The Potential Influence of Absence of Blinding Method: Secondary Analysis From Randomized Controlled Trials Concerned Acupuncture for Depression

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Research

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Abstract

Background

To evaluate the possibility and impact of performance and detection bias in randomized controlled trials due to lack of the blinding method.

Methods

Trials assessing acupuncture for depression published by March 2020 were searched from China National Knowledge Infrastructure database. Through matching, we reassembled the trials of comparing experimental acupuncture and control acupuncture. Meta-analysis with post-treatment HAMD (Hamilton Depression Scale) of the newly reassembled trials was conducted. Changes of HAMD of all included groups were also analyzed, the between groups difference was then analyzed by *t*-test. All statistical analyses were performed using RevMan 5.3 software.

Results

Thirteen pairs of studies were matched from 63 included trials. Re-analysis from the paired studies showed obvious difference of HAMD scales between the experimental and control acupuncture (Mean Difference was -2.95 for HAMD-17, -5.55 for HAMD-24). Re-analysis from all the included groups also showed the statistical difference between groups at four weeks of HAMD-17 ($P=0.01$), and four/six weeks of HAMD-24 ($P<0.01$).

Conclusion

Effectiveness of acupuncture for decreasing the severity of depression was superior in trials that considered acupuncture as experimental treatment, showing performance and detection bias caused by the absence of blinding method is of great significance in acupuncture trials.

Background

The uncertainty principle attaches great significance to the uncertain state of therapeutic effects of the methods used in clinical trials, which is essential for controlling bias. A case in point is a study by Benjamin Djulbegovic discovered that clinical trials sponsored by the pharmaceutical industry result in biased findings, either due to selective report of studies with non-equivalent arms or publication of low-quality papers, wherein unfavorable results are incompletely described [1].

However, it is difficult for researchers to eliminate the participants' preference of intervention effect. Therefore, in order to avoid the influence of subjective will or preference on the research results, the study design principle came into being. Among these principles, blinding method is widely used in randomized controlled trials to avoid performance bias and detection bias [2]. The premise of success in implementing blinding method is that the experimental intervention has a reasonable placebo control, which is almost

impossible for most non-pharmaceutical therapies, such as acupuncture. Thus, in case of absence of blinding, the researcher's values or preference may affect the procedure of the study and the results [3]. Study by Lingling Yang [4] categorizes several clinical trials according to therapy and grouping, and whether acupuncture has significant effect varied remarkably.

For centuries, literatures published about traditional Chinese medicine have been all about personal experiences. Although the rise of clinical epidemiology and evidence-based medicine has greatly improved researchers' understanding of the rigor of research design, trials' methodological quality has not improved substantially [5]. A case in point is a meta-analysis study by Mike Armour suggested that [6] 'A test for between acupuncture and control group differences showed that trials from China had significantly greater reductions in the severity of depression compared to those undertaken outside of China (Mean Difference = 0.58, 95%CI 0.25 to 0.91, $P < 0.001$). This may be caused by selection and reports of favored studies or other bias originated from non-equivalent control.

Performance bias and detection bias, originated from researchers' preference of a certain therapy and insufficient use of the blinding method. To evaluate whether and how these two biases may affect the results of acupuncture clinical trials, we re-analyzed the data from the eligible acupuncture trials through meta-analysis method.

Methods

Eligibility criteria

Published randomized controlled trials with completely reported continuous data were concerned to be included. "Completely reported" means that mean of the outcome measurements for each group must be reported with their standard deviation (SD) or 95% confidence interval (CI) The target diseases are primary or secondary depression diagnosed in accordance with recognized criteria (e.g. Diagnostic and Statistical Manual of Mental Disorders Fifth Edition).

Acupuncture is the intervention of this study. By comparing the groups that were designed as experimental treatment and as control, we were able to explore whether the researchers' expectations will affect the results of acupuncture therapy for depression. Trials which employed acupuncture as experimental treatment may choose no treatment or standard treatment as control, thus we filtered out the trials which compared acupuncture to no treatment or western drugs (such as fluoxetine hydrochloride capsules, etc.). In this case, acupuncture was considered as "experimental treatment" and this arm of the trial was counted as intervention/experiment group in our review. Trials which used acupuncture as control treatment were mostly aimed to investigate the effect of another non-pharmaceutical therapy (e.g. Cognitive therapy, psychotherapy, music therapy. Etc.) for depression, or to verify the effect of a special acupuncture (special manipulation or needle type) for the disease. In this case, the routine acupuncture group was identified as control arm in our review.

Primary outcome of this study was the score of Hamilton Depression Scale (HAMD). Literatures with inaccessible data, as well as the piratical documents would be excluded.

Searching strategy

The Chinese National Knowledge Infrastructure Databases was searched, including the unpublished dissertations. The searching items included 'Acupuncture' AND 'Depression' in the scope of Title/Abstract, and "Random" in full text.

Study screening and data exaction

Two reviewers (RTW and LJC) independently screened the literature to identify trials that potentially meet the above inclusion criteria. Any disagreement was resolved through discussion with a third reviewer (HJC). A predesigned form was used to extract data from the included trials. Extracted information included: i) General information, including document number, title, first author, year(s) conducted, location (city, country), source, etc. ii) Participants information, including diagnostic criteria, inclusion criteria, exclusion criteria, source, sample size, age, gender, disease course. iii) Treatment information, such as the treatment principle, types of acupuncture, information of the acupuncturist, treatment duration, points selection, treatment frequency, co-intervention, etc. iv) Outcome measures, including the type of HAMD scales (17-scores or 24-scores), changes in HAMD score, post-treatment HAMD scores, time of the measurement.

Data analysis

All statistical analyses were performed using RevMan 5.3 (The Cochrane Collaboration) software.

Since data of "experimental acupuncture" and "control acupuncture" to be compared in our study were get from different trials, we tried to make the two acupuncture groups comparable by matching them. After completing the data exaction, we selected the matching experimental and control acupuncture groups to reassemble trials. The first principle of matching is that the two groups of patients have the same type of depression, type of HAMD scale, and the treatment frequency. Besides, there should be no statistical difference ($P > 0.05$) between two groups in baseline information, including age, sex ratio, and the pre-treatment HAMD scores. The prescriptions of the acupoints were also matched, however, we could only guarantee the equality of the main treatment principle between the reassembled groups since most of the trials were with individualized points selection. We then re-analyzed the difference of post-treatment HAMD scores in the new paired-study through RevMan 5.3. A meta-analysis with mean difference (MD) and 95% CI was used to present the results. I² value reflect the statistical heterogeneity among trials. Data from the included groups which failed to be matched were not included in this analysis.

Furthermore, we also analyzed data from all the included groups regarding to the changes of HAMD score pre and post treatment within groups. Then, we separately pooled the data from experimental acupuncture group and control acupuncture group with subgroup meta-analysis. Subgroup was classified according to the type of HAMD scale and treatment duration. Difference of the pooling result between groups was then analyzed by t-test.

Results

Study selection

Totally 1659 clinical trials were retrieved through preliminary searching. After reading the title and abstract, 869 trials were screened out. And further another 700 trials were excluded after reading the full text. Sixty-three randomized controlled trials [7–69] were finally assessed to be eligible (Fig. 1).

All the included trials were published in Chinese. The sample size ranged from 20 to 212. All cases were recruited from the outpatient/inpatient Department. Primary depression was concerned in 46 trials [7–26, 34–50, 55, 57–60, 64–67]. The remaining 17 trials targeted on secondary depression, including eight post-stroke depression [27, 51–54, 61–63], five premenopausal depression [28–31, 56, 69], two postpartum depression [32, 33], one Internet addiction depression [68].

Treatment principle of most of the included trials were regulating spirit and relieving depression, and the most frequently used five acupoints were PC6 (37 studies) [9, 11, 12, 14, 16–18, 20–23, 25, 31, 34–37, 39–40, 42–45, 47, 49–52, 54–58, 61, 63–64, 68], DU20 (31 studies) [11, 12, 16–22, 25, 27, 29–31, 33–37, 40, 46, 51, 52, 55, 56, 58, 60, 62, 64, 66, 68], LR3 (30 studies) [7, 14, 17, 19, 20, 22, 24, 25, 29, 30, 34, 36, 37, 40, 42, 44, 46, 47, 49, 50, 54–59, 64, 66–68], HT7 (23 studies) [12, 13, 17, 19, 20, 23, 25, 34, 40, 42–46, 49–52, 55–58, 64], DU29 (20 studies) [16, 18, 19, 22, 25, 29–31, 34–37, 46, 51, 52, 55, 56, 60, 64, 66]. Thirty included studies used acupuncture as intervention [7–36], 29 of them compared acupuncture with western drugs [7–35] and the remaining trial compared the acupuncture with no treatment [36]. Thirty-three included studies used routine acupuncture as control [37–69], and the interventions of them included special acupuncture [37–60], western medicine plus acupuncture [61, 62], acupuncture plus moxibustion [63, 64], moxibustion [65, 66], cognitive therapy plus acupuncture [67], cognitive therapy [68], and acupoint catgut embedding [69]. Acupuncture with electronic stimulation is adopted in five trials' acupuncture group, four of them in experimental group [14, 21, 24, 26], one in control group [65].

Thirteen trials reported the HAMD-17 in four weeks [7, 8, 28, 29, 32, 37–39, 53, 60, 61, 64, 69], 11 trials reported HAMD-17 in six weeks [9–12, 35, 36, 40, 41, 62, 65, 68], one trial reported HAMD-17 in both four and six weeks [13] and 1 trial reported HAMD-17 in both four and eight weeks [14], one trial reported HAMD-17 in twelve weeks [31]. Seventeen trials reported HAMD-24 in four weeks [15–20, 27, 30, 33, 34, 42, 43, 50–52, 54, 58]. Two trials reported HAMD-24 in four weeks and twelve weeks [49, 66], one trial reported HAMD-24 in eight weeks [56]. Eleven trials reported HAMD-24 in six weeks [22–26, 44, 47, 48, 55, 57, 59]. Five trials reported HAMD-24 in both four and six weeks [21, 45, 46, 63, 67].

Re-analysis from the paired studies

We have successfully got 13 pairs of studies, in which five pairs of them reported HAMD-17 scales [9, 13, 14, 31, 36–38, 41, 65, 69], and the remaining studies reported HAMD-24 scales [15, 18, 20, 22, 23, 25, 27, 30, 43, 44, 46, 56, 57, 63, 66, 67]. The specific information of the paired-studies were listed in Table 1. Meta-analysis shows that the difference of HAMD-17 scales (MD=-2.95, 95%CI -4.75 to -1.16, I² = 74%, 10 trials, 298 participants, P = 0.001) and HAMD-24 scales (MD=-5.55, 95%CI -6.69 to -4.41, I² = 38%, 16 trials,

440 participants, $P < 0.00001$) between the paired experimental and control acupuncture were both statistically significant (Fig. 2). The obvious statistical heterogeneity among the paired studies were caused by the difference of acupoints selection.

Table 1
Characteristics of 13-paired included studies

Pair of the study (Study ID)	Sample size (M/F)	Age (Mean $\pm$ SD)	Type of depression	Acupoint	Outcome	HAMD scores (Mean $\pm$ SD)	
						Baseline	Post-treatment
E: Liu P 2009 [9] C: Wang XN 2017 [41]	6/14 10/13	47.35 $\pm$ 7.5 46.57 $\pm$ 7.46	Primary	GV20, PC6 GV20, EX-HN3, EX-HN1, ST36, EX-HN5, SP6	HAMD-17 6 weeks	19.6 $\pm$ 2.21 20.87 $\pm$ 2.01	7.65 $\pm$ 3.52 13.48 $\pm$ 2.99
E: Zhou X 2011 [13] C: Cheng XF 2017 [38]	12/20 14/16	40.5(22–59) 19–53	Primary	BL15, BL18, BL20, HT7, ST40 RN12, ST25, ST37	HAMD-17 4 weeks	24.72 $\pm$ 7.1 25.8 $\pm$ 10	15.2 $\pm$ 7.2 20.7 $\pm$ 10.3
E: Wang XF 2007 [14] C: Song MQ 2006 [65]	12/18 8/22	18–68 37.41 $\pm$ 12.75	Primary	GB12, LR3, with electronic stimulation BL15, BL18, BL20, PC6, ST36, SP6, with electronic stimulation	HAMD-17 6/8 weeks	26.39 $\pm$ 6.19 24.31 $\pm$ 5.03	7.26 $\pm$ 1.26 8.86 $\pm$ 4.01
E: Li HB 2015 [31] C: Jin YP 2013 [69]	32 42	50.59 $\pm$ 2.94 48.5 $\pm$ 4.20	Secondary	BL23, BL18, BL15, DU20, EX-HN1, DU24, DU29, PC6 BL23, BL15, BL18, BL20, SP6	HAMD-24 12/4weeks	20.69 $\pm$ 1.77 22.1 $\pm$ 4.34	9.14 $\pm$ 4.78 10.83 $\pm$ 3.91

HAMD: Hamilton Depression Scale; M: Male; F: Female; T: Treatment; C: Control; SD: Standard Deviation; CI: confidence level.

Pair of the study (Study ID)	Sample size (M/F)	Age (Mean $\pm$ SD)	Type of depression	Acupoint	Outcome	HAMD scores (Mean $\pm$ SD)	
						Baseline	Post-treatment
E: Xie M 2018 [36] C: Chen YY 2011 [37]	8/22 13/18	42.13 $\pm$ 13.11 35.23 $\pm$ 12.5	Primary	DU29, DU20, PC6, SP6, LR3 DU20, DU29, LR3, PC6	HAMD-17 6 weeks	12.63 $\pm$ 2.91 13.8 $\pm$ 2.32	6.6 $\pm$ 3.96 8.32 $\pm$ 2.61
E: Chen CW 2007 [15] C: Chen L 2015 [45]	11/19 18/11	40.45 $\pm$ 12.54 45.80 $\pm$ 8.40	Primary	GV20, GV16, EX-HN3, EX-HN1, BL18 GV20, CV17, PC6, HT7	HAMD-24 4 weeks	26.6 $\pm$ 6.26 28.86 $\pm$ 2.76	15.31 $\pm$ 4.08 21.24 $\pm$ 0.95
E: Wang C 2007 [18] C: Wang YW 2019 [66]	14/16 16/17	39.73 $\pm$ 13.38 38.26 $\pm$ 11.8	Primary	PC6, SJ5, DU20, DU29 LR3, LI4, DU20, DU29	HAMD-24 12 weeks	30.7 $\pm$ 3.4 29.15 $\pm$ 3.61	13.04 $\pm$ 7.87 18.45 $\pm$ 5.94
E: Wang QS 2016 [20] C: Yao XY 2016 [48]	15/17 4/6	41.3 $\pm$ 5.2 37.40 $\pm$ 8.73	Primary	DU20, SP6, KI3, HT7, PC7, LR3 GV20, EX-HN1, EX-HN5, EX-HN3, LI4	HAMD-24 8/6 weeks	23.65 $\pm$ 2.12 23.6 $\pm$ 2.86	13.74 $\pm$ 2.85 17.3 $\pm$ 4

HAMD: Hamilton Depression Scale; M: Male; F: Female; T: Treatment; C: Control; SD: Standard Deviation; CI: confidence level.

Pair of the study (Study ID)	Sample size (M/F)	Age (Mean $\pm$ SD)	Type of depression	Acupoint	Outcome	HAMD scores (Mean $\pm$ SD)	
						Baseline	Post-treatment
E: Chi H 2011 [30] C: Liu H 2019 [56]	30 29	51.63 $\pm$ 1.72 50.36 $\pm$ 7.94	Secondary	DU20, DU29, EX-HN1, LR14, LR3, KI3, ST36, SP6 DU20, DU29, LR3, HT7, PC6	HAMD-24 4/8 weeks	27.26 $\pm$ 4.33 26 $\pm$ 5.16	11.52 $\pm$ 5.35 15.62 $\pm$ 2.86
E: Duan DM 2005 [22] C: Cheng Y 2006 [46]	6/14 10/10	46.1 $\pm$ 14.5 69.2 $\pm$ 6.9	Primary	DU20, EX-HN1, DU29, PC6, LR3, SP6 DU20, DU24, DU29, EX-HN1, LR3, HT7	HAMD-24 6 weeks	30.1 $\pm$ 5.9 27.36 $\pm$ 6.73	15.8 $\pm$ 6.1 19.56 $\pm$ 5.91
E: Gao C 2011 [23] C: Ren SC 2019 [57]	12/18 5/25	45.23 $\pm$ 9.93 51	Primary	GV20, EX-HN1, EX-HN3, HT7, PC6, SP6, ST36 HT7, PC7, PC6, LR14, BL15, LI4, LR3, LR2, BL18	HAMD-24 6 weeks	22.23 $\pm$ 2.38 23.1 $\pm$ 2.24	13.43 $\pm$ 5.21 19.7 $\pm$ 2.93
E: Yu YS 2012 [25] C: Cai MY 2014 [67]	11/21 28	36.5 $\pm$ 11.3 40.53 $\pm$ 3.38	Primary	DU20, DU29, HT7, PC6, BL18, GB20, LI4, LR3 LR3, GB37, PC7, SJ5	HAMD-24 6 weeks	32.15 $\pm$ 5.92 30.12 $\pm$ 11.63	9.48 $\pm$ 4.7 19.12 $\pm$ 7.83

HAMD: Hamilton Depression Scale; M: Male; F: Female; T: Treatment; C: Control; SD: Standard Deviation; CI: confidence level.

Pair of the study (Study ID)	Sample size (M/F)	Age (Mean ± SD)	Type of depression	Acupoint	Outcome	HAMD scores (Mean ± SD)		
						Baseline	Post-treatment	
E: Su PY 2013 [27]	17/13	58 ± 8	Secondary	DU26, DU20, DU24, DU16, DU14, DU11	HAMD-24	29.43 ± 9.83	18.93 ± 6.49	
	14/16	63.16 ± 6.21				4 weeks/30 days	32.06 ± 4.93	24.86 ± 3.92
C: Wu JX 2010 [63]					BG13, DU24, PC6, SP4			
HAMD: Hamilton Depression Scale; M: Male; F: Female; T: Treatment; C: Control; SD: Standard Deviation; CI: confidence level.								

Re-analysis from the unpaired-study

The results of pooling data from both experimental and control acupuncture groups from 61 studies showed there was significant statistical difference of changed HAMD-17/24 scores after four weeks and six weeks treatment [7–31, 33–55, 57–69]. Details of the characteristics of the unpaired-studies were listed in Table 2.

Table 2
The characteristics of the unpaired included 37 studies

Study ID	Sample size (M/F)	Age (Mean $\pm$ SD)	Type of depression	Acupoint	HAMD Scales	Treatment duration (weeks)
2.1 Acupuncture as intervention						
Han P 2016 [7]	27	-	Primary	GB20, LR3	17	4
Zhang J 2013 [8]	60	-	Primary	BL13, BL15, BL18, BL20, BL23, BL17	17	4
Lv HB 2018 [10]	12/18	39.23 $\pm$ 9.30	Primary	GV20, GV24, EX-HN3	17	6
Xu FM 2009 [11]	6/15	34.00	Primary	DU20, PC6	17	6
Xu W 2010 [12]	10/15	45.16 $\pm$ 6.96	Primary	DU20, EX-HN1, EX-HN5, DU26, PC6, HT7	17	4, 6
Fu WB 2008 [16]	37/69	41.41 $\pm$ 12.77	Primary	PC6, SJ5, DU20, DU29	24	4
Liu KX 2011 [17]	7/23	42.78 $\pm$ 10.39	Primary	ST8, EX-HN5, DU20, GB20, EX-HN1, DU26, PC6, HT7, RN18, BL18, LR3	24	4
Wang QS 2015 [19]	17/18	45.80 $\pm$ 6.80	Primary	HT7, DU20, DU29, LI4, LR3	24	4
Xu WT 2017 [21]	12/16	38.45 $\pm$ 12.7	Primary	SP6, GB34, PC6, DU20, KI3, with electronic stimulation	24	6
Li SW 2011 [24]	11/19	40.33 $\pm$ 11.61	Primary	SP6, LR3, with electronic stimulation	24	4, 6
Zhou L 2011 [26]	15/20	40.00 $\pm$ 4.00	Primary	GB20, Sixth transverse foramen, Emotional area, with electronic stimulation	24	6

HAMD: Hamilton Depression Scale; M: Male; F: Female; T: Treatment; C: Control; SD: Standard Deviation; CI: confidence level.

Study ID	Sample size (M/F)	Age (Mean ± SD)	Type of depression	Acupoint	HAMD Scales	Treatment duration (weeks)
Deng AJ 2008 [28]	29	50.03 ± 4.43	Secondary	RN12, RN10, RN6, RN4	17	4
Li ZF 2015 [29]	30	49.80 ± 3.39	Secondary	RN4, EX-CA1, ST25, SP6, LI4, LR3, DU20, DU29	17	4
Yu SJ 2015 [32]	30	28.00 ± 16.00	Secondary	DU26, DU23, DU16, RN24, PC8	17	4
Chen HL 2007 [33]	22	26.70 ± 4.50	Secondary	DU20, BL15, BL18, LR14, BL20, LR13	24	4
Li QJ 2019 [34]	9/25	44.38 ± 12.79	Primary	DU20, DU29, RN17, HT7, PC7, PC6, SP6, ST36, BL15, BL20, LI4, LR3, BL62	24	4
Liu Q 2019 [35]	4/26	53.16 ± 8.32	Primary	DU29, ST36, RN13, RN12, RN11, RN6, ST25, PC6, DU20, DU24	17	6
2.2 Acupuncture as control						
Li JC 2011 [39]	14/6	42.70 ± 13.24	Primary	EX-HN1, PC6, SP6	17	6
Li C 2011 [40]	15/15	32.27 ± 10.79	Primary	DU20, DU26, PC6, HT7, LR3	24	4
Li C 2017 [42]	13/15	18.00– 55.00	Primary	DU26, PC6, HT7, LR3	17	6
Wang CJ 2017 [43]	7/23	42.17 ± 11.35	Primary	GV20, EX-HN3, PC6, HT7, SP6	24	4
Cheng YZ 2012 [44]	15/15	34.73 ± 8.37	Primary	DU26, HT7, PC6, LR3	24	6

HAMD: Hamilton Depression Scale; M: Male; F: Female; T: Treatment; C: Control; SD: Standard Deviation; CI: confidence level.

Study ID	Sample size (M/F)	Age (Mean ± SD)	Type of depression	Acupoint	HAMD Scales	Treatment duration (weeks)
Du YH 2005 [47]	10/30	42.80 ± 14.90	Primary	LR14, LR3, GB34, SJ6, PC6, ST36	24	6
Fan L 2009 [49]	16/13	34.73 ± 8.37	Primary	DU26, HT7, PC6, LR3	24	4
Su H 2010 [50]	5/23	41.10 ± 11.50	Primary	LR3, SP6, PC6, HT7	24	4
Yu XP 2016 [51]	14/16	53.00 ± 7.00	Secondary	DU29, DU20, EX-HN1, GB20, EX-HN5, PC6, HT7, PC6	24	4
Min XR 2014 [52]	26/14	42.00– 69.00	Secondary	DU20, PC6, SP6, DU29, HT7, RN17, KI3	24	4
Yu XP 2016 b [53]	10/15	56.64 ± 7.59	Secondary	GB20, LI11, SJ5, LI4, GB30, GB34, ST36, ST41, BL60, RN17	17	4
Feng LM 2012 [54]	5/15	54.05 ± 6.40	Secondary	LR14, LR3, GB34, SJ6, PC6, ST36	24	4
Li ZH 2019 [55]	12/24	38.28 ± 9.65	Primary	DU20, DU29, SP6, PC6, HT7, LR3	24	6
Wang HY 2019 [58]	16/14	51.53 ± 8.08	Primary	DU26, DU20, PC6, HT7, RN17, LR3, LR2, GB43	24	4
Xu P 2019 [59]	14/21	43.57 ± 10.86	Primary	LR14, LR3, ST40, BL20, ST36, RN22	24	6
Zhang LX 2019 [60]	11/16	72.22 ± 5.83	Primary	DU20–DU29	17	4
Wu J 2016 [61]	8/28	61.62 ± 6.52	Secondary	PC6, DU26, SP6	17	4

HAMD: Hamilton Depression Scale; M: Male; F: Female; T: Treatment; C: Control; SD: Standard Deviation; CI: confidence level.

Study ID	Sample size (M/F)	Age (Mean ± SD)	Type of depression	Acupoint	HAMD Scales	Treatment duration (weeks)
Zhang ZR 2013 [62]	17/13	61.43 ± 9.91	Secondary	DU20, DU18, BG13, GB9	24	4, 6
Zhang XL 2019 [64]	7/23	43.77 ± 11.14	Primary	DU20, DU29, HT7, LR3, PC6, RN17, BL15, BL20	17	4
Su PZ 2011 [68]	20	20.30 ± 3.13	Secondary	DU20, DU24, PC6, LI4, ST36, SP6, LR3	17	6
HAMD: Hamilton Depression Scale; M: Male; F: Female; T: Treatment; C: Control; SD: Standard Deviation; CI: confidence level.						

The t test results (see Table 3 and Fig. 3) showed there was significant statistical difference between experimental and control acupuncture at four weeks of HAMD-17 ($t = 2.54$, $P = 0.01$, MD = 4.86), four weeks of HAMD-24 ($t = 2.76$, $P = 0.006$, MD = 3.90), and six weeks of HAMD-24 ($t = 3.35$, $P = 0.0009$, MD = 6.57). No statistical difference was found only between groups in six weeks of HAMD-17 ($t = 1.69$, $P = 0.09$, MD = 3.38).

Table 3
t-test results of the comparison between experimental and control acupuncture groups

Outcome	Experimental acupuncture			Control acupuncture			Effect estimates (MD, 95%CI)	<i>t</i>	<i>P</i>
	Effect estimates (MD, 95%CI)	Sample size	I^2	Effect estimates (MD, 95%CI)	Sample size	I^2			
HAMD-17 in 4 weeks	11.41 [8.30, 14.51]	283	96%	6.55 [4.66, 8.44]	246	91%	4.86 [1.24, 8.48]	2.54	0.01
HAMD-17 in 6 weeks	12.23 [9.50, 14.97]	188	91%	8.85 [6.08, 11.61]	149	95%	3.38 [-0.48, 7.24]	1.69	0.09
HAMD-24 in 4 weeks	12.30 [10.05, 14.54]	465	95%	8.40 [7.05, 9.75]	377	81%	3.90 [1.28, 6.52]	2.76	< 0.01
HAMD-24 in 6 weeks	16.31 [11.30, 21.31]	166	96%	8.87 [7.13, 10.62]	305	88%	6.57 [1.43, 11.71]	3.35	< 0.01
HAMD: Hamilton Depression Scale; MD: Mean Difference; SD: Standard Deviation; CI: confidence level.									

Discussion

According to our study, the effectiveness of acupuncture for decreasing the severity of depression was superior in trials which considered acupuncture as experimental treatment compared to those of the acupuncture as control. The difference of post-treatment HAMD-17 scales and HAMD-24 scales were average - 2.95 cores and - 5.55 cores, which were both statistical and clinical meaningful for relieving depression.

This study attempts to quantify the impact of performance and detection bias in acupuncture clinical trials. The application of paired meta-analysis can reduce the system error of indirect comparison as much as possible, and re-analysis from the unpaired-study further confirmed the stability of the results. The data of this study can explain to some extent the consequences of destroying the uncertainty principle caused by the lack of blinding method in the non-pharmaceutical therapy researches represented by acupuncture.

However, since we used indirect comparisons, the strength of the evidence was weakened. Although we used pairing method to reduce the influence of confounding factors, the results of meta-analysis had a certain degree of statistical heterogeneity due to the inconsistency of acupoint selection between acupuncture studies.

As the result showed in the study, we suggest that consideration should be given to existing evidence of acupuncture for depression. When acupuncture is used in the experimental group, the effect of acupuncture may be overestimated; but it may be under estimated when acupuncture appearing in the control group. It is suggested that the actual effectiveness of acupuncture should be carefully considered when referring to the corresponding evidence in clinical practice. Similar consequences may appear in other diseases, as doctors' personal preference could lead to performance and detection bias, therefore implicates study results. Moreover, it can be speculated that detection bias could cause due to patients' self-assessment, which is highly subjective.

According to this study, blinding method, applied with extra means to ensure its success, is the key solution to avoid performance and detection bias during acupuncture clinical trials. We suggest that future trials should either use adequate random allocation and concealment, blinding the outcome assessors and statisticians, or improve the monitoring mechanism, so that the research designer does not intervene in the implementation process of intervention and does not directly contact patients, so as to reduce the impact of bias on the research. However, blinding method is hard to be used in the non-placebo-controlled trial. Thus, some special types of randomized trials can be used in acupuncture clinical trial. For example, sequential multiple assignment randomized trial can improve external authenticity and get closer to the real treatment process through building and comparing dynamic treatment regimens [70–72]. In previous studies, we also proposed the feasibility and advantages of partially randomized patient preference trial adopted in evaluation of non-drug therapy (e.g. Acupuncture) by analyzing the application status of modified clinical trials considered patients' preferences [73, 74].

Conclusions

This study found that the effectiveness of acupuncture for decreasing the severity of depression was superior in trials those employed acupuncture as experimental treatment, which showed that performance and detection bias caused by the absence of blinding method played an important role in acupuncture clinical trials.

Abbreviations

CI
confidence interval
HAMD
Hamilton Depression Scale
MD
Mean Difference
SD
standard deviation

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary information files.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

RTW and LJC analyzed basic characteristics of trials and analyzed data, and were major contributors in writing the manuscript. JPL and YTF assisted with the research methods and result explanation. MH participated in research designing, data analyzing and interpretation of indicators. HLC ensure that original data, original figures, materials and code upon which the submission is based are preserved following best practices in the field so that they are retrievable for reanalysis; and confirm that data, figures, materials and code presentation accurately reflects the original; and foresee and minimize obstacles to the sharing of data, materials, code described in the work. HLC also ensure that the entire author group is fully aware of and in compliance with best practices in the discipline of publication. All authors read and approved the final manuscript.

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Figures

Figure 1

Study flow chart.

Figure 2

Forest plot of 13-paired included studies.

Figure 3

Boxplots of the differences between experimental and control acupuncture for Hamilton Depression Scales. (a) Hamilton Depression-17 Scales in four weeks; (b) Hamilton Depression-17 Scales in six weeks; (c) Hamilton Depression-24 Scales in four weeks; (d) Hamilton Depression-24 Scales in six weeks.