Journal of Affective Disorders 124 (2010) 9–21

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Review

The effectiveness and safety of acupuncture therapy in depressive disorders: Systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 28 March 2009
Received in revised form 2 July 2009
Accepted 2 July 2009
Available online 26 July 2009

Keywords:
Acupuncture
Major depressive disorder
Post-stroke depression
Meta-analysis

ABSTRACT

Background: Although acupuncture has been used as an alternative treatment for depressive disorders, its effectiveness and safety are not well defined. The purpose of this systematic review with meta-analysis was to evaluate the effectiveness of acupuncture as monotherapy and as an additional therapy in treating various depressive conditions, particularly major depressive disorder (MDD) and post-stroke depression (PSD).
Methods: Following systematic review, meta-analysis was conducted on high-quality randomized controlled trials (RCTs).
Results: Of 207 clinical studies of acupuncture for various depression retrieved, 113 (54.6%) were on MDD and 76 (36.7%) on PSD. Twenty RCTs of MDD (n = 1998) and 15 of PSD (n = 1680) identified for high-quality protocol (Jadad score ≥3) were included for meta-analysis. The efficacy of acupuncture as monotherapy was comparable to antidepressants alone in improving clinical response and alleviating symptom severity of MDD, but not different from sham acupuncture. No sufficient evidence favored the expectation that acupuncture combined with antidepressants could yield better outcomes than antidepressants alone in treating MDD. Acupuncture was superior to antidepressants and waitlist controls in improving both response and symptom severity of PSD. The incidence of adverse events in acupuncture intervention was significantly lower than antidepressants.
Conclusions: Acupuncture therapy is safe and effective in treating MDD and PSD, and could be considered an alternative option for the two disorders. The efficacy in other forms of depression remains to be further determined.

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doi:10.1016/j.jad.2009.07.005

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1. Introduction

Although the development of various classes of antidepressant drugs, represented by selective serotonin reuptake inhibitors (SSRIs), has considerably improved the prognosis and the tolerability in the treatment of depressive disorders, the currently available antidepressant therapy is unsatisfactory (Arroll et al., 2005). There remains a large portion of depressed patients who cannot obtain full responses and experienced recurrent episodes. Furthermore, undesirable side effects and delay in the onset of the therapeutic action also have hampered the clinical use of antidepressant medications (Arroll et al., 2005). In order to overcome these shortcomings, strenuous attempts have been made to search for alternative strategies that could improve the outcomes of antidepressant treatments (van der Watt et al., 2008).

As an ancient therapeutic modality, acupuncture therapy has become a widely recognized alternative therapy in today clinical practice. As a result, numerous clinical studies aimed at evaluating the efficacy and safety of acupuncture in patients with depressive disorders have been reported over the past decades, especially for major depressive disorder (MDD) and post-stroke depression (PSD) (He and Shen, 2007; Leo and Ligot, 2007; Mukaino et al., 2005; Smith and Hay, 2005; Wang et al., 2008). Nonetheless, great discrepancies are present in the results reported and prior meta-analyses failed to yield significant conclusions, largely due to the incompleteness of data collection and lack of detailed subgroup analyses of different diagnoses of depressive disorders (Leo and Ligot, 2007; Mukaino et al., 2005; Smith and Hay, 2005; Wang et al., 2008).

In the present study, systematic review and meta-analysis performed to evaluate the effectiveness and safety of acupuncture therapy for depression were based on standardized classification of depressive disorders and the definition of high-quality randomized, controlled trials (RCTs) of MDD and PSD. The present study also included several newer trials which were not included in previous meta-analyses.

2. Methods

2.1. Search strategy

All case and controlled studies of acupuncture therapy in patients with various depressive disorders were searched. Since most relevant studies were published in English and Chinese bibliographies, the searches were mainly conducted in the following two language databases: PubMed (1950–), MEDLINE (1950–), Cochrane Central Register of Controlled Trials (CENTRAL), China Journals Full-text Database (1915–), China Master and Doctor Theses Full-text Database (1999–), and China Proceedings of Conference Full-text Database (1999–).

In order to determine which forms of depression deserved to be included in meta-analyses, all terms and keywords related to depressive symptoms were searched. These included: depression, MDD, depressive neurosis, dysthymia, dysthymic disorder, PSD, postpartum depression, postnatal depression, and postmenopausal depression in combination with acupuncture, electroacupuncture, auricular acupuncture, scalp acupuncture, or wrist–ankle acupuncture. Any trials testing nontraditional acupuncture modalities only, i.e., no acupuncture needles are inserted into the body, such as acupressure (Cho and Tsay, 2004) and laser acupuncture (Quah-Smith et al., 2005), were excluded.

2.2. Inclusion criteria and diagnostic criteria of depressive conditions

All clinical investigations which included subjects who had a diagnosis of a depressive condition and were assigned to an acupuncture modality treatment were taken into account. Based on our preliminary searches, the studies

could be classified into case studies and randomized controlled trials (RCTs). Only those rated for high-quality RCTs were included in meta-analysis (see below). The diagnoses of depressive disorders should be made based on a standardized diagnostic instruction, such as International Classification of Diseases (ICD), Chinese Classification of Mental Disorders (CCMD) or Diagnostic and Statistical Manual of Mental Disorders (DSM), and the definition of the severity of depressive symptoms, as evaluated with the Hamilton Rating Scale for Depression (HAMD), Zung's self-rating depression scale or other instruments for depression. For PSD, additional diagnostic criteria should include neuroimaging verification of pathological alterations in the brain (thrombo-embolic stroke or intracerebral hemorrhages), no prior history of depression, and no dysphasia or severe disarticulation, as demonstrated by their ability to correctly answer questions (Turner-Stokes and Hassan, 2002).

2.3. Assessment of methodological quality of RCTs

Methodological quality of RCTs was assessed using modified five-point Jadad scale (Mukaino et al., 2005; Jadad et al., 1996): (1) description of randomization; (2) adequate and appropriate randomization method; (3) description of single- or double-blindness; (4) assessors blinded to treatment conditions; and (5) description of withdrawals and dropouts. In addition, allocation concealment, mask assessment of outcomes, intent-to-treat analysis and dropouts were also taken into the assessment. Only those rated for 3 points or higher were included for meta-analysis. All trials were reviewed by at least two reviewers and any disagreement was resolved through the involvement of a third reviewer in consensus conferences.

2.4. Data extraction

The protocol and treatment outcome data were extracted from the trials retrieved for meta-analysis. The protocol information included diagnostic instruments and efficacy measures, treatment regime (monotherapy and additional therapy), controlled conditions (antidepressants, sham acupuncture, and waitlist), acupoints used (body, scalp, and/or ear points), acupuncture stimulation modes (electrical and manual), number of acupuncture treatment sessions, and duration of treatment.

Treatment outcomes included dichotomous and continuous data as well as incidences of adverse events. Dichotomous data were response rates, generally defined as a ≥50% reduction in scores on depressive scales (mainly HAMD) from baseline to endpoint for active acupuncture and controlled groups. Continuous data were means of baseline-to-endpoint changes in score on depressive scales (mainly HAMD) and pooled standard deviations were calculated for each arm accordingly. Incidences of adverse events were pooled for analysis.

2.5. Statistical analyses

Statistical analyses to compare the overall and subgroup treatment effects between acupuncture intervention (monotherapy and adjunctive therapy) and controlled conditions (antidepressants, sham acupuncture, and waitlist) were performed using the Review Manager Program (Revman 5.0), which was developed based on Deeks et al. method (2001). Dichotomous (response rates) and continuous data were analyzed with risk ratio (RR) and weighted mean difference (WMD) with 95% confidence intervals (95% CI), respectively. Differences in means of baseline-to-endpoint changes in depressive severity between related two arms were obtained using Cohen's *d* formula. The overall effects and the heterogeneity for both dichotomous and continuous data across trials were examined by calculating *Z* values and χ^2 distributed Cochrane *Q* values, respectively. Random model of Mantel–Haenszel method was applied if *P* values of heterogeneity tests were less than 0.10; otherwise fixed model was applied. The I^2-test of heterogeneity was also conducted to obtain I^2 values based on the formula ($I^2 = 100\%*(Q - \text{degree of freedom})/Q$)) (Higgins et al., 2003). Less than 25% of I^2 values indicate low heterogeneity, 25%–50% moderate, and >50% high. Publication bias was determined using Egger's test to detect funnel plot asymmetry (Egger et al., 1997).

Table 1
The number and quality of clinical trials of acupuncture treatment for depressive disorders included in the present study.

	Case study	RCT (Jadad score)					# of HQ RCTs [a]	Total # of patients in HQ RCT
		I	II	III	IV	V		
MDD	40	31	13	18	6	5	29 (20) [b]	1998 [b]
PSD	18	19	19	18	2	0	20 (15) [c]	1680 [c]
PMD	2	3	4	2	0	0	2	126
PND	0	2	0	0	1	0	1	61
CMD	0	0	1	0	1	0	1	60
PTD	1	1	0	0	0	0	0	0
Subtotal	61	56	37	38	10	5		
(%)	(29.5)	(27.1)	(17.9)	(18.3)	(4.8)	(2.4)		
Total	207 studies							

MDD: major depressive disorder; PSD: post-stroke depression; PMD: postmenstrual depression; PND: peri-natal depression; CMD: comorbid depression; PTD: post-traumatic depression.

[a] Numbers of high-quality RCTs (HQ RCTs) are a sum of RCTs rated with III or higher of Jadad score.

[b] Eight trials that were scrutinized for duplicate publication and one trial with laser acupuncture were excluded, leaving 20 trials involving 1998 patients for meta-analysis.

[c] Five trials that were scrutinized for duplicate publication were excluded, leaving 15 trials involving 1680 patients for meta-analysis.

Table 2
Characteristics of 20 RCTs of acupuncture treatment in MDD patients included for meta-analysis.

Authors	Diagnostic criteria	No. of subjects in each arm					Acupoints used			ACP stimulation		# of ACP sessions [b]	Treatment duration (weeks)	Jadad score
		ACP alone	ACP + drug	Drug alone [a]	Sham ACP	Waitlist	Body	Scalp	Ear	Electric	Manual			
Allen et al. (2006)	DSM-IV/HAMD	50			50	52	UK	UK	UK		+	12	8	V
Chen and Zhuang (2007)	CCMD/HAMD	30		30 (FLX)			+	+	+		+	36	12	III
Fu et al. (2008)	CCMD/HAMD	176		176 (FLX)	88		+	+	+		+	24	12	V
Han and Li (2002)	CCMD/HAMD	30		31 (MPT)			+	+		+		36	6	III
Huang et al. (2004a,b)	CCMD/SCL-90R	50		48 (FLX)				+		+		36	6	III
Li and Du (2003)	CCMD/HAMD	78		25 (FLX)			+	+			+	30	6	III
Lin et al. (2005)	CCMD/HAMD		30 (+ FLX)	23 (FLX)			+	+			+	30	6	III
Lu and Wang (2004)	CCMD/HAMD		36 (+ SSRIs)	30 (SSRIs)			+	+		+		30	6	III
Luo et al. (1998)	CPA/HAMD	133		108 (AMP)				+		+		36	6	III
Luo et al. (1990)	ICD-9/HAMD	27		20 (AMP)				+		+		36	6	III
Luo et al. (2003)	DSM-IV/HAMD	31			32			+		+		30	6	V
Pei et al. (2006)	CCMD/HAMD	62		58 (FLX)			+				+	30	6	III
Qiao and Cheng (2007)	CCMD/HAMD	20		20 (FLX)			+	+			+	40	8	III
Röschke et al. (2000)	DSM-III/HAMD		22 (+ MSR)	24 (MSR)			+				+	12	4	V
Wang and Fu (2007)	CCMD/HAMD	28		28 (FLX)			+	+	+		+	24	12	III
Xu et al. (2004)	CCMD/HAMD	30		30 (PLX)			+	+		+		20	4	III
Zhang and Zhao (2007)	CCMD/HAMD	50		50 (AMP)			+	+			+	28	4	III
Zhang et al. (2004)	CCMD/HAMD	29		29 (AMP)				+		+		30	6	IV
Zhang et al. (2007)	CCMD/HAMD	38		42 (PLX)			+			+		40	6	III
Zhao and Jin (2005)	CCMD/HAMD	28		26 (FLX)			+	+		+		20	6	IV

ACP: Active acupuncture; AMP: Amitriptyline; CCMD: Chinese Classification of Mental Disorders; CPA: Chinese Psychiatric Association: DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; FLX: Fluoxetine; HAMD: The Hamilton Rating Scale for Depression; ICD-9: International Statistical Classification of Diseases and Related Health Problems, 9th Edition; MPT: Maprotiline; MSR: Mianserin; PLX: paroxetine; SCL-90R: Symptom Checklist-90-R; SSRIs: Selective Serotonin Reuptake Inhibitors; UK: Unknown.

[a] Doses used are seen in the text.

[b] Each treatment session generally lasted 30–50 min.

3. Results

3.1. Classification of studies and depressive conditions

A total of 207 studies were retrieved (Table 1). Sixty-one (29.5%) were case studies and 93 (44.9%) were rated for poor-quality RCTs (Jadad score ≤2). The remaining 53 (25.6%) were identified for relatively high-quality RCTs (Jadad score ≥3). Although the studies covered six depressive conditions: MDD, PSD, postmenstrual depression (PMD), peri-natal depression (PND, including postpartum depression and depression during pregnancy), comorbid depression (CMD), and post-traumatic depression (PTD), most studies (91.3%, 189/207) were aimed at MDD and PSD.

Among 53 trials identified as high-quality RCTs, 29 trials studied MDD; however, eight trials with duplicate publication and one trial with laser acupuncture (Quah-Smith et al., 2005) were excluded, leaving 20 trials involving 1998 patients for meta-analysis. Twenty trials of PSD were assessed for high-quality RCTs, but five trials with duplicate publication were excluded, leaving 15 trials involving 1680 patients for meta-analysis. Two trials for PMD (Qian et al., 2007; Zhou, 2007) and one trial each for PND (Manber et al., 2004) and CMD (Sun and Zhang, 2007) identified as high-quality RCTs were not included for meta-analysis, due to the small size of pooled samples for each condition (Table 1).

3.2. Methodological characterization of high-quality RCTs

3.2.1. MDD

Detailed methodological information of 20 included RCTs of MDD is shown in Table 2. Nineteen trials utilized the Chinese Classification of Mental Disorders (CCMD, 15 trials) or the Diagnostic and Statistical Manual of Mental Disorders (DSM, four trials) as diagnostic instruments and the Hamilton Rating Scale for Depression (HAMD) to evaluate changes in the severity of depressive symptoms. There were 19 trials comparing acupuncture monotherapy to antidepressants (15 trials), sham acupuncture (three trials, defined as the insertion of needles into non-acupoints), and waitlist controls (one trial), and three trials comparing acupuncture combined with antidepressants to antidepressants alone. The three most commonly used antidepressants were fluoxetine (FLX, nine trials; 20 mg/day in seven trials), amitriptyline (AMP, 50–250 mg/day, four trials), and paroxetine (PLX, 20–40 mg/day, two trials). The combination of body and scalp acupoints was used in 11 trials. The four most frequently used acupoints were Baihui (Du-20), Yintang (EX-HN3), Taichong (LR-3), and Shenmen (HT-7). There were 10 trials applying electrical stimulation and other 10 trials applying manual stimulation. The numbers of treatment sessions and the durations of treatment were 24–60 and 4–12 weeks, respectively; the majority (70%, 14/20 trials) was 24–40 sessions within 4–6 weeks.

3.2.2. PSD

Detailed methodological information of 15 included RCTs of PSD is shown in Table 3. All the included trials used CCMD and the Chinese Classification of Cerebrovascular Diseases (CCCD) as diagnostic instruments and HAMD to evaluate changes in the severity of depressive symptoms, and verified pathological alterations in the brain by utilizing computed tomography (CT) and magnetic resonance imaging (MRI). All 15 included trials compared acupuncture monotherapy to antidepressants (12 trials) or waitlist controls (three trials). FLX (20 mg/day) was used in seven trials and AMP (25–300 mg/day) in three trials. Twelve trials (80%) utilized combination sets of bilateral body and scalp acupoints which were selected based on TCM diagnosis. There were 11 trials applying manual stimulation and only four with electrical stimulation. The

Table 3
Characteristics of 15 RCTs of acupuncture treatment in PSD patients included for meta-analysis.

Authors	Diagnostic criteria[a]	No. of subjects in each arm			Acupoints used			ACP stimulation		No. of ACP sessions[c]	Treatment duration (weeks)	Jadad score
		ACP alone	Drug alone[b]	Waitlist	Body	Scalp	Ear	Electric	Manual			
Cheng and Zhao (2007)	CCCD/CCMD/HAMD	39		19	+	+		+		21	6	IV
Chu et al. (2007)	CCCD/CCMD/HAMD	36	36 (FLX)		+	+		+		40	8	III
Ding and Yu (2003)	CCCD/DSM-III/HAMD	30	30 (FLX)		+	+			+	50	8	III
Gu (2005)	CCCD/CCMD/HAMD	30	30 (FLX)		+				+	56	4	III
He and Shen (2007)	CCCD/CCMD/HAMD	180	76 (AMP)		+	+			+	56	4	III
He et al. (2006)	CCCD/CCMD/HAMD	118	113 (FLX)		+	+			+	40	8	III
Huang et al. (2004a,b)	CCCD/CCMD/HAMD	42	43 (AMP)			+			+[d]	48	8	III
Peng and Tan (2007)	CCCD/CCMD/HAMD	30	30 (FLX)		+	+		+		24	4	III
Tang et al. (2003)	CCCD/CCMD/HAMD/Zung	30		30	+	+		+	+	15–20	4	III
Wang (2003)	CCCD/CCMD/HAMD	30	30 (FLX)		+	+			+	24	4	III
Wang et al. (2004)	CCCD/CCMD/HAMD	30	30 (DZP + CZP)		+	+	+		+	20	4	IV
Yang and Yan (2007)	CCCD/CCMD/HAMD/Zung	60	60 (FLX)		+	+			+	60	8	III
Yin (2004)	CCCD/CCMD/HAMD	100	80 (AMP)		+	+			+	56	8	III
Zhai et al. (2004)	CCCD/CCMD/HAMD	38		30	+	+			+	20	4	III
Zhao and Zhao (2007)	CCCD/CCMD/HAMD	126	124 (CLP)			+			+	56	4	III

ACP: Active acupuncture; AMP: Amitriptyline; CCCD: Chinese Classification of Cerebrovascular Diseases; CCMD: Chinese Classification of Mental Disorders; CLP: Chlorimiopramine; CZP: Clozapine; DSM-III: Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition; DZP: Diazepam; FLX: Fluoxetine; HAMD: Hamilton Rating Scale for Depression.

[a] The diagnoses had been verified by utilizing neuroimaging approaches in all included trials.

[b] Doses used are seen in the text.

[c] Each treatment session generally lasted 45–60 min.

[d] Following manual acupuncture manipulation, liquid extracted of the herbal medicine breviscapine was injected into the acupoints.

numbers of treatment sessions and the durations of treatment were 15–60 and 4–8 weeks, respectively.

3.3. Clinical responses of MDD

3.3.1. Monotherapy

Nine trials assessed the effectiveness of acupuncture monotherapy (n = 833) on response rates in comparison with antidepressants (Chen and Zhuang, 2007; Fu et al., 2008; Li and Du, 2003; Luo et al., 1998; Pei et al., 2006; Qiao and Cheng, 2007; Xu et al., 2004; Zhao and Jin, 2005), sham acupuncture (Allen et al., 2006; Fu et al., 2008), or waitlist controls (n = 662) (Allen et al., 2006). There was no statistically significant difference in pooling treatment effect on response rate between acupuncture and antidepressant treatment (RR = 1.09, 95% CI = 0.92–1.30, $P = 0.31$), with high heterogeneity ($I^2 = 71\%$) (Fig. 1).

Subgroup analysis on eight trials comparing with antidepressants also revealed no significant difference between the two groups (RR = 1.06, 95% CI = 0.97–1.17, $P = 0.20$), but with no evidence of statistical heterogeneity ($I^2 = 9\%$) (Chen and Zhuang, 2007; Fu et al., 2008; Li and Du, 2003; Luo et al., 1998; Pei et al., 2006; Qiao and Cheng, 2007; Xu et al., 2004; Zhao and Jin, 2005). Although one trial showed a significantly greater response to acupuncture than antidepressants (Fu et al., 2008), other seven trials demonstrated similar responses in the two treatment strategies (Chen and Zhuang, 2007; Li and Du, 2003; Luo et al., 1998; Pei et al., 2006; Qiao and Cheng, 2007; Xu et al., 2004; Zhao and Jin, 2005).

In two trials that compared active acupuncture with sham acupuncture (Allen et al., 2006; Fu et al., 2008), one trial found that patients treated with active acupuncture had significantly greater responses than sham acupuncture (Fu et al., 2008), but another did not (Allen et al., 2006). Pooled analysis did not yield significant results favoring active acupuncture (RR = 1.30, 95% CI = 0.26–6.37, $P = 0.75$), with high heterogeneity ($I^2 = 94\%$).

There was only one trial comparing the effects of active acupuncture with waitlist controls (Allen et al., 2006),

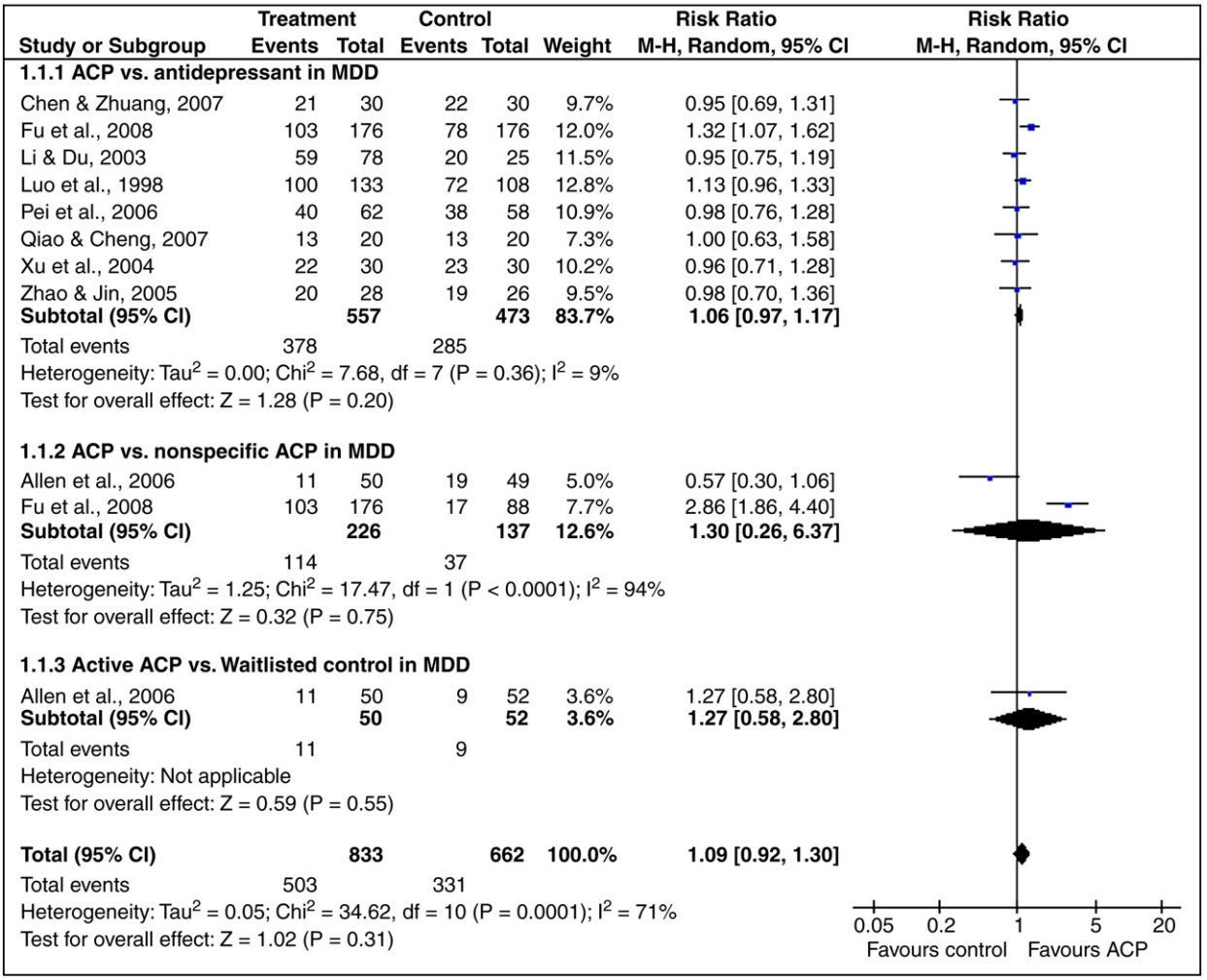

Fig. 1. Treatment effects of acupuncture monotherapy on clinical response in MDD patients with compared to antidepressants (1.1.1), nonspecific acupuncture (1.1.2) and waitlisted controls (1.1.3). ACP, acupuncture; MDD, major depressive disorders; M–H, Mantel–Haenszel method.

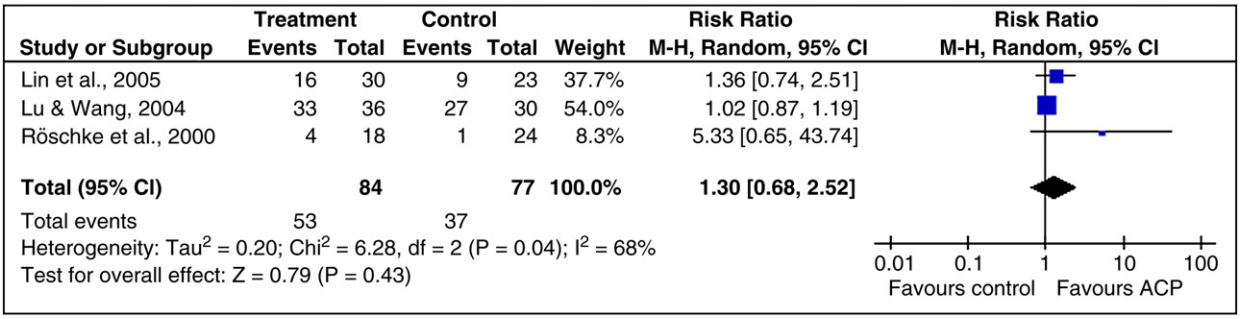

Fig. 2. Treatment effects of acupuncture combined with antidepressants on clinical response in MDD patients with compared to antidepressants alone. M–H, Mantel–Haenszel method.

showing no significant difference in response rate between the two conditions (RR = 1.27, 95% CI = 0.58–2.80, $P = 0.55$).

3.3.2. Additional therapy

Three trials compared acupuncture as an additional therapy with antidepressants (n = 84) to antidepressants alone (n = 77) (Lin et al., 2005; Lu and Wang, 2004; Röschke et al., 2000). Neither individual trials nor pooled analysis showed significant differences between the two groups (RR = 1.30, 95% CI = 0.68–2.52, $P = 0.43$), with high heterogeneity ($I^2 = 68\%$) (Fig. 2).

3.4. Improvement on depressive symptoms of MDD

3.4.1. Monotherapy

Sixteen trials evaluated the effects of acupuncture monotherapy (n = 1040) in improving depressive symptoms in comparison with antidepressants (Fu et al., 2008; Han and Li, 2002; Huang et al., 2004a,b; Li and Du, 2003; Luo et al., 1990, 1998; Pei et al., 2006; Qiao and Cheng, 2007; Wang and Fu, 2007; Xu et al., 2004; Zhang et al., 2004, 2007; Zhang and Zhao, 2007; Zhao and Jin, 2005) and sham acupuncture (Allen et al., 2006; Fu et al., 2008; Luo et al., 2003) (n = 860). The

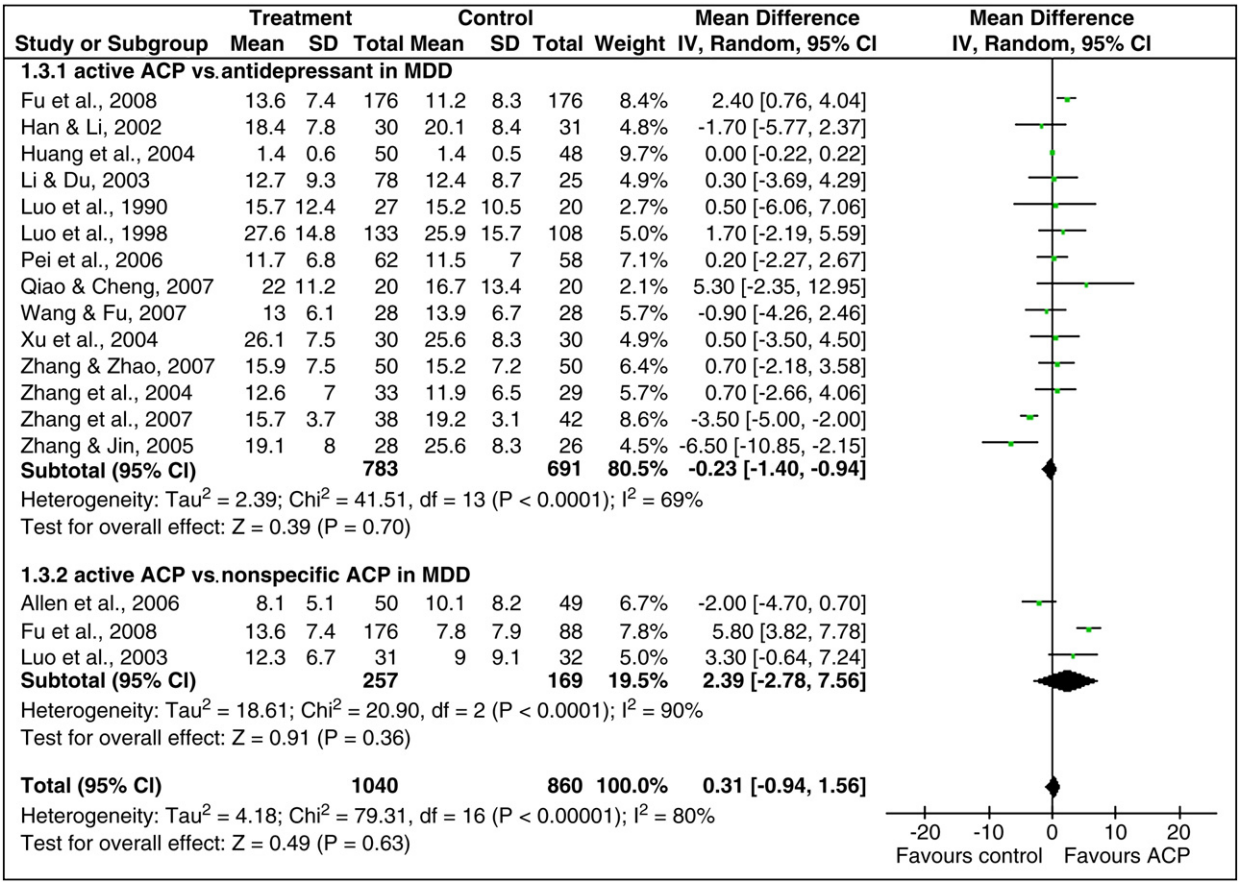

Fig. 3. Treatment effects of acupuncture monotherapy on mean differences in reducing depressive severity in MDD patients with compared to antidepressants (1.3.1) and nonspecific acupuncture (1.3.2). ACP, acupuncture; MDD, major depressive disorders.

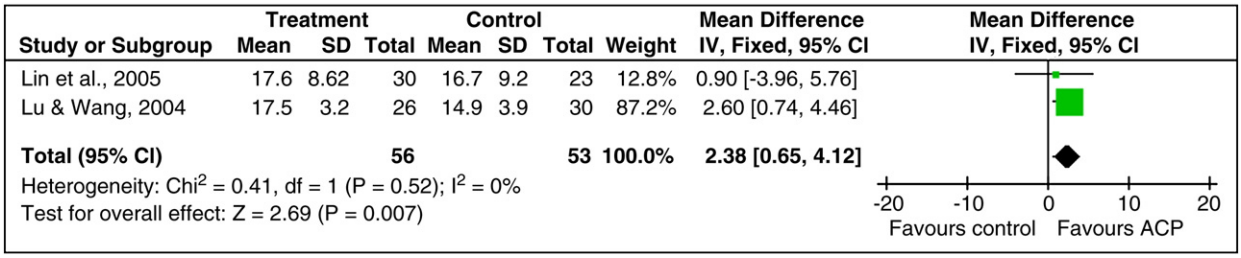

Fig. 4. Treatment effects of acupuncture combined with antidepressants on mean differences in reducing depressive severity in MDD patients with compared to antidepressants alone.

overall effects were not statistically different between the two treatment conditions (WMD = 0.31, 95% CI = −0.94–1.56, $P = 0.63$), with high heterogeneity ($I^2 = 80\%$) (Fig. 3).

Neither individual trials nor subgroup analysis of 14 trials with antidepressants as comparator had significant difference (WMD = −0.23, 95% CI = −1.40–0.94, $P = 0.70$), with high heterogeneity ($I^2 = 69\%$) (Fu et al., 2008; Han and Li, 2002; Huang et al., 2004a,b; Li and Du, 2003; Luo et al., 1990, 1998; Pei et al., 2006; Qiao and Cheng, 2007; Wang and Fu, 2007; Xu et al., 2004; Zhang et al., 2004, 2007; Zhang and Zhao, 2007; Zhao and Jin, 2005).

In three trials that compared active acupuncture with sham acupuncture (Allen et al., 2006; Fu et al., 2008; Luo et al., 2003), significant greater improvements on HAMD were observed in two trials (Fu et al., 2008; Luo et al., 2003), but not in Allen et al. (2006). Pooled analysis could not yield significant results favoring active acupuncture (WMD = 2.39, 95% CI = −2.78–7.56, $P = 0.36$), with high heterogeneity ($I^2 = 90\%$).

3.4.2. Additional therapy

Two trials compared acupuncture as additional treatment with antidepressants (n = 56) to antidepressants alone

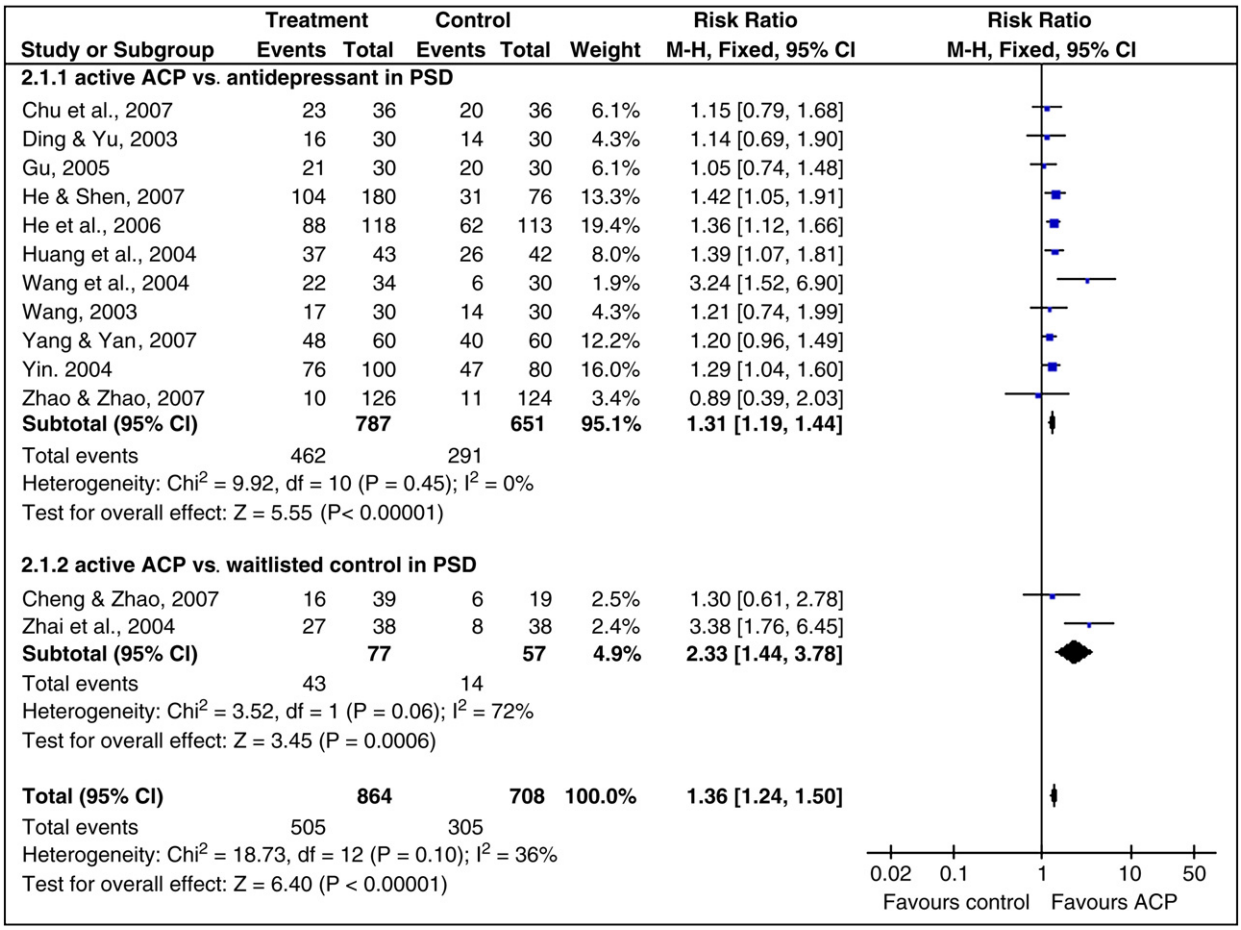

Fig. 5. Treatment effects of acupuncture monotherapy on clinical response in PSD patients with compared to antidepressants (2.1.1) and waitlisted controls (2.1.2). ACP, acupuncture; PSD, post-stroke depression; M–H, Mantel–Haenszel method.

(n = 53) (Lin et al., 2005; Lu and Wang, 2004). One trial showed better outcomes in improving HAMD in the combination treatment than antidepressants alone (Lu and Wang, 2004), but another trial did not (Lin et al., 2005). Pooling treatment effects reached significant level (WMD = 2.38, 95% CI = 0.62–4.12, $P = 0.007$), with low heterogeneity ($I^2 = 0\%$) (Fig. 4).

3.5. Clinical responses of PSD

There were 13 trials comparing the effects of acupuncture monotherapy (n = 864) on clinical response in comparison with antidepressants and waitlisted controls (n = 708) (Cheng and Zhao, 2007; Chu et al., 2007; Ding and Yu, 2003; Gu, 2005; He et al., 2006; He and Shen, 2007; Huang et al., 2004a,b; Wang, 2003; Wang et al., 2004; Yang and Yan, 2007; Yin, 2004; Zhai et al., 2004; Zhao and Zhao, 2007). Pooled analysis across 13 trials exhibited that patients in acupuncture intervention had significantly higher response than controls (RR = 1.36, 95% CI = 1.24–1.50, $P < 0.00001$), with moderate heterogeneity ($I^2 = 36\%$) (Fig. 5).

Of 11 trials comparing the effects of acupuncture with antidepressants, five trials (He et al., 2006; He and Shen, 2007; Huang et al., 2004a,b; Wang, 2003; Wang et al., 2004) observed significantly greater responses to acupuncture than antidepressants, but other six trials (Chu et al., 2007; Ding and Yu, 2003; Gu, 2005; Yang and Yan, 2007; Yin, 2004; Zhao and Zhao, 2007) showed similar responses between the two therapeutic regimes. Pooled analysis produced significant treatment effects in favor of acupuncture (RR = 1.31, 95% CI = 1.19–1.44, $P < 0$), with low heterogeneity ($I^2 = 0\%$).

In two trials that compared active acupuncture to waitlist controls, one trial found that patients treated with acupuncture had significantly higher response than waitlist controls (Zhai et al., 2004), but another trial did not observe the positive results (Cheng and Zhao, 2007). Pooled analysis yielded significant results in favor of acupuncture (RR = 2.33, 95% CI = 1.44–3.78, $P = 0.0006$), with high heterogeneity ($I^2 = 72\%$).

3.6. Improvement on depressive symptoms of PSD

Fourteen trials assessed the effectiveness of acupuncture monotherapy (n = 824) versus antidepressants and waitlist controls (n = 688) in alleviating the symptoms of PSD (Cheng and Zhao, 2007; Chu et al., 2007; Ding and Yu, 2003; Gu, 2005; He et al., 2006; He and Shen, 2007; Huang et al., 2004a,b; Peng and Tan, 2007; Tang et al., 2003; Wang, 2003; Wang et al., 2004; Yang and Yan, 2007; Zhai et al., 2004; Zhao and Zhao, 2007). The overall treatment effect across 14 trials was significantly different between the two groups in favor of acupuncture (WMD = 2.54, 95% CI = 1.11–3.97, $P = 0.0005$), but with high heterogeneity ($I^2 = 79\%$) (Fig. 6).

Among 11 trials comparing acupuncture to antidepressants, four trials observed significantly greater improvements in acupuncture-treated patients (He and Shen, 2007; Wang et

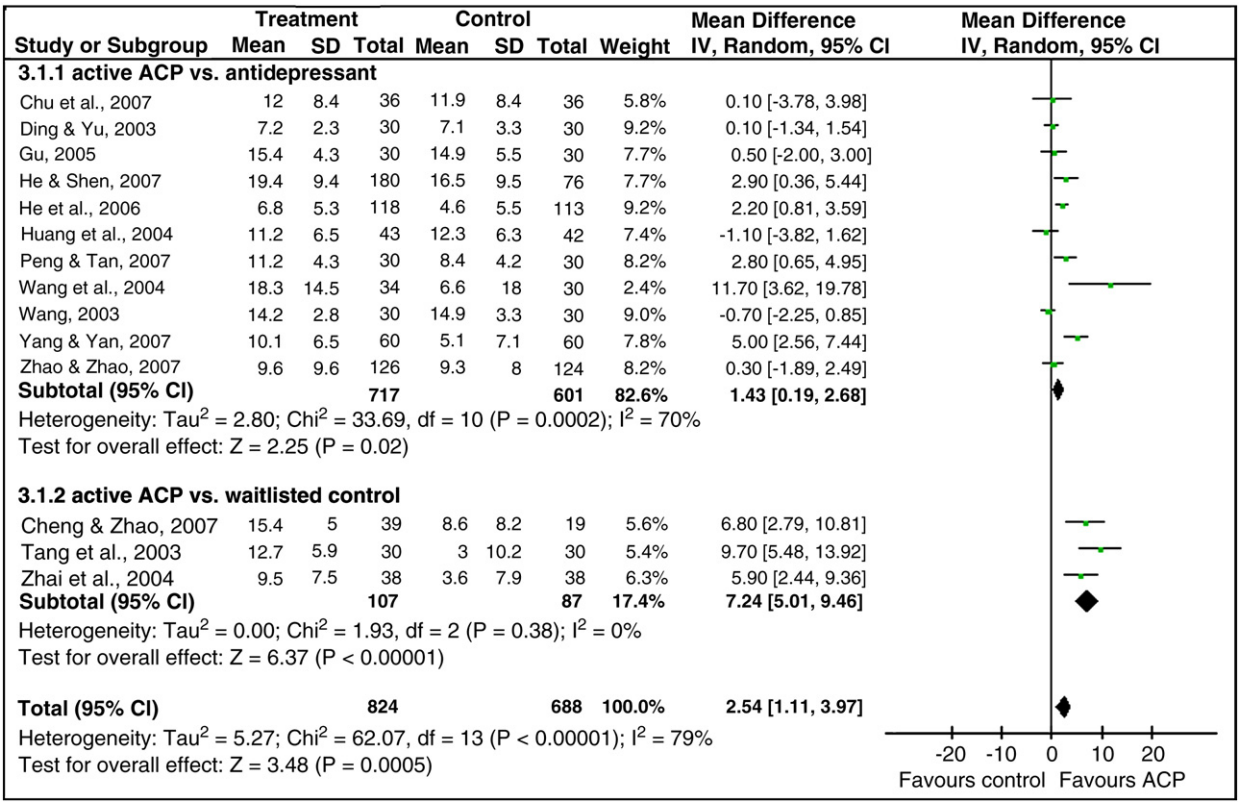

Fig. 6. Treatment effects of acupuncture monotherapy on mean differences in reducing depressive severity in PSD patients with compared to antidepressants (3.1.1) and waitlisted controls (1.3.2). ACP, acupuncture; PSD, post-stroke depression.

al., 2004; Yang and Yan, 2007; Peng and Tan, 2007); other seven trials did not (Chu et al., 2007; Ding and Yu, 2003; Gu, 2005; He et al., 2006; Huang et al., 2004a,b; Wang, 2003; Zhao and Zhao, 2007;). When all 11 trials were pooled for meta-analysis, significant treatment effects in favor of acupuncture were obtained (WMD = 1.43, 95% CI = 0.19–2.68, $P = 0.02$), with high heterogeneity ($I^2 = 70\%$).

Three trials that compared acupuncture with waitlist controls consistently showed significantly greater improvements in patients receiving acupuncture therapy (Cheng and Zhao, 2007; Tang et al., 2003; Zhai et al., 2004). Pooled analysis also found a significant difference favoring acupuncture therapy (WMD = 7.24, 95% CI = 5.01–9.46, $P < 0.00001$), with low heterogeneity ($I^2 = 0\%$).

3.7. Incidences of adverse events

Of all 35 trials of MDD and PSD, 21 trials provided data regarding incidences of adverse events with log records, Asberg's Antidepressant Side-effect Rating Scale or Treatment Emergent Symptom Scale (TESS). These trials reported that patients treated with active and sham acupuncture had fewer

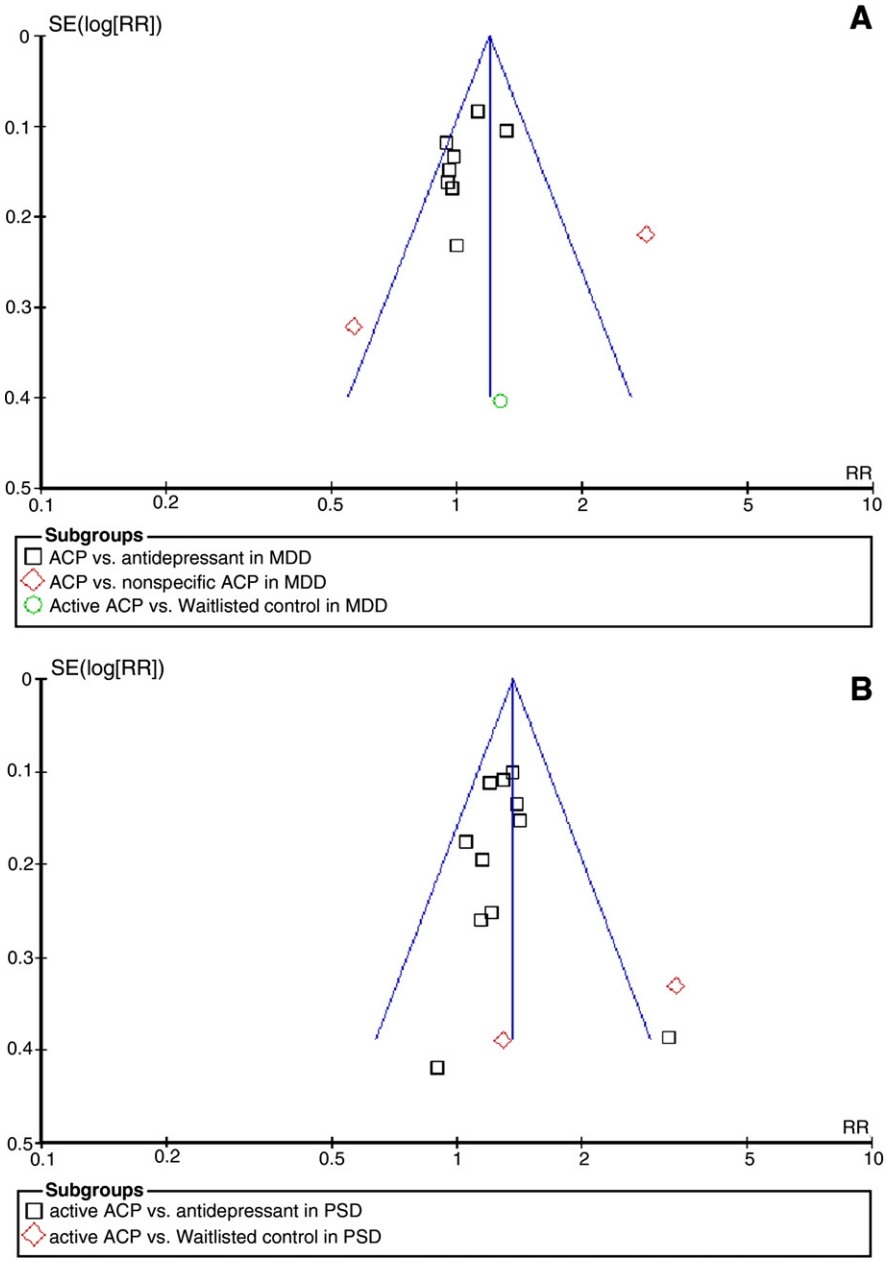

Fig. 7. Funnel plots of randomized controlled trials of acupuncture monotherapy in MDD (A, n = 11) and PSD (B, n = 13), detecting publication bias with Egger's tests. *X*- and *Y*-axes represent risk ratio (RR) and standard error of log risk ratio (SE(log(RR))), respectively. ACP, acupuncture; MDD, major depressive disorders; PSD, post-stroke depression.

side effects or lower scores on side-effect scales compared to antidepressants. When patients experiencing various adverse events in related trials were pooled for acupuncture (active and sham) and antidepressants (mainly SSRIs), respectively, 10.2% (179/1756) of the incidence was observed in acupuncture-treated patients, significantly lower than 40.4% (554/1372) in antidepressant-treated patients ($\chi^2 = 389.457$, d.f. = 1, $P < 0.001$). The most commonly experienced side effects were needling pain, transient dizziness, and nausea in acupuncture-treated patients, and headache, insomnia, and tiredness in SSRIs-treated patients.

3.8. Publication bias

The funnel plots of RRs against precision (SE) showed symmetrical manner in both MDD and PSD trials (Fig. 7). Egger's tests demonstrated no significant publication bias (MDD: bias = −2.54, 95% IC = −5.46–0.38, n = 11, $P = 0.081$; PSD: bias = 0.34, 95% IC = −2.77–3.34, n = 13, $P = 0.839$).

4. Discussion

The present study represents a systematic investigation reviewing clinical studies of acupuncture therapy in various depressive disorders and determining treatment effects in MDD and PSD with meta-analysis. Unlike previous meta-analyses, in which subgroup analyses for different treatment regimes and different diagnoses of depressive disorders were in general not conducted and poorly-designed RCTs were often included (Leo and Ligot, 2007; Mukaino et al., 2005; Smith and Hay, 2005), the present study was based on the classification of depressive conditions, the inclusion of relatively high-quality RCTs, and the exclusion of nontraditional acupuncture modalities (acupressure and laser acupuncture). Different treatment regimes (monotherapy and additional therapy) and data settings (dichotomous and continuous) were also analyzed separately. In addition, several trials not included in previous analyses were included in the present study. These advantages in methodology should enhance the accuracy of the assessment of the effects of acupuncture therapy in treating depressive disorders.

4.1. The effects in treating MDD

Although there have been several meta-analyses of acupuncture for MDD, the conclusions drawn were generally equivocal, largely due to the incompleteness of data collection and low rigorousness of the included trials, with only 7–9 trials involving nearly 500 unclassified subjects (Leo and Ligot, 2007; Mukaino et al., 2005; Smith and Hay, 2005; Wang et al., 2008). The present study included 20 relatively high-quality trials involving nearly 2000 MDD-diagnosed patients.

The present study showed that the overall effects of acupuncture monotherapy were similar to the pooled control in improving clinical responses and in reducing depressive symptoms in MDD patients (Figs. 1 and 3). Subgroup analyses comparing acupuncture with antidepressants also obtained similar results. These findings indicate that the effectiveness of acupuncture intervention in reducing and attenuating depression in MDD patients is comparable to antidepressants. Our recent pilot study also demonstrated that additional acupuncture treatment significantly accelerates the clinical response to paroxetine (PLX) in MDD patients and this effect is associated with increased platelet serotonin (5-HT) levels and decreased expression of platelet 5-HT_{1A} receptors (Zhang et al., 2008), suggesting that acupuncture also could shorten the latency of response to SSRI treatment and serotonergic mechanisms may be involved in the antidepressant actions of acupuncture observed.

Nonetheless, the effects of active acupuncture were not different from sham acupuncture in either improving clinical response or reducing depressive severity of MDD patients. Allen et al. (2006) even failed to observe the significantly greater response to active acupuncture than waitlist controls as expected (Fig. 1).When acupuncture combined with antidepressants was compared to antidepressants alone, the superior effect was only present in improving depressive symptoms (Fig. 4), but not clinical responses (Fig. 2). These inconsistent and unexpected results appear to be mainly due to the limited numbers of trials and small-size pooled samples available for the analyses, resulting in insufficient power to detect statistical significance. In addition, large variations in study protocols, especially in the definition of sham acupoints, manipulation, number of treatment sessions, and duration of treatment may also be important factors causing the failures of differentiating the effects of acupuncture intervention from controls (see below).

4.2. The effects in treating PSD

Post-stroke depression is a commonly occurring consequence in stroke patients (Paolucci, 2008). Although a large number of clinical studies of acupuncture intervention for PSD have been reported (Park et al., 2001; Shiflett, 2007; Wu et al., 2006; Xie et al., 2008), there were no review articles specifically dealing with acupuncture therapy for PSD. In the present study, 15 high-quality RCTs involving nearly 1700 PSD patients in acupuncture monotherapy were identified for meta-analysis. The study results showed that acupuncture intervention produced better outcomes when compared to conventional therapy, as evidenced by the fact that the overall effects of acupuncture intervention were significantly greater than the pooled control in improving both clinical responses and depressive symptoms. Subgroup analyses further revealed that the effects of acupuncture were also superior to either antidepressants or waitlist control. Moreover, both RR (1.36) and WMD (2.54) values observed in PSD were greater than those in MDD (RR = 1.09 and WMD = 0.31), suggesting that the antidepressant efficacy of acupuncture seems more robust on PSD than MDD.

The robust effects of acupuncture on PSD could be, at least in part, explained by multiple therapeutic effects of acupuncture therapy for stroke patients. In addition to the serotonergic mechanisms as mentioned above, acupuncture intervention may also have beneficial effects in enhancing stroke rehabilitation and in treating post-stroke neurological disorders, including limb disabilities, aphasia, dysphagia, urinary and defecation incontinence (Park et al., 2001; Shiflett, 2007; Wu et al., 2006; Xie et al., 2008). These positive effects of acupuncture have been confirmed in neuroimaging studies, showing that electrical stimulation of

certain acupuncture points significantly improves activities of affected cortical areas in chronic stroke patients (Jeun et al., 2005; Lee et al., 2003; Li et al., 2006; Schaechter et al., 2007). The improvements in the physical disabilities have been found to be greatly helpful in reducing depressive symptoms (Paolucci, 2008).

4.3. The limitations of the study

There are several limitations in the study. First, high heterogeneities, indicated as greater than 50% of I^2 values, were present in some overall and subgroup comparisons, especially in acupuncture monotherapy versus antidepressants on WMD data sets, sham acupuncture and waitlist controls, and acupuncture combined with antidepressants versus antidepressants alone. These heterogeneities among the studies made the results difficult to compare and integrate. As shown in Tables 2 and 3, the most considerable heterogeneities include numbers and locations of acupoints used, stimulation modes, numbers of treatment sessions and treatment durations. Numerous neuroimaging studies exploring acupuncture mechanisms have found that brain regions activation and intensity are associated with acupoint locations, stimulation paradigms, needling depth, manipulation type (electrical or manual), and stimulus duration (Dhond et al., 2007). Many studies also have shown the similarities in neuroimaging and biochemical changes induced by stimulations of specific and nonspecific acupoints (Dhond et al., 2007). These similarities could partially explain no differences in treatment effects between sham and active acupuncture. It should be noted that frequencies of treatment sessions in China-based trials were generally much more than other regions-based trials (5–7 versus 2–3 sessions weekly). These differences could largely account for the heterogeneities observed in the present study.

Second, although publication biases were not detected in the current study, several potential factors that may cause biases should be addressed. Sample sizes in the majority of individual trials included in the present study were small, with less than 40 subjects in each arm. This may reduce the sensitivity and accuracy of the analyses and result in either over- or under-estimating the overall treatment effects. Moreover, many trials included in the present analysis did not set up blinding conditions and placebo or sham acupuncture to exclude psychological effects of acupuncture. This is particularly important when sampling frames were restricted to Chinese populations who have distinctive perceptions of acupuncture treatment. Thus, differences in expectancies for treatment outcomes should be considered in the interpretation of the study results.

Finally, as mentioned in all previous meta-analyses of acupuncture (Leo and Ligot, 2007; Mukaino et al., 2005; Smith and Hay, 2005; Wang et al., 2008), a large portion of the trials included in this study did not provide detailed demographic and methodological information, such as durations of illness, number of mood episodes, medication history, random sequence, allocation concealment, intention-to-treat analyses and masking. We could not further determine associations of treatment effects with demographic factors and potential biases derived from methodological flaws. In addition, other depressive conditions were not included in meta-analyses and remain to be further investigated.

4.4. Implications for clinical practice and future research

Given the limited efficacy of antidepressant treatment (Arroll et al., 2005; Paolucci, 2008), the present study provides evidence in supporting the viewpoint that acupuncture is an effective and safe alternative treatment for depressive disorders, and could be considered an alternative option especially for patients with MDD and PSD, although evidence for its effects in augmenting antidepressant agents remains controversial.

The standardization of acupuncture protocols would be greatly helpful in improving methodological quality of acupuncture studies of depression. These may include the principles of selections of acupoints, stimulation modes, and manipulation. Large-scale, well-designed, controlled trials are required to address the effectiveness of standardized acupuncture therapy and determine which demographic and methodological factors could affect treatment effects of acupuncture for depression. Whether acupuncture as additional therapy could shorten the latency of response to SSRIs and enhance the antidepressant efficacy is under investigation by our research team.

Role of funding source

No any fund agencies listed herein have roles in the design, conduct and data analysis of this work.

Conflict of interest

All authors declare that they have no any conflict of interest in this study.

Acknowledgements

The present study was supported by the Hospital Authority of Hong Kong. The authors thank Mr. Steven E. Zhang for grammatically reading the manuscript.

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