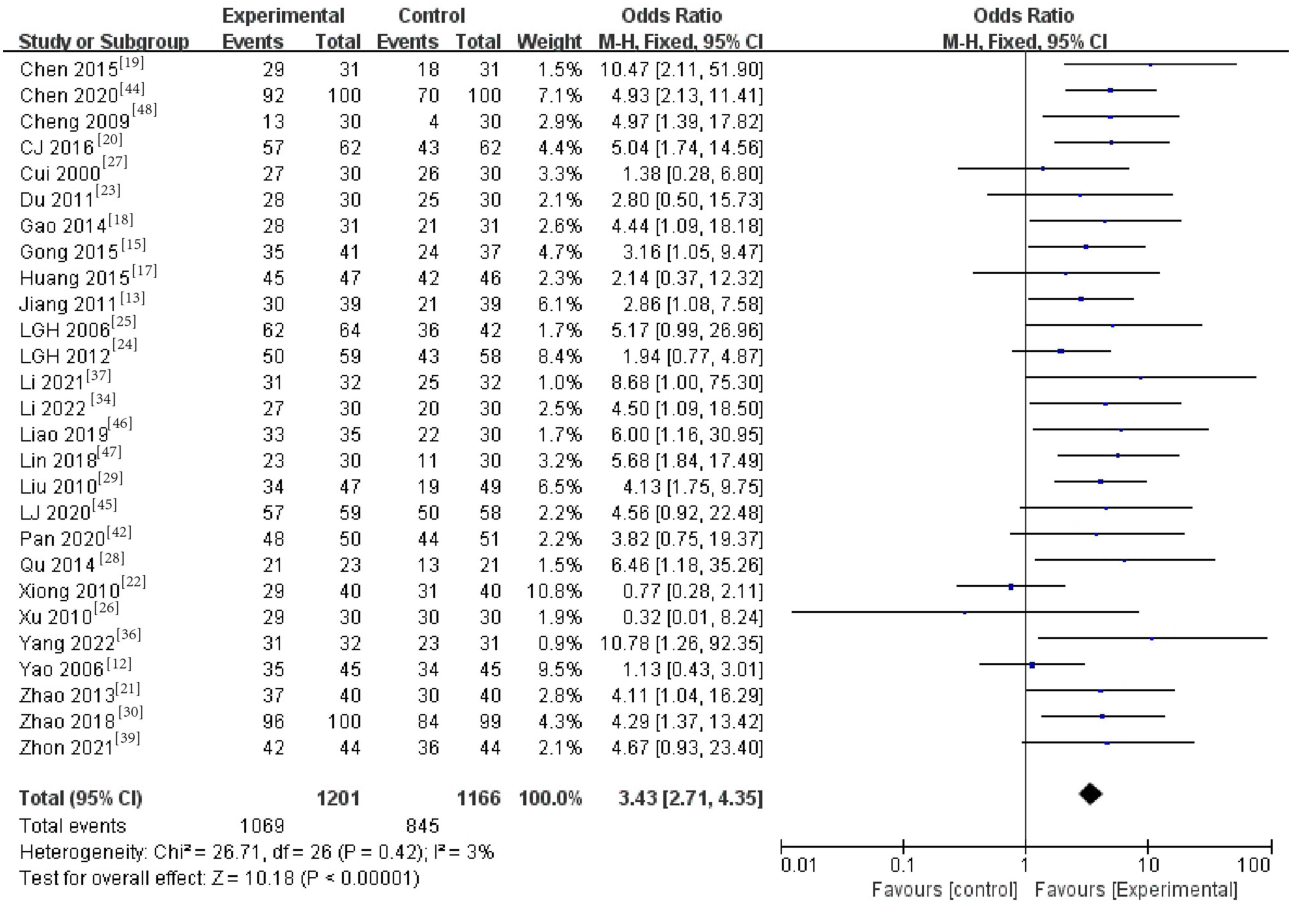

Figure 3 Forest Plot for Overall Response Rate.

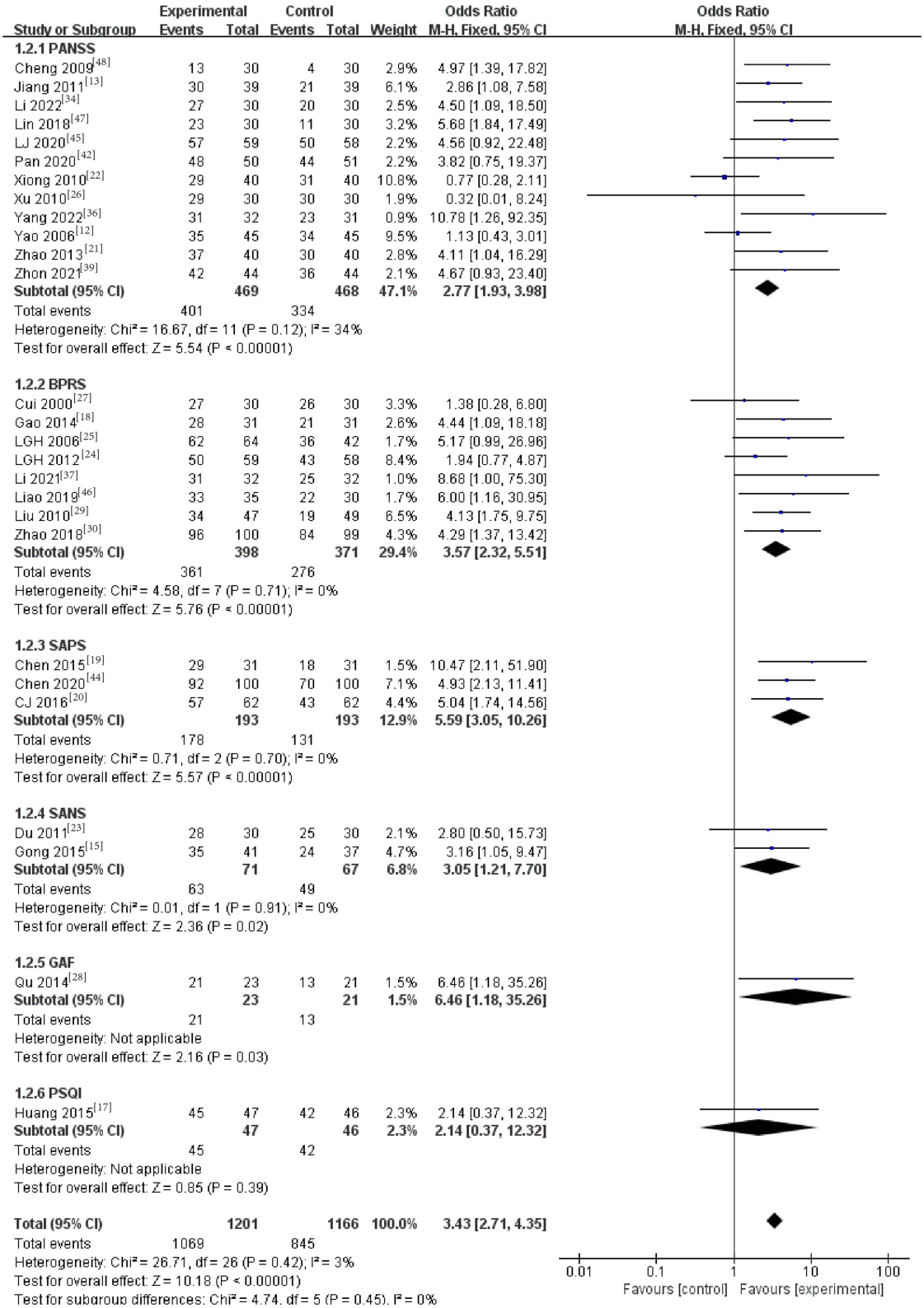

Figure 4 Forest Plot of Total Effective Rate Subgroup Analysis Meta-Regression.

Table 2 Regression Table of Total Effective Rate and Treatment Time

_ES	Exp(b)	Std. Err.	t	P>|t|	[95% Conf.	Interval]
timeoftherapyday	0.9874736	0.0060944	−2.04	0.052	0.9750013	1.000105
_cons	5.563176	1.541055	6.20	0.000	3.144505	9.842224

SANS

2 studies[15,23] used the SANS scale to assess the overall response rate to acupuncture. The analysis revealed that acupuncture had a more pronounced effect on SANS scores when compared to the control group [MD=3.05 (95% CI: 1.21, 7.70), P=0.02, I^2=0%]. (Figure 4)

One study[28] reported the use of GAF to assess the overall response rate (OR: 6.46, 95% CI: 1.18–35.26), and one study[17] mentioned the use of PSQI to assess the overall response rate (OR: 2.14, 95% CI: 0.37–12.32).

Subgroup difference test showed no heterogeneity among different comparison groups (P=0.45, I^2=0%).

Meta-Regression

In this study, we used meta-regression analysis to explore the relationship between treatment duration and treatment effectiveness. In a meta-analysis that included 27 studies, we found a negative correlation between treatment duration and treatment effectiveness, but this relationship did not reach statistical significance (P = 0.052) (Table 2). Specifically, for every one-day increase in treatment duration, the index level of treatment effectiveness decreased to 0.987. This result was validated in the meta-regression modified by Knapp-Hartung (b = 5.56, 95% CI [3.14, 9.84]) (Table 2). The results indicate that for the treatment of schizophrenia, prolonged treatment may not be beneficial to patients' recovery, and further optimization of treatment plans is needed. (Figure 5).

Secondary Outcomes

PANSS has broad applicability and high reliability, which can accurately assess the symptoms of SZ patients. BPRS is a simple and easy-to-use tool that evaluates positive symptoms, negative symptoms, affective symptoms, and cognitive

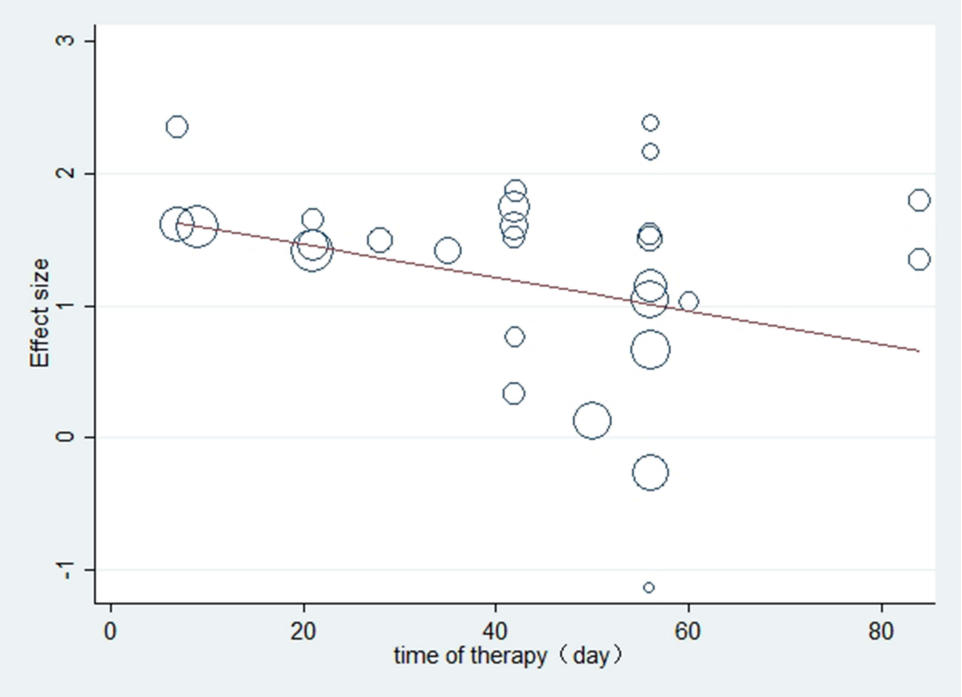

Figure 5 Total response rate and treatment duration regression plot.

symptoms. SANS and SAPS can accurately evaluate the core symptoms of schizophrenia but may not fully reflect the patient's comprehensive symptoms.

PANSS

PANSS evaluates the severity and changes of patients' psychotic symptoms before and after treatment to determine the effectiveness of acupuncture. A total of 21 RCTs[12–14,17,22,26,31,33–36,38,40–43,45–49] with 1566 patients were included in the random effects model meta-analysis. The results showed that compared with the control group, acupuncture treatment for schizophrenia patients had a significant treatment advantage, with MD=−5.75 (95% CI: −8.08, −3.42) and Z=4.84 (P<0.00001). The heterogeneity test showed significant heterogeneity among the included studies (I^2=88%, P<0.00001), indicating significant differences among the included studies (Figure 6).

BPRS

The Brief Psychiatric Rating Scale (BPRS) is mainly used to assess the psychopathological symptoms of psychiatric patients to observe the effect of acupuncture on psychiatric symptoms. A total of 10 RCTs[16,18,23,27,29,32,33,43,46] were included with a total of 698 patients. The random-effects model meta-analysis showed that compared with the control group, acupuncture had a greater impact on BPRS with a MD of −7.02 (95% CI: −10.59, −3.46). The heterogeneity test showed significant heterogeneity among the included studies (I^2=94%, P=0.0001) (Figure 7).

SANS

The SANS scale is used to evaluate negative symptoms in patients and assess the effectiveness of acupuncture. A total of 15 RCTs[13–17,22,23,31,34,38,42,43,47–49] with 1106 patients were included. The random-effects model meta-analysis showed that the effect of acupuncture on SANS was not greater than that of the control group, with no significant difference [MD=−2.66 (95% CI: −6.84, 1.51), P=0.21, I^2=99%] (Figure 8).

Subgroup Analysis

Different Intervention Measures

Manual Acupuncture Vs Control

7 studies[15,17,31,38,42,43,49] conducted a comparison between manual acupuncture and a control group using SANS

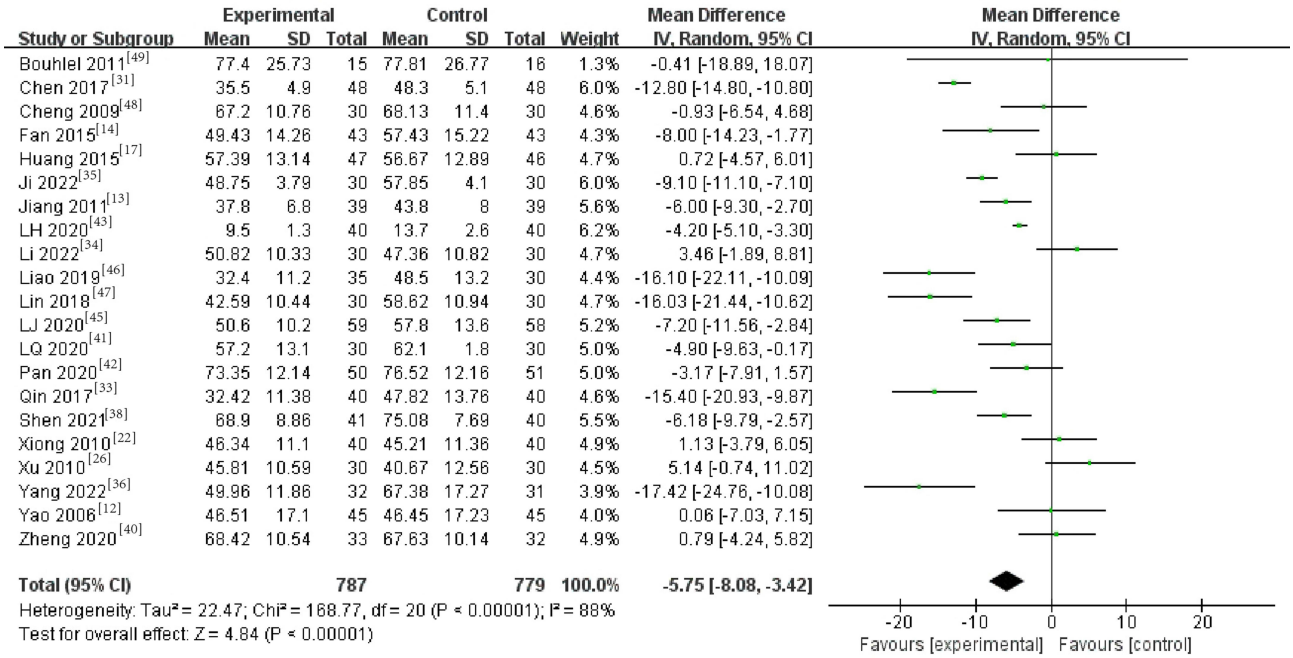

Figure 6 Forest plot of PANSS scores.

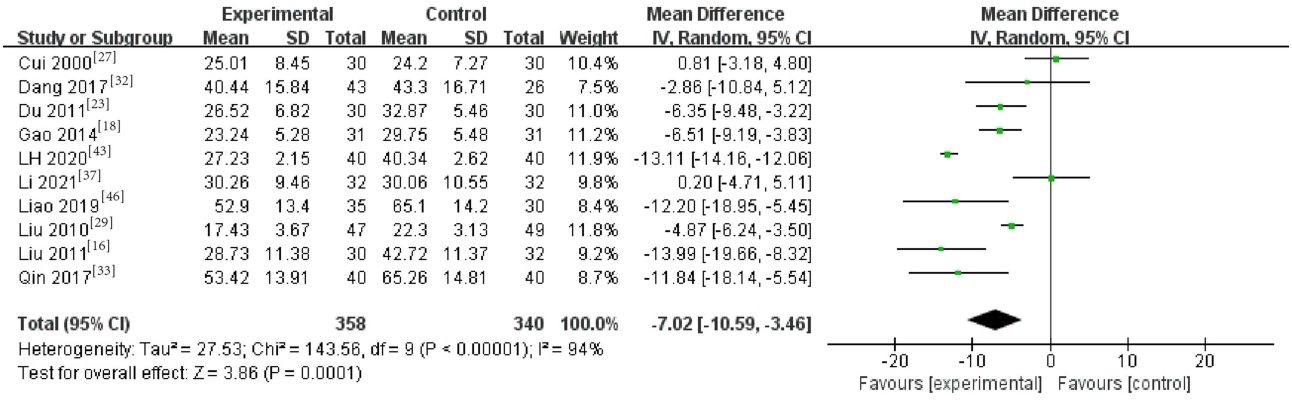

Figure 7 Forest plot of BPRS scores.

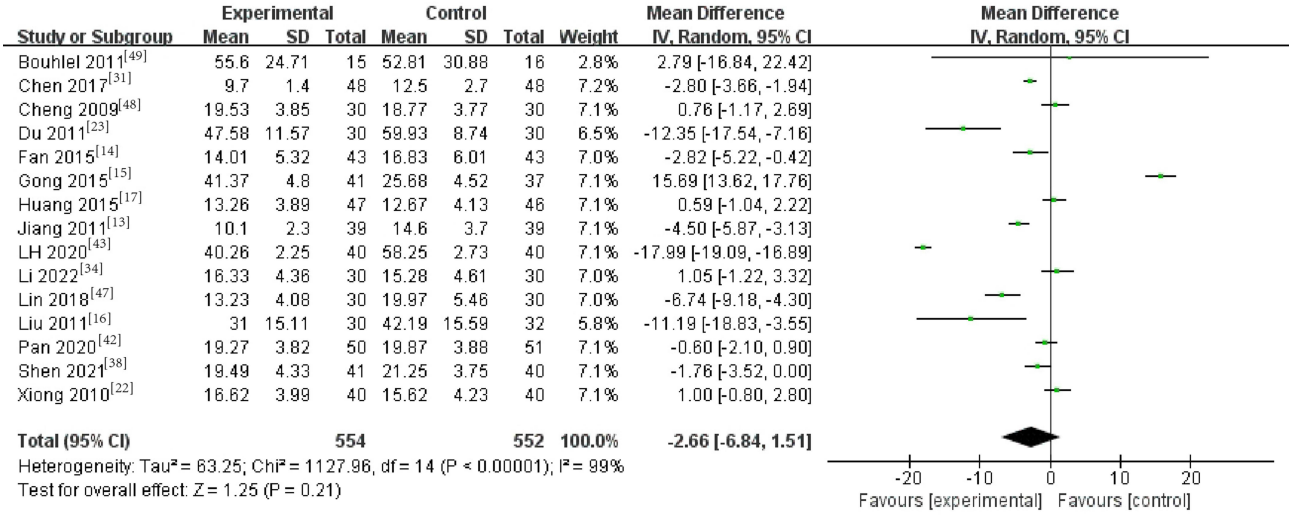

Figure 8 Forest Plot of SANS Scores.

assessment. The analysis revealed that acupuncture did not have a significantly greater impact on SANS scores when compared to the control group [MD: −0.86 (−8.53, 6.80), P=0.82, I²=99%] (Figure 9).

Electroacupuncture VS Control

8 studies[13,14,16,22,23,34,47,48] compared the effectiveness of electroacupuncture with a control group using SANS assessment. The analysis showed that acupuncture had a greater impact on SANS scores compared to the control group [MD: −3.52 (−6.22, −0.82), *P*=0.01, *I*²=90%] (Figure 9).

After the primary meta-analysis, the result of SANS score showed *P*=0.21, which is greater than 0.05. However, during the subgroup analysis, we divided acupuncture into two groups: electroacupuncture and manual acupuncture. The result revealed that the electroacupuncture group had a P-value of 0.01, which is less than 0.05. Therefore, we can infer that electroacupuncture treatment may be more effective than manual acupuncture in terms of SANS score.

SAPS

The SAPS scale is used to assess positive symptoms and measure symptom changes in patients, aiming to evaluate the effectiveness of acupuncture. A total of 11 RCTs[13,14,16,17,22,31,34,38,42,48,49] with 828 patients were included in the random-effects model Meta-analysis. The results demonstrated that acupuncture had a greater impact on SAPS compared

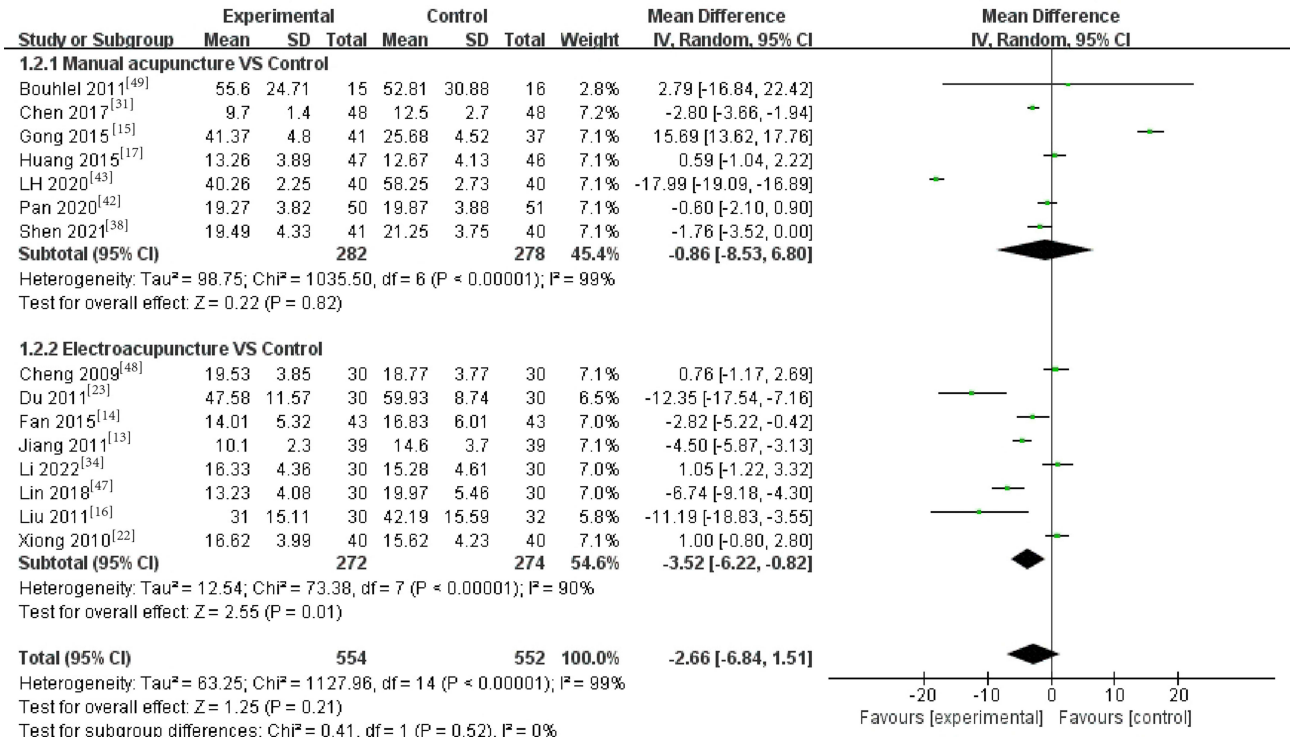

Figure 9 Forest plot of subgroup analysis for SANS.

to the control group, and the difference was statistically significant [MD=−1.26 (95% CI: −2.55, −0.02), P=0.05, I^2=86%]. Please refer to Figure 10 for details.

Sensitivity Analysis

To determine the robustness of the summary data for the main outcome measures, we performed a sensitivity analysis by removing each study one by one. The results of the sensitivity analysis showed no significant changes in the combined results, which supports the statistical advantage of acupuncture in overall efficacy ($P < 0.0001$).

Adverse Events

A total of 15 RCTs[12,13,17,21,22,24,30,33–35,37,42,45–47] were included, including 1344 patients. 1 study[35] reported both count data and continuous data. 9 RCTs[12,24,30,34,35,37,42,46,47] reported count data and were analyzed using the odds ratio (OR)

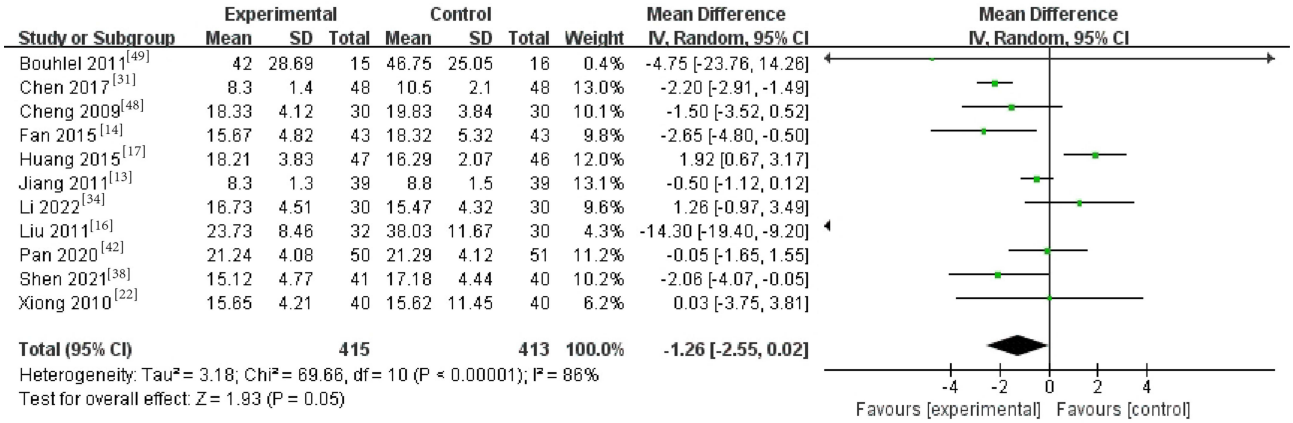

Figure 10 Forest plot of SAPS score.

and its 95% confidence interval (CI). Based on the fixed-effect model, the results of the heterogeneity test of the 9 studies showed statistical advantage of acupuncture over the control group in terms of adverse events (OR=0.55, 95% CI (0.42, 0.71), $P<0.00001$), with moderate statistical heterogeneity ($Chi^2=13.01$, df=8, $P=0.11>0.1$, $I^2=39\%$) (Figure 11).

7 RCTs[13,17,21,22,33,35,45] reported continuous data and were analyzed using the mean difference (MD) and its 95% CI. Based on the random-effects model, the results of the heterogeneity test of the 7 studies showed statistical advantage of acupuncture over the control group in terms of adverse events (MD=−1.82, 95% CI (−2.94, −0.71), $P=0.0001$), with high statistical heterogeneity ($Chi^2=50.06$, df=6, $P<0.00001<0.1$, $I^2=88\%$) (Figure 12).

As can be seen, acupuncture as an adjunctive therapy can effectively reduce adverse reactions in clinical practice.

Publication Bias of Included Literature

Funnel plot and Egger's test were used to evaluate the publication bias of the overall effective rate. The funnel plot and Egger's test (t=1.00, $P=0.329$) showed no evidence of publication bias. As shown in Figure 13 and Table 3.

GRADE Evidence Quality Assessment

For the adverse reaction incidence rate, we divided it into two outcome indicators based on the different types of variables: incidence rate of adverse reactions for binary variables and TESS score for continuous variables. There were a total of 7 outcome indicators, including Effective rate, incidence rate of adverse reactions, PANSS score, BRPS score, SANS score, SAPS score, and TESS score. The results showed that the quality of Total Effective rate and incidence rate of adverse reactions was Moderate, while the quality of PANSS score, BRPS score, SANS score, SAPS score, and TESS score was very low. Details can be found in Table 4.

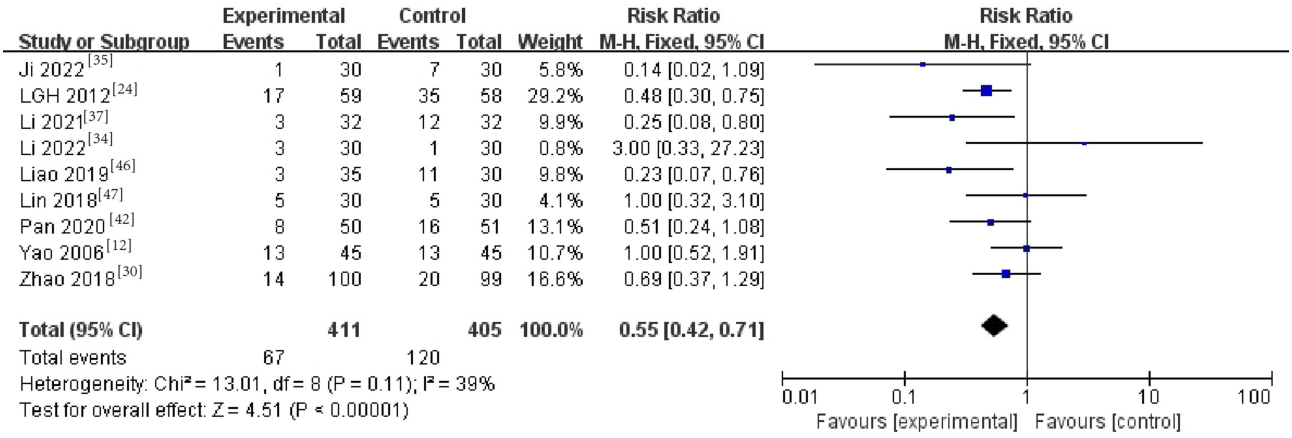

Figure 11 Forest plot of adverse events for binary variables.

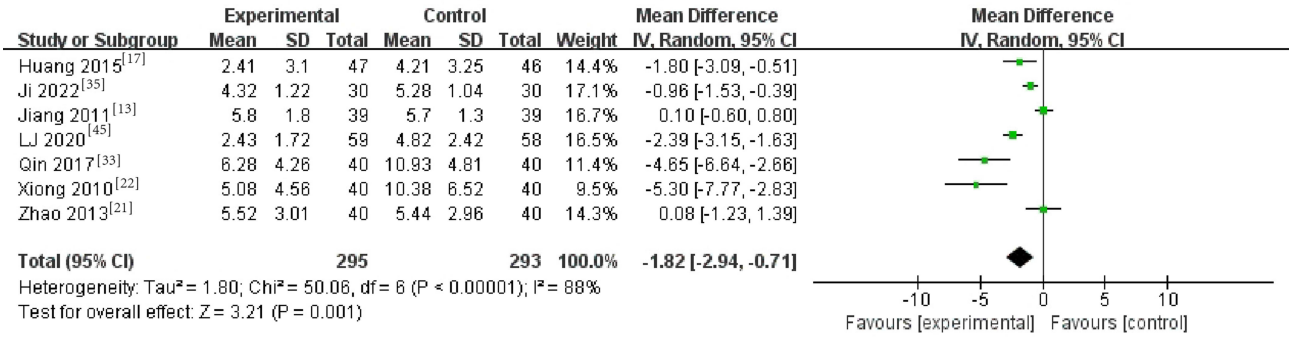

Figure 12 Forest plot of adverse events for continuous variables.

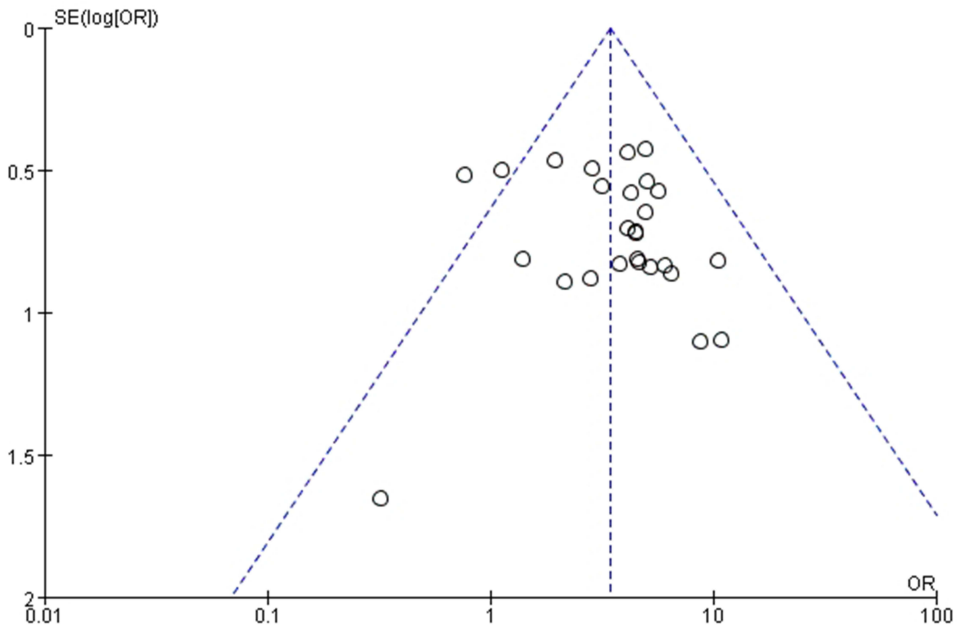

Figure 13 The Funnel plot for publication bias of overall effectiveness.

Discussion

Overview

This meta-analysis included 38 randomized controlled trials with a total of 3143 patients, comparing the efficacy and safety of acupuncture combined with another therapy versus the use of the therapy alone. The results indicated that acupuncture, as an adjunctive therapy in conjunction with Western medicine or other therapies, could improve the overall effective rate of SZ patients ($P<0.00001$) while reducing the adverse reactions caused by medication. We conducted subgroup analyses on the overall effective rate, comparing different outcome measures, and the results showed no heterogeneity among the different measures ($P=0.45$, $I^2=0\%$), indicating the stability of acupuncture treatment across various outcome measures and its reliability as a treatment option.

Regarding the mechanism of acupuncture in the treatment of schizophrenia, some studies have suggested[50,51] that structural changes occur in the default mode network (DMN) brain regions of schizophrenia patients, and the dysfunction between the frontoparietal control system and the DMN may be one of the causes of schizophrenia. Acupuncture acts by regulating and normalizing the lateral parietal-occipital network (LPNN), including the default mode network (DMN), thereby balancing bodily functions and improving clinical symptoms in Schizophrenia patients[5,52]

Comparison with Previous Studies

Compared with previous studies, we have also concluded the effectiveness of acupuncture in the treatment of schizophrenia. In a meta-analysis[6] published in 2018, researchers found that when comparing acupuncture combined with conventional antipsychotic medication to the use of antipsychotic medication alone, acupuncture combined with antipsychotic medication showed significantly better efficacy in treating SZ. In our study, we focused on the primary

Table 3 Egger's Test for Publication Bias in Overall Effectiveness

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	0.7866153	0.4445966	1.77	0.089	−0.1290485	1.702279
bias	0.6819208	0.6843093	1.00	0.329	−0.7274405	2.091282

Table 4 GRADE Evidence Quality Assessment

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Experimental**	**Control**	**Relative(95% CI)**	**Absolute (95% CI)**		
Total effective rate												
27	Randomised trials	Serious[a]	Not serious	Not serious	Not serious	None	1069/1201 (89.0%)	845/1166 (72.5%)	**OR 3.43**(2.71 to 4.35)	**176 more per 1000** (from 152 more to 195 more)	⊕⊕⊕◯ Moderate	CRITICAL
Incidence rate of adverse reactions												
9	Randomised trials	Serious[a]	Not serious	Not serious	Not serious	None	67/411 (16.3%)	120/405 (29.6%)	**RR 0.55**(0.42 to 0.71)	**133 fewer per 1000** (from 172 fewer to 86 fewer)	⊕⊕⊕◯ Moderate	CRITICAL
TESS score												
7	Randomised trials	Serious[a]	Very serious[b]	Not serious	Not serious	None	295	293	–	MD 1.82 lower (2.94 lower to 0.71 lower)	⊕◯◯◯ Very low	CRITICAL
PANSS score												
21	Randomised trials	Serious[a]	Very serious[b]	Not serious	Not serious	None	787	779	–	MD 5.75 lower (8.08 lower to 3.42 lower)	⊕◯◯◯ Very low	IMPORTANT
BRPS score												
10	Randomised trials	Serious[a]	Very serious[b]	Not serious	Not serious	None	358	340	–	MD 7.02 lower (10.59 lower to 3.46 lower)	⊕◯◯◯ Very low	IMPORTANT
SANS score												
15	Randomised trials	Serious[a]	Very serious[b]	Not serious	Not serious	None	554	552	–	MD 2.66 lower (6.84 lower to 1.51 higher)	⊕◯◯◯ Very low	NOT IMPORTANT
SAPS score												
11	Randomised trials	Serious[a]	Very serious[b]	Not serious	Not serious	None	415	413	–	MD 1.26 lower (2.55 lower to 0.02 higher)	⊕◯◯◯ Very low	NOT IMPORTANT

Notes: [a]There is a large bias in the included studies in randomization, assignment hiding, blind method and other methods. [b]If the confidence interval overlaps less or the I2 value of the combined result is larger, 50%<I^2<75%, minus 1 point, and I^2≥75%, minus 2 points. Bolded text indicates statistically significant effect sizes with moderate to high-quality evidence.

Abbreviations: CI, confidence interval; **MD**, mean difference; **OR**, odds ratio; **RR**, risk ratio.

outcome measure of overall effectiveness rate and selected PANSS, BPRS, SANS, and SAPS as secondary outcome measures, providing a more comprehensive reflection of the effectiveness of acupuncture treatment.

In published network meta-analyses,[7] researchers compared the efficacy of acupuncture combined with Western medicine to the use of Western medicine alone and found that acupuncture had the best efficacy when combined with body acupuncture. In contrast, our meta-analysis has several unique features. Firstly, we performed GRADE evidence grading for each outcome to ensure the reliability of the research findings. Secondly, we conducted subgroup analyses for the overall effectiveness rate to explore differences among different subgroups. Additionally, we performed a meta-regression specifically for the primary outcome measure (overall effectiveness rate) and found that prolonged treatment may not be beneficial for patient recovery.

Clinical Implementation

The findings suggest that acupuncture treatment is an effective adjunctive therapy for schizophrenia and can be used as a supplement or alternative to traditional medication, providing clinicians with a new treatment option.

The Inspiration for Future Directions

Although the meta-analysis results demonstrate the effectiveness of acupuncture, further exploration is needed regarding the treatment mechanisms and long-term effects of acupuncture. Additionally, considering the methodological limitations and quality issues in the studies, more high-quality, large-sample, multicenter clinical trials are required to validate and strengthen these findings. A more comprehensive evaluation of acupuncture's clinical applications in patients with SZ will provide healthcare professionals and patients with more reliable treatment evidence and decision-making support.

Strengths and Limitations

Based on our understanding, this is the first systematic review to evaluate the efficacy and safety of acupuncture as an adjunctive therapy for improving clinical symptoms in patients with schizophrenia.

Our strengths lie in several aspects. First, we selected the total effective rate as the primary outcome measure and conducting subgroup analysis on the primary outcome measure, which allows for a more accurate evaluation of the effect size between different subgroups and further confirms the effectiveness of acupuncture. Second, we performed a meta-regression on the effective rate and found a negative correlation trend between treatment duration and treatment effect, suggesting that longer treatment duration may not be beneficial for patient recovery. Third, we conducted a GRADE assessment on the outcome measures, enhancing the credibility of the results.

We also analyzed the acupoints mentioned in the literature and found that the most frequently mentioned acupoints were Baihui (GV20) (26 times), Neiguan (PC6) (15 times), Yintang (EX-HN3) (13 times), Zusanli (ST36) (13 times), Taichong (LR3) (13 times), Fenglong (ST40) (13 times), Sanyinjiao (SP6) (12 times), Hegu (LI4) (12 times), Shenmen (HT7) (12 times), and Sishencong (EX-HN1) (8 times). Clinical practitioners can use these findings to selectively choose these acupuncture points for acupuncture treatment, aiming to enhance treatment effectiveness. Furthermore, the discovery of these high-frequency acupuncture points provides valuable clues for further exploring the mechanisms of acupuncture treatment and contributes to a deeper understanding of the specific role and pathways of acupuncture in the treatment of SZ.

This study has several limitations: (1) Most of the included studies did not mention the implementation of allocation concealment and blinding, which may introduce selection bias. (2) The interventions included in the studies, such as the types of adjunctive medication, forms of acupuncture, duration of treatment, and techniques used, varied, which could affect the accuracy of the results.

Conclusion

Existing evidence suggests that acupuncture, as an adjunctive therapy used in conjunction with Western medicine or other treatments, can improve the overall effectiveness in patients with SZ, reduce adverse reactions, and improve the mental condition, alleviating the severity of symptoms in SZ patients. However, due to limitations in the quality of the included studies, further high-quality research is needed to validate the above conclusions.

Data Sharing Statement

All data relevant to the study are included in the article or uploaded as Online Supplemental Information. The data used in this review was collected from the thirty-eight eligible studies and therefore available in the public domain.

Author Contributions

All authors have made significant contributions to the work reported, whether in the conception, study design, execution, data acquisition, analysis and interpretation, or in all of these areas. They have all been involved in drafting, revising, or critically reviewing the article, and have given final approval for the version to be published. They have also agreed on the journal to which the article has been submitted and committed to being accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest to declare for this work.

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