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Acupuncture for treatment of anxiety, an overview of systematic reviews

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ABSTRACT

Purpose: To evaluate the methodological quality and summarize evidence of important outcomes of systematic reviews (SRs)/Meta analyses (MAs) of acupuncture for anxiety.

Methods: We conducted a comprehensive literature search for SRs/MAs in PubMed, EMBASE, Cochrane library, Chinese Biomedical Databases (CBM), Wanfang database and China National Knowledge Infrastructure (CNKI) until November 30, 2018. Three reviewers independently extracted data and assessed the methodological quality of the reviews according to the Assessing the Methodological Quality of Systematic Reviews 2 (AMSTAR-2), the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) was used to rate the quality of evidence. In the pre-experiment, we used the intra-class correlation coefficient (ICC) to assess reviewer agreement, the ICC value for overall score was 0.978.

Results: Ten reviews were included. The assessment results of AMSTAR-2 showed that the methodological quality of all included studies was critically low. The lowest score were item "provide a list of excluded studies and justify the exclusions" and item "report sources of funding for the included studies", none of studies provided information about the above two items, followed by the "providing a priori design" item with only two (20%) studies conforming to this item. For GRADE, of the 7 outcomes, high quality evidence was provided in only 1 (14.3%), moderate in 2 (28.6.7%), and low in 4 (57.1%).

Conclusion: Although most of the included reviews indicated that acupuncture group was more effective than control group in the treatment of anxiety, more importantly, the methodological quality of the included reviews and the quality of evidence were low. More high-quality evidence is needed to determine whether acupuncture is more effective than other treatments.

1. Introduction

Anxiety ranks in the top ten causes of disability worldwide and is the most prevalent psychiatric condition in the European Union with over 60 million people being affected by this condition [1] it has been reported to contribute substantially to the Global Burden of Disease as stated in the 2015 report (GBD 2015).[2]

Pharmacotherapy and psychotherapy are conventional treatments for anxiety, and pharmacotherapy has always been considered the standard treatment [3] Nonetheless, pharmacotherapy is not free from concern since they can lead to habituation (especially in long-term treatments), and present side effects and drug interactions, among other problems [4,5] Therefore, there is a need for more effective, safer interventions for anxiety. This has led to an increase in the attention

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received by complementary and alternative interventions such as acupuncture, which is the most widely used of such approaches.[6] Patients benefit from the lack of side effects and relatively low cost involved in acupuncture.[7]

Some randomized clinical trials (RCTs) investigated acupuncture or acupuncture combined other treatments in anxiety and anxiety disorders.[8–10] However, most studies have been small and the overall results have remained mixed or inconclusive. Several systematic reviews (SRs) and meta-analyses (MAs)[11–13] have been conducted to reveal the effectiveness and safety of acupuncture for the treatment of anxiety. This form of evidence is more comparable than individual trial data, as it uses similar outcome measures (pooled effect sizes, such as standardized mean differences or risk ratios), derived from all randomized clinical trials, and can be systematically reviewed for the risk of bias. However, the quality of these SRs and MAs has not been evaluated, which is an indispensable step before treatment recommendations can confidently be made.

The current study aimed to fill these gaps in the literature. We performed an overview of SRs/MAs to (1) evaluate the methodological quality of these SRs/MAs using AMSTAR-2, (2) rate the quality of evidence of important outcomes from included SRs/MAs using the GRADE approach and (3) summarize the conclusions of these SRs/MAs.

2. Material and methods

The overview was conducted according to the Cochrane handbook.[14] Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement as well as some high quality methodological articles.[15,16]

2.1. Search strategy

We conducted a computer-based search without language restrictions. Using PubMed, EMBASE, Cochrane library, Chinese Biomedical Databases (CBM), Wanfang database and China National Knowledge Infrastructure (CNKI) until November 30,2018, to find SRs/MAs of any type acupuncture or acupuncture combined with other treatments or acupressure for anxiety and anxiety disorders using the following search terms: (“anxiety” OR “anxiety disorders” OR “anxiousness” OR “angst”) AND (“acupunct*” OR “acupress*” OR “acupoint*” OR “electroacupunct*” OR “electro-acupunct*” OR “auriculotherap*” OR “auriculoacupunct*” OR “moxibust*”) AND (“systematic review” OR “meta-analysis”). Reference lists of included reviews and pertinent reviews were hand-searched for additional relevant meta-analyses.

2.2. Inclusion and exclusion criteria

The SRs/MAs of RCTs about acupuncture for anxiety or anxiety disorders were included. Subjects included should be diagnosed as anxiety or anxiety disorders, no restrictions on gender, age, race, onset time and source of cases. Treatment group intervention: acupuncture therapy (such as acupuncture, electro-acupuncture, auricular acupuncture, body acupuncture, etc.) or acupuncture combined with other therapies or acupressure treatment; Control group intervention: comfort therapy (placebo, pseudo-acupuncture or blank control), other therapies (Western medicine, traditional Chinese medicine or non-drug therapy, etc.).

Literature on non-major intervention of acupuncture in the treatment group or literature on acupuncture as an intervention in the control group, repeated publication, comments, meeting abstracts, and studies on which the data could not be extracted were all excluded.

2.3. Literature screening and data extraction

All the retrieved articles were imported into the EndNote X7 software and the duplicate publications were excluded. Then three authors (MX-L, YQ-X and WB-H) independently screened and extracted data. SRs/MAs were excluded if they did not meet the inclusion criteria, first at the title/abstract level, and later at the methods section level if necessary. Disagreements were resolved through discussion and consensus, or by consulting a fourth member (L-Y) of the review team.

According to the characteristics of the selected documents, we extracted the following basic information: the first author, publication year, Country, number of included studies, sample size, treatment interventions, control interventions, quality assessment methods, outcomes and main conclusions of each included article.

2.4. Quality assessment

The quality of included reviews was evaluated by three authors (MX-L, WB-H and M-W) independently using AMSTAR-2 tool, which contains 16 items, among which seven are critical domains. AMSTAR-2 items may not only be able to give an overall score,[17] but also an overall rating based on weaknesses in critical domains. Moreover, AMSTAR-2 classifies the overall confidence of the results of the review into four levels: high, moderate, low, and critically low, and the evaluation option is reduced to three options, “Yes”, “Partial Yes” and “No”.[18] In this study, the total AMSTAR score was calculated by summing 1 point for each “Yes”, 0.5 points for each “Partial Yes” and 0 point for each “No”, resulting in summary scores from 0 to 16. Discrepancies between reviewers were resolved by discussion or by a fourth reviewer (L-Y) in cases when a consensus was not reached.

We used the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) system[19] to assess the quality of evidence associated with specific outcomes. Assessment of the quality of evidence considers five aspects: limitations, inconsistencies, indirectness, inaccuracy, and publication bias.[14,20]

2.5. Assessment of reviewer agreement

To assess the consistency of quantitative measurements in the pre-experiment, the intra-class correlation coefficient (ICC) was used. In brief, three reviewers independently assessed the quality of eligible SRs/MAs. The ICC value for overall score was 0.978.

3. Results

3.1. Study selection

The literature search yielded 252 reports, of which 41 were excluded because of duplication, and 182 were excluded on the basis of title or abstract that was irrelevant to the topic, and 19 were excluded from the remaining 29 articles after reading the full text. Therefore, 10 SRs/Mas[11,21–29] were included in this overview. The PRISMA flow chart of literature studies for SRs/MAs is illustrated in Fig. 1.

3.2. Characteristics of included studies

The characteristics of the included reviews are summarized in Table 1. All articles were published between 2007 and 2018, including 5 articles[22,26–29] from China, 2[21,24]from UK, 1[25] from US, 1[23]from South Korea and 1[11] from Portugal. 7 SRs/MAs (70%)[11,21–26] were published in English and the remaining three (30%)[27–29] were published in Chinese, and all SRs/MAs included RCTs.

Five reviews [21–2326,29] used Cochrane risk of bias criteria to evaluate the quality of literature, one review[27] used Jadad scale, one[25] used Quality Score for Acupuncture Trials (QSAT),one[24] used criteria recommended by the National Health Service (NHS) Centre for Reviews and Dissemination. Two[11,28] did not assess the risk of bias of included studies. The number of studies included in each SR/MA ranged from 3 to 14 and the total participants ranged from 207 to 1232. The intervention measures were mostly acupuncture therapy (AT), auricular

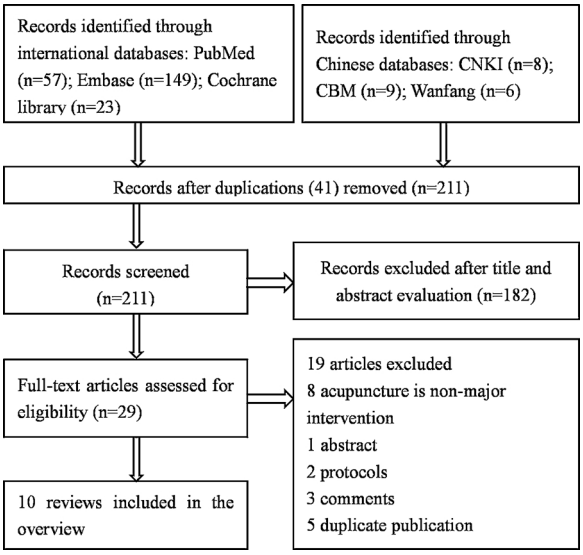

Fig. 1. Flow chart of the literature search and study selection process.

acupuncture (AA), body acupuncture (BA), manual acupuncture(MA), laser acupuncture(LA) or electro-acupuncture (EA) in the treatment group and drugs, sham AT, no treatment or placebo in the control group.

3.3. Effectiveness of Acupuncture for anxiety and anxiety disorders

A total of four MAs[21,22,25,26] reported pooled results of AT versus sham acupuncture. Their results showed that the effect of acupuncture on anxiety is controversial. A meta-analysis (6RCTs)[21] compared acupuncture to placebo/sham acupuncture using the (80-point) State-Trait Anxiety Inventory (STAI) score, they found a clinically irrelevant and non-significant reduction (mean differences (MD) = −1.54, 95% CI − 4.73 to 1.64). However, Doreen et al[22] combined results of the five trials showed a greater overall reduction in anxiety in the acupuncture group than in the sham controls (standardized mean differences (SMD) = −1.11; 95% CI − 1.61 to −0.61). The other two reviews[25,26] concluded that acupuncture seems to be an effective approach in relieving anxiety, and placebo effects may partially contribute to the benefits. All of them mentioned that there is currently insufficient research evidence for firm conclusions to be drawn.

One review[23] focused on AT versus non treatment. Results showed that acupuncture interventions led to greater reductions in preoperative anxiety relative non treatment (STAI score, MD = 5.63, $p < 0.00001$, 95%CI 4.14-–7.11, 14RCTs).

Three reviews[27–29] compared EA with conventional treatment or drug treatment on the effectiveness on anxiety. All showed higher overall efficacy in the EA group, Luo et al[27] pooled OR = 1. 98, 95%CI (1. 10, 3. 55), p = 0.02, $I^2 = 0$, 5 RCTs).

Two reviews[11,24] had no restrictions on control measures, they just summarized the treatment intervention and control measures of their included studies. They concluded that there is good scientific evidence encouraging acupuncture therapy to treat anxiety disorders as it yields effective outcomes, with fewer side effects than conventional treatment.

3.4. Methodological quality of systematic reviews

The results of AMSTAR-2 assessment are given in Table 2. AMSTAR-2 score showed that all included SRs/MAs were critically low-quality, the key factors affecting the quality of the literature included item 2 (just 2 reviews[25,26] contained an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol), item 7(none of studies provided a list of excluded studies and justify the exclusions) and item 10(none of the studies reported on the sources of funding for the studies included in the review).

3.5. GRADE evidence quality classification

The 10 SRs/MAs included 7 outcomes related to the effectiveness of acupuncture for anxiety, we did not include the descriptive analysis of individual outcome indicators. The results of GRADE evaluation showed that 2 (2/7, 28.6%) outcomes provided moderate quality evidence, 4 (4/7, 57.1%) provided low quality evidence (Table 3), 1 (1/7, 14.3%) provided high quality evidence. Risk of bias (n = 5, 71.4%) was the most common of the downgrading factors in the included reviews, followed by inconsistency (n = 3, 42.9.6%), publication bias (n = 2, 28.6%), imprecision(n = 0, 0.0%)and indirectness (n = 0, 0.0%).

4. Discussion

The number of SRs/MAs of acupuncture for anxiety is increasing annually. The purpose of this overview was to evaluate the methodological quality and quality of evidence from published SRs/MAs and to provide an evidence-based assessment and an objective summary on the effectiveness of acupuncture for anxiety.

To our knowledge, this overview of meta-analyses is the first one to systematically evaluate the SRs/MAs of acupuncture treatment of anxiety. Our overview included 10 SRs/MAs, published in 2007–2018, the number of studies included in each SR/MA ranged from 3 to 14 and the total participants ranged from 207 to 1232. We found most of the included reviews concluded that acupuncture was more effective than other therapies on treatment of anxiety, however, the overall methodological quality of the included reviews was critically low, the quality of evidence for the reported outcomes was also low. We downgraded quality of evidence by one or two levels for the following reasons: serious risk of bias and inconsistency of results.

It is worth noting that although most of included reviews indicated that acupuncture seems to be an effective approach in relieving anxiety, most of them did not wish to draw firm conclusions due to the small size of the included trials or their low methodological quality. Therefore, in future, more high-quality randomized trials or MAs are needed to determine whether acupuncture or its combination therapies is more effective than other treatments.

Assessment of various aspects of the methodological quality of the included SRs/MAs using the AMSTAR-2 tool revealed common areas for improvement. For item 2(whether a protocol was established prior to the conduct of the review), only two studies provided a clear a priori design, therefore, publications may be duplicated if the inclusion criteria and exclusion criteria are only indicated in the text. Consequently, inaccurate inclusion or exclusion of clinical trials evidence from systematic reviews can result in following inaccurate recommendations in clinical practice[30–32]. For items 7, all included reviews did not provide a list of excluded studies, it may influence reliability of the results. In order to ensure transparency, a potentially relevant study that does not qualify for inclusion should provide a list and give specific reasons for exclusion.[33]For item 10, none of the ten studies reported on the sources of funding for the included studies in their review. Providing sources of funding are important to avoid other bias, since the results of the research considering corporate funding are more biased towards the funder, the results of the study are less likely to be published, so the fund information included in the study can be used to judge the impact on the research results.[34]

In addition, search of gray literature, assess the likelihood of publication bias and heterogeneity were also not adequately reported or conducted. The exclusion of gray literature from SRs may introduce bias and undermine the validity, which can result in overestimation of an intervention effect by an average of 12% [35] Thus, to avoid publication bias, gray literature without language and nationality

Table 1
Characteristics and categorization of the included reviews.

First Author; year	Country	Number of included trials	Sample size	Treatment Intervention	Control Intervention	Quality assessment tools	Overall conclusions
Amorim[11] 2018	Portugal	13	1232	BA; AA; EA	No restrictions	NR	There is good scientific evidence encouraging acupuncture therapy to treat anxiety disorders as it yields effective outcomes, with fewer side effects than conventional treatment.
Allan[21] 2018	UK	6	800	AT;AT + CT	Placebo; No treatment;	Cochrane criteria	There is limited evidence from two good quality trials that auricular acupuncture can achieve a significant and clinically meaningful reduction of anxiety in dental patients when compared with a sham/placebo control.
Au[22] 2015	China	5	314	Acupressure	SA; ST	Cochrane criteria	Acupressure seems to be effective in providing immediate relief of pretreatment anxiety among adults, and has a medium effect size.
Bae[23] 2014	Korea	14	1034	AT	No treatment; Placebo	Cochrane criteria	Acupuncture therapy aim in gat reducing preoperative anxiety has a statistically significant effect relative to placebo or non treatment conditions.
Pilkington[24]2007	UK	12	1103	AA; EA; Acupressure	No restrictions	NHS criteria	Positive findings are reported for acupuncture in the treatment of anxiety disorder or anxiety
Sniezek[25] 2013	US	6	605	MA; EA; LA	SA; Drugs	QSAT	There is high-level evidence to support the use of acupuncture for treating major depressive disorder in pregnancy.
Wang[26] 2016	China	11	1073	MA; EA; Acupressure	SA; ST	Cochrane criteria	AT seems to be an effective approach in relieving depression and anxiety in cancer patients
Luo[27] 2012	China	5	372	EA	Usual care; Drugs	Jadad score	Acupuncture therapy was more effective than drugs therapy for treatment anxiety
Ma[28] 2007	China	6	673	EA	Usual care; Drugs	NR	Acupuncture therapy was more effective and without side effects than drugs therapy for treatment anxiety, more randomized controlled trials are needed to confirm this.
Yue[29] 2009	China	3	207	EA	Usual care; Drugs	Cochrane criteria	Compared with drug therapy, acupuncture therapy for generalized anxiety disorder may be equally effective and safe. However, due to the poor quality of clinical trial methodology, high-quality trials are still needed

MA: manual acupuncture; EA: electro-acupuncture; BA: body acupuncture; AA: auricular acupuncture; AT: acupuncture therapy; CT: conventional therapy; LA: laser acupuncture; SA : sham acupuncture; ST: standard treatment.

Table 2
Critical appraisal of studies included, through using the AMSTAR-2 tool.

Included studies	AMSTAR-2																Overall
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	**quality**
Amorim[11] 2018	1	0	1	1	0	0	0	1	0	0	0	0	0	0	0	1	CL
Allan[21] 2018	1	0	0	1	1	0	0	1	1	0	1	0	1	0	1	1	CL
Au[22] 2014	1	0	1	1	1	1	0	0.5	1	0	1	0	1	0	0	0	CL
Bae[23]2014	1	0	1	1	1	0	0	1	1	0	1	1	0	1	1	1	CL
Pilkington[24] 2007	1	0	1	1	1	1	0	1	1	0	0	1	1	0	0	0	CL
Sniezek[25] 2013	1	1	1	1	1	0	0	0.5	1	0	0	0	0	0	0	1	CL
Wang[26] 2015	1	1	0	1	1	0	0	1	1	0	1	0	0	1	1	1	CL
Luo[27] 2005	1	0	0	0.5	0	1	0	0	1	0	1	0	1	1	0	0	CL
Ma[28] 2007	1	0	0	0.5	0	0	0	0.5	0	0	1	0	0	0	0	0	CL
Yue[29] 2009	1	0	0	0.5	0	1	0	0.5	1	0	0	0	1	0	0	0	CL
Number of 1(%)	10(100)	2(20)	5(50)	7(70)	6(60)	4(40)	0(0)	5(50)	8(80)	0(0)	6(60)	34(100)	5(50)	3(30)	3(30)	5(50)	

1: Yes; 0.5: partial Yes; 0: No; CL: Critically low; L: Low; H: High.
Q1: Did the research questions and inclusion criteria for the review include the components of PICO?
Q2: Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?
Q3: Did the review authors explain their selection of the study designs for inclusion in the review?
Q4: Did the review authors use a comprehensive literature search strategy?
Q5: Did the review authors perform study selection in duplicate?
Q6: Did the review authors perform data extraction in duplicate?
Q7: Did the review authors provide a list of excluded studies and justify the exclusions?
Q8: Did the review authors describe the included studies in adequate detail?
Q9: Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?
Q10: Did the review authors report on the sources of funding for the studies included in the review?
Q11: If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?
Q12: If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?
Q13: Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?
Q14: Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?
Q15: If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?
Q16: Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?.

Table 3
Quality of evidence in included systematic reviews with GRADE.

First author; year	Outcomes	Included RCTs (patients)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Quality of evidence
Allan[21] 2018	STAI score	2(249)	Serious[a]	Not serious	Not serious	Not serious	Not serious	Moderate
	STAI score	1(182)	Serious[a]	Not serious	Not serious	Not serious	Not serious	Moderate
Au[22] 2014	VAS score	5(314)	Not serious	Serious[b]	Not serious	Not serious	Serious[c]	Low
Bae[23] 2014	STAI score	7(378)	Not serious	Not serious	Not serious	Not serious	Not serious	High
	VAS score	5(283)	Serious[a]	Serious[b]	Not serious	Not serious	Not serious	Low
Wang[26] 2015	HADS score	2(137)	Serious[a]	Serious[b]	Not serious	Not serious	Not serious	Low
Luo[27] 2005	Effectiveness	5(372)	Serious[a]	Not serious	Not serious	Not serious	Serious[c]	Low

HADS: Hospital Anxiety and Depression Scale; STAI: State Trait Anxiety Inventory; VAS: visual analogue scale.
[a] The design of the experiment with a large bias in random, distributive hiding or blind.
[b] The confidence interval overlaps less, the heterogeneity test P is very small, and the I^2 is larger.
[c] Fewer studies are included and there may be greater publication bias.

limitations should be researched in addition to all relevant literature published both at home and abroad.

The GRADE system was used to classify the evidence quality of the included SRs/MAs. We found that the most of the evidence quality grades were low, only 1 (1/7, 14.3%) outcome provided high quality evidence. Most of the outcome indicators were demoted because of the limitations caused by bias in random, distributive hiding or blind. Through further analyzed, we found that the limitation in this respect was mainly due to the particularity of acupuncture therapy, which cannot be blind to patients. Therefore, future studies should pay more attention to above aspects, and avoid the risk of bias.

5. Strengths and limitations

This overview is the first study to assess the methodological quality of SRs/MAs using the AMSTAR and GRADE approach to evaluate the quality of evidence for the efficacy of acupuncture in anxiety patients, and in order to ensure the reliability of our evaluation results, we used ICC to assess reviewer agreement.

However, our study has some limitations. First, we did not re-extract data from original research, although this was outside the scope of our review, which aimed to describe available evidence from already published systematic reviews. Second, there was a significant paucity in high quality studies, most of the included reviews had a small sample size and a low quality, which could be challenged regarding results interpretation.

6. Conclusion

Most of the included reviews suggested that the acupuncture group was more effective than traditional medicine and sham acupuncture in the treatment of anxiety, nevertheless, the results of this study showed

that the methodological quality of most of the included reviews and the quality of evidence were low, more high-quality randomized trials and MAs are needed to determine whether acupuncture is more effective than other treatments.

Conflict of interest

The authors declare that they have no conflict of interest.

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