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Systematic review of acupuncture for the treatment of alcohol withdrawal syndrome

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ABSTRACT

Background Acupuncture has been used as a potential therapy for alcohol withdrawal syndrome (AWS), but evidence for its effects on this condition is limited.
Objective To assess the effects and safety of acupuncture for AWS.
Data sources Central Register of Controlled Trials (CENTRAL), PubMed, Embase, the Cochrane Library, PsycINFO, Chinese Biomedicine Literature (CBM), China National Knowledge Infrastructure (CNKI) and Wan-Fang Database were searched from their inception to August 2016.
Study eligibility criteria Randomised controlled trials (RCTs) of drug plus acupuncture or acupuncture alone for the treatment of AWS were included.
Data collection and analysis Continuous data were expressed as mean difference (MD) with 95% confidence intervals (95% CI). Dichotomous data were expressed as risk ratio (RR) with 95% CI.
Results Eleven RCTs with 875 participants were included. In the acute phase, two trials reported no difference between drug plus acupuncture and drug plus sham acupuncture in the reduction of craving for alcohol; however, two positive trials reported that drug plus acupuncture was superior to drug alone in the alleviation of psychological symptoms. In the protracted phase, one trial reported acupuncture was superior to sham acupuncture in reducing the craving for alcohol, one trial reported no difference between acupuncture and drug (disulfiram), and one trial reported acupuncture was superior to sham acupuncture for the alleviation of psychological symptoms. Adverse effects were tolerable and not severe.
Conclusion There was nosignificant difference between acupuncture (plus drug) and sham acupuncture (plus drug) with respect to the primary outcome measure of craving for alcohol among participants with AWS, and no difference in completion rates (pooled results). There was limited evidence from individual trials that acupuncture may reduce alcohol craving in the protracted phase and help alleviate psychological symptoms; however, given concerns about the quantity and quality of included studies, further large-scale and well-conducted RCTs are needed.
Protocol registration PROSPERO CRD42016039862.

INTRODUCTION

Alcohol addiction is considered a public health issue. In 2010, alcohol misuse became the third leading risk factor contributing to the global disease burden,[1 2] and in 2012, 5.9% of deaths globally were attributed to alcohol consumption.[3] A report from the WHO in 2014 revealed that, worldwide, approximately 16% of drinkers (older than 15 years old) had engaged in heavy episodic drinking,[3] which is a significant health threat. Alcohol withdrawal syndrome (AWS) usually occurs in the initial period of abstinence,[4] and the common clinical manifestations include paroxysmal sweating, insomnia, nightmares, nausea, vomiting, fever, tremor, seizures, tachycardia, hallucinations, increased agitation, and delirium.[5–7] Guidelines for AWS management[8] emphasise drug treatment for the prevention of symptoms such as delirium, seizures and Wernicke's encephalopathy; however, recommendations regarding local support services or other adjunctive options for AWS are lacking.

Acupuncture, a method of complementary medicine, has been used to alleviate AWS symptoms.[9] In animal research, recent findings have shown that acupuncture reduced voluntary alcohol intake in rats via an opiate-sensitive mechanism.[10] Studies have also indicated that acupuncture upregulates HSP70 and HSP105 expression and reduces apoptosis to repair brain damage in a rat model of heroin addiction,[11] and that acupuncture mediates anxiety-like behaviours by normalising the levels of catecholamines in the amygdala during ethanol withdrawal in rats.[12] These experiments have provided preliminary evidence in support of beneficial effects of acupuncture for AWS. Some clinical trials have also been conducted to evaluate the effects of acupuncture for the

treatment of AWS;[13-15] however, an earlier systematic review found insufficient qualified evidence to show that it reduced the desire for alcohol or alleviated psychological symptoms.[16] The aim of this study was to provide an updated review of randomised controlled trials (RCTs) assessing the effects of traditional acupuncture plus conventional drugs, or traditional acupuncture alone, on the craving for alcohol or psychological symptoms among patients with AWS.

METHODS

Protocol and registration
We conducted this review according to the PRISMA statement.[17] The protocol has been registered in the PROSPERO database (http://www.crd.york.ac.uk/PROSPERO); the registration number is CRD42016039862.

Eligibility criteria
Types of studies
RCTs reporting the treatment effects (including psychological effects) of acupuncture for AWS were included. The included trials were required to contain specific descriptions of the randomisation methods, explicit diagnoses, eligible outcomes and statistical methods. Mechanistic studies, animal studies, reviews or those without full text were excluded. There were no restrictions placed on publication date or publication status. We searched English and Chinese databases.

Types of participants
Participants diagnosed with AWS were included. The diagnostic criteria comprised DSM-III-R, DSM-IV, DSM-V,[18] ICD-10,[19] CCMD-3-R[20] and customised diagnostic criteria. In this review, participants with other types of substance abuse (such as heroin) were excluded. In addition, participants with severe disease or who were pregnant or taking anti-psychotic drugs were excluded.

Types of interventions
In this review, the acupuncture intervention was specifically limited to traditional acupuncture, which requires penetration of the skin of the participant by needles. RCTs of body acupuncture, electroacupuncture and ear acupuncture were included. Interventions such as laser acupuncture, ear acupressure, acupuncture point injections and transcutaneous electrical nerve stimulation were excluded. For the acute and protracted phases, comparisons were designated as 'drugs plus acupuncture versus drugs plus sham/placebo acupuncture' and 'drugs plus acupuncture versus drugs', respectively.

Types of outcome measures
Craving for alcohol, as assessed using a visual analogue scale (VAS), was designated as the primary outcome for this review; completion rate, Clinical Institute

Withdrawal Assessment (CIWA)[21] and average alcohol consumption, as well as Symptom Checklist-90-Revised (SCL-90-R)[22] and Hamilton Anxiety Scale (HAMA) scores,[23] were used as secondary outcomes. In addition, adverse events recorded in the trials were reported in this review.

Information sources and search
Literature searches were performed in the following databases: Central Register of Controlled Trials (CENTRAL), PubMed, Embase, the Cochrane Library, PsycINFO, Chinese Biomedicine Literature (CBM), China National Knowledge Infrastructure (CNKI) and Wan-Fang database. The time frame was from the inception of the database to August 2016, and the date of the last search was 1 September 2016.

The search strategy focused on terms related to acupuncture, AWS, alcohol dependence, and RCTs (strategy information can be seen in the online supplemental file and at https://www.crd.york.ac.uk/PROSPEROFILES/39862_STRATEGY_20170106.pdf). Moreover, grey literature, conference studies and the reference lists of included trials were also searched.

Study selection
Two reviewers (XL and XZ) independently searched the databases, exported references and deleted duplications using Endnote X7 software (Thomson Reuters, NY, USA). Titles and abstracts were independently scanned to assess the suitability of articles for inclusion; any disagreement was referred to ZL for discussion and resolution.

Data collection process
The same two reviewers (XL and XZ) independently extracted data using an extraction form. Questions about trials or missing data were referred to the first author of the respective publication via email or phone. If there was no response, we omitted the trial from data synthesis. Any uncertainty or disagreement was resolved by discussion with ZL.

Data items
Extracted and recorded data included the following information: (a) author information (country); (b) participants' characteristics (age, diagnosis); (c) interventions and controls (for acupuncture: type, points, manipulation; for drugs: types, doses, frequency); (d) outcomes; and (e) follow-up and adverse events.

Risk of bias in individual studies
The risk of bias of eligible RCTs was evaluated according to the Cochrane Collaboration tool.[24] Information recorded on the data extraction form included sequence generation, allocation concealment, blinding of participants, blinding of outcome assessments, incomplete outcome data, selective reporting and other biases. In this review, other potential biases were

considered in relation to sample size, type of acupuncture and manipulation. Bias was independently recorded and assessed by the same two reviewers (XL and ZQ).

Summary measures

Continuous data (scales) were expressed as mean difference (MD) with 95% confidence intervals (95% CI); for data reported before and after treatment, we estimated the changes according to methods recommended by the Cochrane Collaboration Handbook (chapter 16.1.3.2, Imputing standard deviations for changes from baseline). Categorical data (dichotomous variables) were expressed as risk ratio (RR) with 95% CI. If there were no means and standard deviations in a manuscript, we used the original data to express the treatment effects.

Synthesis of results

Data analysis was performed using RevMan 5.3.5 software. Considering the choice of scales for outcome measurements, we combined continuous data in the form of MDs. Heterogeneity was assesed using Cochrane's I^2 test ($I^2 > 50\%$ indicated the existence of heterogeneity). Based on the I^2 values, if there was no evidence of heterogeneity we applied a fixed effects model for analysis; otherwise we applied a random effects model.

Assessment of publication bias

We had planned to use a funnel plot to examine for the existence of publication bias.[25] However, in this review, the numbers of eligible trials were insufficient to do so.

Subgroup analysis or sensitivity analysis

In this review, given that we restricted the type of acupuncture to traditional acupuncture, and the number of eligible trials were limited, we did not perform a subgroup analysis. In reporting completion rates for acupuncture plus drug versus sham acupuncture plus drug, we successfully conducted a sensitivity analysis to identify the source of heterogeneity.

RESULTS
Study selection

A total of 663 studies were obtained from databases, and 82 duplications were omitted by the software. By scanning titles and abstracts, we first ruled out studies that were not RCTs, animal experiments and mechanistic studies, studies that addressed mixed substance abuse, and studies on irrelevant topics. Of 28 potentially eligibile studies, five studies were not true RCTs, one study addressed laser acupuncture, two studies included complicated interventions, and nine studies included acupuncture techniques that did not penetrate the skin, such as transcutaneous electrical
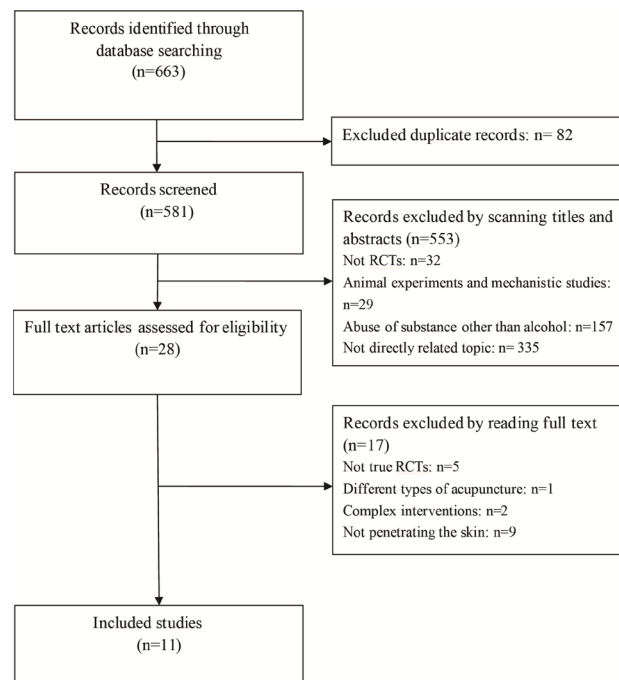

Figure 1 Flow diagram of the study selection process.

stimulation or acupressure. Therefore, 11 studies met the inclusion criteria.

The study selection process is presented in figure 1.

Study characteristics

Eleven studies (from the USA, Germany, Korea, Sweden, Bulgaria and China) with a total of 875 participants were included in this summary. All studies[26–36] were designed as single centre RCTs. Interventions included acupuncture, acupuncture plus drug, and electroacupuncture plus drug. Six trials chose craving for alcohol as the outcome, for which the evaluations comprised slight to no cravings, VAS, 5-point rating scale, and questionnaire. Others reported completion rate, alcohol consumption, drinking pattern, and/or CIWA, SCL-90, PACS (Penn Alcohol Craving Scale), SF-36 (Short Form Health Survey), HAMA or HAMD (Hamilton Depression scale) scores.

Seven studies described follow-up periods. Five studies reported completion rates and craving for alcohol after treatment. Two studies reported on the timing of repeat drinking by participants. Of all studies, only three of them reported adverse effects during the trial.

The specific characteristics of the included studies are presented in table 1.

Risk of bias within studies

The risk of bias assessment was performed according to the methods in the Cochrane Handbook. The results are presented in figures 2 and 3. All studies emphasised randomisation and published expected outcomes. For allocation concealment, two studies[26 27] emphasised

Table 1 Summary of included studies

Reference	Participants/mean age (years)/ diagnosis	Experimental intervention	Control intervention	Acupuncture points	Outcomes	Adverse events
Sapir-Weise et al, 1999, Sweden[26]	72 participants; men: 46.9±9.2/45.4±9.8; women: 41.1±4.4/42.8±7.1; ICD-10	Drug plus acupuncture	Drug plus placebo acupuncture (non-specific points); drug: disulfiram or carbamide	Ear Sympathetic, *Shenmen*, Lung	Completion rate, drinking pattern, craving for alcohol	NR
Bullock et al, 2002, USA[27]	265 participants; 39.3±9.9/38.4±10.7; self-made diagnosis	Drug plus acupuncture	Drug plus placebo acupuncture (non-specific points); drug: NR	Ear *Shenmen*, Lung, Sympathetic, Liver	Desire for alcohol (5-point rating scale), completion rate	NR
Karst et al, 2002, Germany[28]	34 participants; 43.3; ICD-10.	Drug plus acupuncture	Drug plus placebo acupuncture (blunt needle); drug: carbamazepine	GV20, *Yintang*, LI4, plus ear Sympathetic, *Shenmen*, Lung, Kidney, Liver	CIWA, BDI, STAI, EWL 60S	NR
Zhang et al, 2010, China[29]	64 participants; 40±4; CCMD-3-R	Drug plus EA	Drug plus placebo EA (non-specific points); drug: fluoxetine hydrochloride	GV20, *Yintang*	SCL-90, HAMD, HAMA	NR
Tong et al, 2015, China[30]	80 participants; 45.6; ICD-10	Drug plus acupuncture	Drug (naltrexone)	GV20, GV24, GB13, GB20	Average alcohol consumption, SF-36	Tess Scale (2nd, 4th, 6th week after treatment)
Zhang et al, 2014, China[31]	60 participants; 40.51±8.14/41.26±7.84; ICD-10	Drug plus EA	Drug (benzodiazepine)	LI4, ST36	SCL-90, PACS, HAMA	NR
Lee et al, 2015, Korea[32]	20 participants; 43.0±6.8/44.5±7.9; DSM-IV	Acupuncture	Placebo acupuncture (blunt needle)	KI9	Craving for alcohol (VAS)	No complaints or side effects
Bullock et al, 1987, USA[33]	54 participants; 42; self-made diagnosis	Acupuncture	Placebo acupuncture (non-specific points)	Ear *Shenmen*, Lung, Liver/Kidney/ Occiput, LI4, TE5	Completion rate, alcohol need, drinking episodes, admission to detoxification	NR
Worner et al, 1992, USA[34]	40 participants; 41.9±2.3/38.9±2.0; self-made diagnosis	Acupuncture	Sham acupuncture (non-penetrating)	LR3, ST36, TE5, LI4, GV20, plus ear *Shenmen*, Lung,	Completion rate, attendance at treatment	NR
Miao and Wu, 2015, China[35]	68 participants; 18–24; DSM-V	Acupuncture	Drug (disulfiram)	GV24, GB13	Craving for alcohol (VAS), drinking time and consumption	Fainting (2) after acupuncture, nausea (8) after drugs
Toteva and Milanov, 1996, Bulgaria[36]	118 participants; 32.3/34.5; DSM-IV	Acupuncture	Drug (benzodiazepines etc)	LI4, LI11, PC6, TE5, SI4, GB8, GB14, HT7, *Yintang*, *Taiyang*	Desire for alcohol, depressive symptoms, completion rate	NR

BDI, Beck Depression Inventory; CCMD, Classification and Diagnostic Criteria of Mental Disorders; CIWA, Clinical Institute Withdrawal Assessment; DSM, Statistical Manual of Mental Disorders; EA, electroacupuncture; EWL, Eigenschaftswoerterliste; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; ICD-10, International Classification of Diseases; NR, not reported; PACS, Penn Alcohol Craving Scale; SCL-90, Symptom Checklist-90-Revised; SF-36, Short Form Health Survey; STAI, State-Trait Anxiety Inventory.
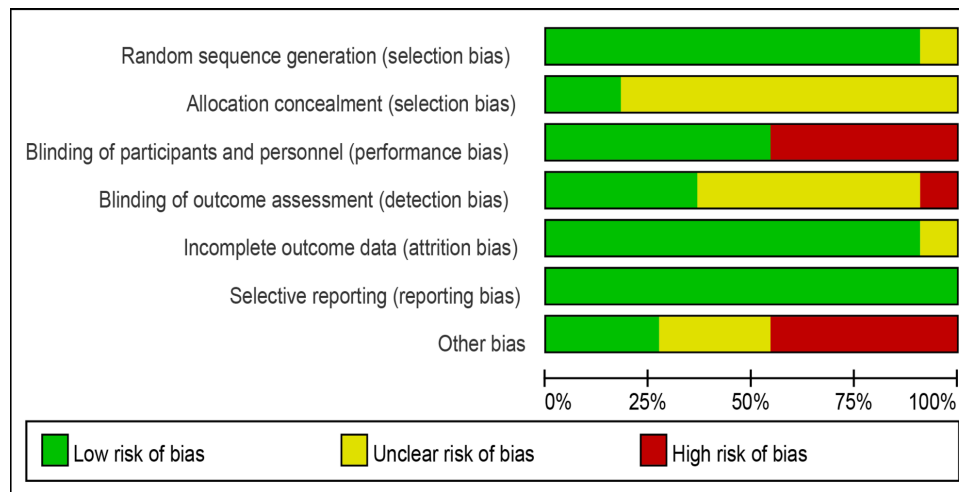
Figure 2 Risk of bias graph: the authors' judgement about each risk of bias item presented as a percentages across all included studies.

it while the other nine lacked evidence. Blinding of participants and acupuncturists was not possible by design in two studies[30 31] comparing acupuncture

Figure 3 Risk of bias summary: the authors' judgement about each risk of bias item for each included study.

plus drug versus drug, and two studies[35 36] comparing acupuncture versus drug; accordingly these trials were considered to be at high risk of performance bias. For blinding of outcome assessments, six studies lacked evidence and one study[33] was considered to be at high risk of detection bias, as the acupuncturist responded for assessments. In terms of incomplete data, one study[31] described dropouts during the treatment and follow-up period but did not describe specific methods of data analysis. We judged this as being at unclear risk for the lack of evidence. The other 10 studies were deemed low risk.

For other potential assessment biases, we judged one study[32] to be high risk due to the small sample size (20 participants) and four studies[26–28 33] to be high risk due to the selection of non-specific acupuncture points in the ear as a control intervention. Distances between traditional acupuncture points in the ear are extremely short, which may introduce bias with respect to the assessment of the specific effects of ear acupuncture. We judged one study[28] to be of unclear risk due to the needle type (0.3*0.3 mm and 0.2*0.15 mm) and two studies[29 31] to be of unclear risk for not describing the doses of drugs during treatment.

Synthesis of results

Acupuncture plus drug versus placebo acupuncture plus drug

Slight to no craving for alcohol

One study recorded 72 participants reporting 'slight to no craving for alcohol' in the follow-up period.[26] After 1 month, there was no difference between the acupuncture and sham acupuncture groups (RR 1.04, 95% CI 0.79 to 1.37).

Completion rates

Two studies with 337 participants comparing acupuncture with sham acupuncture (using non-specific acupuncture points) reported completion rates.[26 27] The results of a meta-analysis showed that there was no significant difference between acupuncture and

sham acupuncture (RR 1.10, 95% CI 0.93 to 1.30; $I^2=25\%$). The forest plot is presented in figure 4A.

Clinical Institute withdrawal assessment
One study with 34 participants compared acupuncture plus carbamazepine with sham acupuncture plus carbamazepine and found no significant difference in CIWA scores between the two groups.[28] However, there were fewer AWS signs in the acupuncture group on day 14 (p=0.045).

Symptom checklist-90
One study with 64 participants suggested that, compared with sham electroacupuncture plus fluoxetine, a combination treatment of electroacupuncture and fluoxetine was more effective at relieving symptoms, as quantified by SCL-90 (MD −3.05, 95% CI −3.63 to −2.47).[29]

Hamilton anxiety scale
The same study with 64 participants suggested that, in terms of mental health status, there was a greater improvement in HAMA scores in the electroacupuncture plus fluoxetine group compared with the sham electroacupuncture plus fluoxetine group (MD 4.00, 95% CI 3.30 to 4.70).[29]

Acupuncture plus drug versus drug
Average alcohol consumption
One study with 80 participants reported no difference between acupuncture plus naltrexone and naltrexone alone in the reduction of average alcohol consumption after treatment (MD −0.08, 95% CI −2.32 to 2.16).[30]

Symptom checklist-90-revised
One study with 60 participants suggested a significantly greater improvement with acupuncture plus diazepam over diazepam alone in terms of SCL-90-R scores (MD 6.90, 95% CI 5.51 to 8.29).[31]

Hamilton anxiety scale
The same study with 60 participants suggested a significantly greater improvement with acupuncture plus diazepam compared with diazepam alone in terms of HAMA scores (MD 4.04, 95% CI 1.51 to 6.57).[31]

Acupuncture versus placebo acupuncture
Craving for alcohol
One study with 20 participants reported that acupuncture at KI9 was effective at reducing alcohol craving.[32] The primary outcome was the VAS score, and the evaluation time points were at baseline and the first, second and fourth week after treatment. All results suggested acupuncture at KI9 was more effective than placebo acupuncture in reducing craving for alcohol in AWS patients (all p<0.01).

Slight to no craving for alcohol
One study recorded 54 participants reporting 'neutral or no craving for alcohol' during treatment.[33] After three phases of treatment, the result indicated favourable effects of acupuncture on reductions in craving for alcohol (RR 3.83, 95% CI 0.95 to 15.40).

Completion rate
Two studies with 94 participants comparing acupuncture with sham acupuncture reported completion rates.[33 34] The final results of the meta-analysis showed
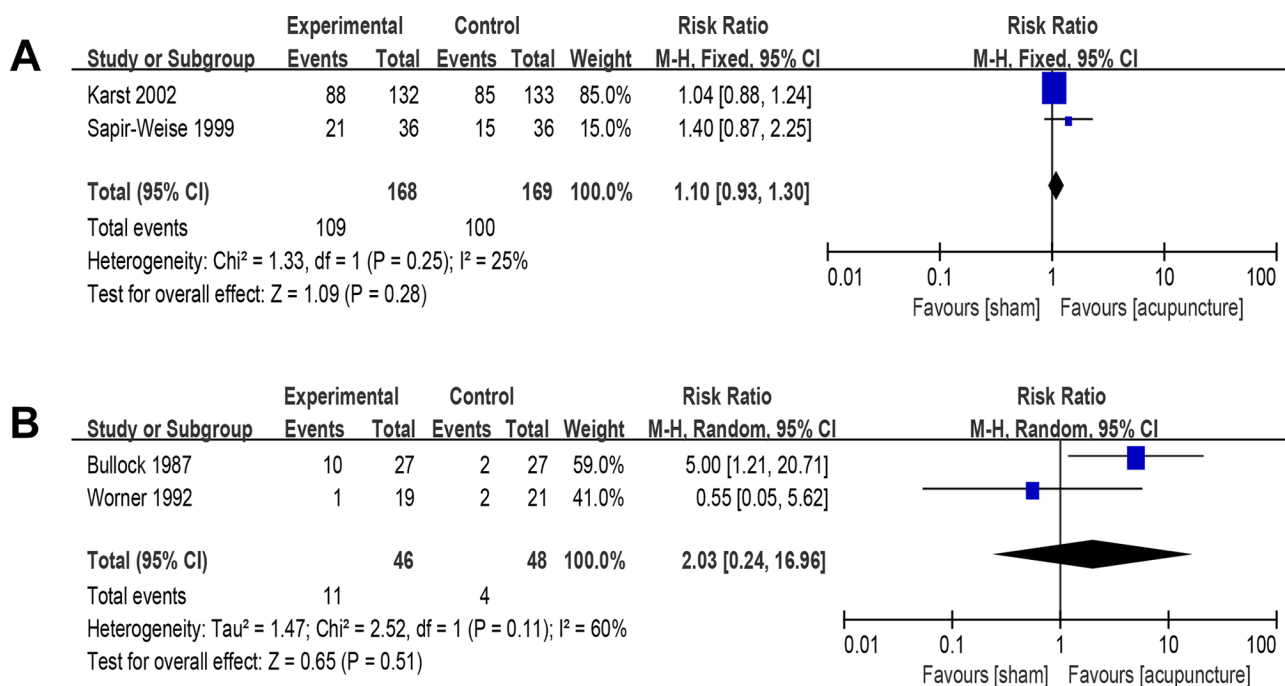

Figure 4 Forest plot of completion rate: (A) acupuncture plus drug versus sham acupuncture plus drug; (B) acupuncture versus sham acupuncture.

that there was no significant difference between acupuncture and sham acupuncture (using random effects model due to high heterogeneity: $I^2 = 60\%$; RR 2.03, 95% CI 0.24 to 16.96). The forest plot is presented in figure 4B.

Acupuncture versus drug
Visual analogue scale

One study with 68 participants tested the effects of acupuncture on college students with AWS.[35] The result suggested that disulfiram had an earlier effect than acupuncture with respect to the alleviation of withdrawal symptoms measured by VAS (MD −2.00, 95% CI −2.43 to −1.57); however, after 8 weeks, acupuncture was as effective as disulfiram treatment (there was no significant difference between the two groups).

Completion rates

One study with 118 participants compared acupuncture with benzodiazepine and set completion rates as an outcome. The results indicated no significant difference between the acupuncture group and benzodiazepine group (RR 0.18, 95% CI 0.06 to 0.56).[36]

Average alcohol consumption

One study with 68 participants reported the average alcohol consumption after a follow-up period of 3 months after treatment.[35] Twelve participants in the acupuncture group and 13 participants in the disulfiram group had stopped drinking (RR 0.87, 95% CI 0.47 to 1.62). There was no significant difference between the two groups.

Adverse effects

Three studies reported adverse effects. Tong *et al* used the Tess Scale to measure adverse effects.[30] After 6 weeks of treatment, there was no significant difference in adverse effects between the two groups (3.42±1.13 in treatment group vs 4.02±0.63 in control group). Lee *et al* reported no adverse effects associated with acupuncture in their trial.[32] In the study by Miao and Wu,[35] two participants in the acupuncture group fainted and eight participants in the disulfiram group complained of nausea. With proper rest and a reduction of dose or drug, the symptoms were relieved. No severe or intolerable adverse effects were reported.

DISCUSSION
Summary of evidence

This review describes the characteristics of RCTs that assessed the effects and safety of the use of traditional acupuncture to treat AWS. Eleven studies involving 875 participants were included. However, meta-analyses were hard to conduct because: (1) the types of measurements reported in the studies differed; and (2) the treatment and control groups in the studies varied greatly. Consequently, we evaluated the evidence in support of using traditional acupuncture for the alleviation of AWS symptoms mainly based on descriptive rather than quantitative analysis.

In the acute phase, participants received pharmacological treatment as a basic treatment and acupuncture as an adjunctive treatment. The results[26 27] demonstrated no difference between acupuncture and sham acupuncture in the reduction of craving for alcohol. However, the results suggested that acupuncture, when used as an adjunctive treatment, had a superior tendency to alleviate AWS symptoms.[26 28] In addition, five studies[26 28–31] confirmed that acupuncture tended to improve psychological symptoms in AWS patients. Both studies by Zhang *et al*[29 31] indicated acupuncture improved symptoms when quantified by SCL-90. Tong *et al*[30] indicated acupuncture improved mental health measured on the SF-36 scale and Karst *et al*[28] reported a weak tendency towards better performance of the acupuncture group with respect to State-Trait Anxiety Inventory (STAI) scores. Finally, Sapir-Weise *et al*[26] reported a stronger reduction of anxiety amongst women during treatment. Psychiatric conditions are relatively common in alcoholics, with an estimated prevalence of up to 65%.[37 38] Based on these findings, acupuncture could be used as an adjunctive treatment to alleviate anxiety symptoms.

In the protracted phase, acupuncture was used as the main intervention. Lee *et al* reported that acupuncture was superior to placebo acupuncture at reducing the craving for alcohol.[32] However, the sample size of 20 participants was too small to provide persuasive evidence and no follow-up assessment was performed. In a comparison of acupuncture and low-dose drugs, no difference was shown by Miao and Wu.[35] The subjects were college students in Sichuan Province, who have the advantages of age, educational background and a shorter period of addiction. Therefore, before strong conclusions can be drawn, the effects of acupuncture on AWS need to be further explored. Toteva and Milanov[36] demonstrated that depressive symptoms were significantly improved in the acupuncture group compared with the control group. Psychological symptoms were not mentioned in the other three trials.

In the literature assessments, we regarded trials of acupuncture plus drug versus drug[30 31] and acupuncture versus drug[35 36] as being at high risk of performance bias or detection bias due to challenges with blinding. The use of non-specific acupuncture points in the ear as a control intervention in several trials may have led to an overestimation of the effects of placebo acupuncture. Also, the needle type (0.3*0.3 mm) used by Karst *et al*[28] may have influenced manipulation, thereby reducing the effects of acupuncture. These design issues should be noted when planning future research.

Comparisons with previous studies

Cho *et al* conducted a systematic review (11 trials, 1110 participants) of acupuncture for the treatment of alcohol dependence in 2009 and the conclusion was equivocal.[16] Considering that: (1) psychiatric improvement was not included in the outcome assessment even though emotional regulation is important for the treatment of AWS; (2) clinical heterogeneity due to the inclusion of other forms of acupuncture (such as acupressure, non-penetrating acupuncture, laser acupuncture and transcutaneous electrical nerve stimulation) could potentially have clouded the results; and (3) in the past 7 years, many studies using more rigorous methods and more cautious reporting of conclusions have been published; we focused on traditional acupuncture and the formulation of more rigorous standards to explore the effects and safety of traditional acupuncture for the treatment of AWS.

Limitations

This review has some limitations. First, the varied outcome assessments inhibited data synthesis. Researchers used completion rate, average alcohol consumption and timing of repeat drinking as outcomes, even though a strong desire or compulsion to use alcohol is listed at the top of the ICD-10[39] for the diagnosis of alcohol dependence. Second, the sample sizes were insufficient to reach a robust conclusion. We attempted to formulate rigorous standards for trial inclusion to obtain a relatively reliable conclusion. However, the number of high quality studies published in relevant fields was inadequate. Third, males and females react differently to treatment.[39 40] The information in the available studies was insufficient for the exploration of differential effects of acupuncture according to gender. In addition, inadequate evidence of allocation concealment and the blinding of outcome assessors may have led to bias in some studies.

Conclusions

Our study demonstrates that there is no difference between acupuncture (plus drug) and sham acupuncture (plus drug) with regard to the primary outcome measure of craving for alcohol among participants with AWS, and no difference in completion rates (pooled results). There was limited evidence from individual trials that acupuncture may reduce alcohol craving in the protracted phase and help alleviate psychological symptoms; however, given concerns about the quantity and quality of included studies, further large-scale and well-conducted RCTs are needed to confirm our findings and support implementation of within the clinical practice of acupuncture for AWS in clinical practice.

REFERENCES

1 Lim SS, Vos T, Flaxman AD, *et al*. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380:2224–60.

2 National Institute on Alcohol Abuse and Alcoholism. Global Burden. http://www.niaaa.nih.gov/alcohol-health/special-populations-cooccurring-disorders/older-adults

3 World Health Organization (WHO). Global Status Report on Alcohol and Health, 2014. http://www.who.int/substance_abuse/publications/global_alcohol_report/msb_gsr_2014_1.pdf

4 Dissanaike S, Halldorsson A, Frezza EE, *et al*. An ethanol protocol to prevent alcohol withdrawal syndrome. *J Am Coll Surg* 2006;203:186–91.

5 Schmidt KJ, Doshi MR, Holzhausen JM, *et al*. Treatment of severe alcohol withdrawal. *Ann Pharmacother* 2016;50:389–401.

6 Schuckit MA. Recognition and management of withdrawal delirium (Delirium Tremens). *N Engl J Med Overseas Ed* 2014;371:2109–13.

7 Carlson RW, Kumar NN, Wong-Mckinstry E, *et al*. Alcohol withdrawal syndrome. *Crit Care Clin* 2012;28:549–85.

8 Rudd A, Stewart S, Bakker A, *et al*. *Alcohol Use Disorders: Diagnosis and Clinical Management of Alcohol-Related Physical Complications*: Royal College of Physicians, 2010.

9 Bullock ML, Culliton PD, Olander RT. Controlled trial of acupuncture for severe recidivist alcoholism. *Lancet* 1989;1:1435–9.

10 Overstreet DH, Cui CL, Ma YY, *et al*. Electroacupuncture reduces voluntary alcohol intake in alcohol-preferring rats via an opiate-sensitive mechanism. *Neurochem Res* 2008;33:2166–70.

11 Zhang Y, Cai XH, Zhang RJ, *et al*. Acupuncture regulates the unfolded protein response and inhibits apoptosis in a rat model of heroin relapse. *Acupunct Med* 2016;34:441–8.

12 Zhao ZL, Zhao GW, Li HZ, *et al*. Acupuncture attenuates anxiety-like behavior by normalizing amygdaloid

catecholamines during ethanol withdrawal in rats. *Evid Based Complement Alternat Med* 2011;2011:1–8.

13 Zhao Z, Kim SC, Zhao R, *et al*. The tegmental-accumbal dopaminergic system mediates the anxiolytic effect of acupuncture during ethanol withdrawal. *Neurosci Lett* 2015;597:143–8.

14 Brewer C. Second-line and 'alternative' treatments for alcohol withdrawal: alpha-agonists, beta-blockers, anticonvulsants, acupuncture and neuro-electric therapy. *Alcohol Alcohol* 1995;30:799–803.

15 Tang YL, Hao W, Leggio L. Treatments for alcohol-related disorders in China: a developing story. *Alcohol Alcohol* 2012;47:563–70.

16 Cho SH, Whang WW. Acupuncture for alcohol dependence: a systematic review. *Alcohol Clin Exp Res* 2009;33:1305–13.

17 Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.

18 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Washington, DC: APA, 1987, 2000, 2013.

19 World Health Organization. *The ICD-10 Classification of Metal and Behavioral Disorders: Clinical Descriptions and Diagnostic Guidelines*, 1992.

20 Psychiatry Branch of the Chinese Medical Association. *Classification and Diagnostic Criteria of Mental Disorders. 3rd text version (CCMD-3-R)*. Jinan: Shandong Science and Technology Press, 2001.

21 Stuppaeck CH, Barnas C, Falk M, *et al*. Assessment of the alcohol withdrawal syndrome--validity and reliability of the translated and modified Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-A). *Addiction* 1994;89:1287–92.

22 Derogatis LR. *SCL-90-R: Administration, Scoring, and Procedures Manual*. 3rd ed. Minneapolis: National Computer Systems, Inc, 1994.

23 Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol* 1959;32:50–5.

24 Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions, 2009. Version 5.0.2. http://handbook.cochrane.org/

25 Deeks JJ, Higgins JPT, Altman DG. Analysing data and undertaking meta-analysis. In: Higgins JPT, Green S, *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*: The Cochrane Collaboration, 2011. Updated Mar 2011. www.cochrane-handbook.org (accessed Jun 2014).

26 Sapir-Weise R, Berglund M, Frank A, *et al*. Acupuncture in alcoholism treatment: a randomized out-patient study. *Alcohol Alcohol* 1999;34:629–35.

27 Bullock ML, Kiresuk TJ, Sherman RE, *et al*. A large randomized placebo controlled study of auricular acupuncture for alcohol dependence. *J Subst Abuse Treat* 2002;22:71–7.

28 Karst M, Passie T, Friedrich S, *et al*. Acupuncture in the treatment of alcohol withdrawal symptoms: a randomized, placebo-controlled inpatient study. *Addict Biol* 2002;7:415–9.

29 Zhang YH, Zhang RG, Chen YC, *et al*. Observation on therapeutic effect of electro-acupuncture for treatment of emotional disturbance of patients with alcohol dependence syndrome in hospital. *Med J Chin People's Health* 2010;22:1197–8.

30 Tony X, Zhao FZ, Tong ZL. Clinical observation on combination of acupuncture and medicine treating with alcohol withdrawal syndrome. *J Clin Acupuncture and Moxibustion* 2015;31:24–5.

31 Zhang QF, Zhang L, Han HY, *et al*. Clinical effect of electro-acupuncture for patient with alcohol withdrawal syndrome. *Med J Chin People's Health* 2014;26:13–15.

32 Lee JS, Kim SG, Jung TG, *et al*. Effect of Zhubin (KI9) acupuncture in reducing alcohol craving in patients with alcohol dependence: a randomized placebo-controlled trial. *Chin J Integr Med* 2015;21:307–11.

33 Bullock ML, Umen AJ, Culliton PD, *et al*. Acupuncture treatment of alcoholic recidivism: a pilot study. *Alcohol Clin Exp Res* 1987;11:292–5.

34 Worner TM, Zeller B, Schwarz H, *et al*. Acupuncture fails to improve treatment outcome in alcoholics. *Drug Alcohol Depend* 1992;30:169–73.

35 Miao MM, Wu JM. Effect of acupuncture combined with auricular point pressing therapy in the treatment of college student alcohol dependence. *Clini J Trad Chin Med* 2015;27:1283–5.

36 Toteva S, Milanov I. The use of body acupuncture for treatment of acupuncture dependence and withdrawal syndrome: a controlled study. *Am J Acupunct* 1996;24:19–25.

37 Hall W, Zador D. The alcohol withdrawal syndrome. *The Lancet* 1997;349:1897–900.

38 Schuckit MA. Comorbidity between substance use disorders and psychiatric conditions. *Addiction* 2006;101(Suppl 1):76–88.

39 Schuckit MA. Alcohol-use disorders. *Lancet* 2009;373:492–501.

40 Yeo S, Rosen B, Bosch P, *et al*. Gender differences in the neural response to acupuncture: clinical implications. *Acupunct Med* 2016;34:364–72.