



Acupuncture methods put to the test for a tinnitus study: A Bayesian analysis

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ABSTRACT

Background: This study evaluated the effectiveness of different methods of acupuncture in the treatment of tinnitus due to neurological causes. In total, eight treatment methods were selected for this study: traditional acupuncture, electroacupuncture, moxibustion acupuncture, medicine only without acupuncture, traditional acupuncture with supplementary medicine, electroacupuncture with supplementary medicine, moxibustion acupuncture with supplementary medicine, and an electroacupuncture and moxibustion acupuncture combination. All sample data come from the results of clinical treatment studies.

Methods: Both Chinese- and English-language online databases were searched. The Chinese language databases included the Wanfang database, the China National Knowledge Infrastructure (CNKI) database, and the VIP Chinese Science and Technique Journals database. The English language databases included PubMed, Web of Science, Embase and Cochrane Library. After the previously mentioned eight interventions for the treatment of neurological tinnitus were tested in a randomized controlled trial (RCT), the data were extracted, and the effectiveness of each intervention was evaluated. A meta-analysis was performed using Stata14.0 and GeMTC 0.14.3 statistical software.

Results: A total of 40 studies were included, which contained a total of 3657 patients and 8 intervention methods. There was a trend of greater effectiveness of moxibustion acupuncture, followed by moxibustion acupuncture combined with electroacupuncture, moxibustion acupuncture combined with supplementary medicine, acupuncture combined with drugs, electroacupuncture with supplementary medicine, electroacupuncture, traditional acupuncture, and medicine only without acupuncture. There was no significant difference between the results of indirect comparisons and direct comparisons.

Conclusions: Eight interventions are all effective in the treatment of neurological tinnitus, but moxibustion acupuncture seems to be a better trend treatment for tinnitus.

1. Introduction

Tinnitus is an auditory phantom sensation (ringing of the ears) experienced when no external sound is present. Most but not all cases are associated with hearing loss induced by exposure to a prolonged noise environment or by ageing. Currently, no treatments have been proven capable of eliminating tinnitus itself,¹ but there are still possible treatment options. Intratympanic dexamethasone injection (ITDI) is one of the potential treatment options,² and psychological interventions that reduce anxiety and depression associated with tinnitus are reported by patients to be beneficial, despite the tinnitus sensation itself normally still being persistent.³ However, these medicines have multiple side effects, so tinnitus treatment has always been a medical challenge.

As a complementary or alternative therapy for tinnitus, acupuncture

has been recommended to alleviate the symptoms of subjective tinnitus in some patients.⁴ Animal and human studies have shown that the stimulation of acupuncture at certain points leads to alterations in the release of neurotransmitters, such as serotonin, oxytocin and endorphins, through the central nervous system (CNS). Furthermore, functional MRI has shown changes in blood circulation in different parts of the brain caused by acupuncture stimulation.⁵ There are many types of acupuncture, including traditional acupuncture, moxibustion acupuncture, electroacupuncture, and acupuncture with supplementary medicine. Many studies have attempted to conduct research on therapeutic results. However, there is still an insufficient number of meta-analyses on the therapeutic effects in studies with large sample sizes; thus, patients still have too little information about which method works best for their own cases. We found that many systematic reviews

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have investigated acupuncture for the treatment of tinnitus,^{6–8} but those research papers only compare their own therapeutic results against their own targeted treatments. There is no meta-analysis that compares the therapeutic results of different acupuncture methods; therefore, in this paper, we conducted a comparative study of the therapeutic effects of different acupuncture methods to provide better guidelines for physicians to select the most effective treatment on a clinical level. Thus, the purpose of this systematic review was to critically evaluate the current evidence from RCTs on the use of different acupuncture methods in patients with tinnitus.

2. Methods

2.1. In search of strategies

We performed a systematic search for published RCTs. The languages of the trials were limited to either English or Chinese, but there were no restrictions on publication year or publication status. The date of the search was from the inception of online databases until 26 November 2017. The databases were searched electronically. Chinese language databases included Wanfang data, CNKI database, and VIP Chinese Science and Technique Journals database. English language databases included PubMed, Web of Science, Embase and Cochrane Library. Manual searches were also used for collecting papers. The Chinese search keywords included the following: “traditional acupuncture”, “electroacupuncture”, “moxibustion acupuncture”, and “medicine”. The English search keywords included the following: “acupuncture”, “acupuncture and drugs”, “electroacupuncture”, and “moxibustion acupuncture”. The search strategy for PubMed is described in the supplementary information. Similar search terms were adopted for the other databases.

2.2. Data inclusion standards

Studies were included based on the following criteria: (1) the study must be a controlled clinical trial (CCT), and the initially diagnosed symptom should be tinnitus; (2) the interventions administered in the experimental group of the original study were traditional acupuncture, electroacupuncture, moxibustion acupuncture, a combination of any two of these methods, or a combination of any of these methods with any extra medicine; additionally, the interventions for the control group were medicine or acupuncture therapy that differed from that of the treatment group; (3) the study must have an acceptable public health recovery result, and the result could be quantified; (4) the study must have a statistical result; (5) the study must have a sample size of more than 20 cases; and (6) the study must allow full access to its content, with languages limited to Chinese and English.

2.3. Data exclusion standards

The following studies were excluded; (1) studies that have identified tinnitus with a clear cause, for instance, physical injury and nerve damage; (2) studies that have no RCT experiments; (3) studies in which no acupuncture is the dominant treatment method for patients; (4) studies that have no statistical data or data that could not be extracted; and (5) studies that have low readability or trustworthiness.

2.4. Literature screening and data extraction

The first step in the screening of studies is to use Endnote to exclude duplicates. The next step is to have two independent reviewers read the full text of rescreening studies to include or exclude data according to data inclusion/exclusion standards. When there is a disagreement, it is resolved by introducing a third reviewer to discuss either the inclusion or exclusion of data. Finally, the information extracted from each study includes study topic, follow-up schedule, number of research cases,

disease duration, patients' ages, intervention measures, specific major acupoint selection, and basis of neurological tinnitus diagnosis.

2.5. Study quality evaluation process

According to the Cochrane Handbook for Systematic Reviews of Interventions 5.3.3, the quality of the included studies is evaluated by the following guidelines:¹ (1) whether randomization is ever mentioned, and whether the randomization method is acceptable; (2) whether the covert group is mentioned, and whether the covert method is acceptable; (3) whether blindness is mentioned, and whether the method of blindness is acceptable; (4) whether the outcome data are complete; (5) whether there are selective reports; and (6) whether there are other biases, such as the use of funding, early termination of research, and fraudulent behaviour. Risk of bias was assessed using Review Man5.3 software. Journals often require both the manufacturer's name and location for specialized equipment and software.

2.6. Statistical analysis

We use Stata software to map the network diagram for each intervention. Bayesian inference is performed using GeMTC0.14.3 statistical software GeMTC (Generate Mixed Treatment Comparisons) and Markov Chain Monte Carlo (MCMC) methods, and the posterior probability is inferred according to the prior probability. Estimations and inferences are made assuming that the MCMC has reached a stable convergence state. When running the GeMTC program, we set the initial value (initial values scaling) to 2.5, the number of iterations (simulation iterations) to 50,000, and the first 20,000 iterations for annealing (tuning iteration) to eliminate the influence of the initial value. The step size (thinning interval) is 10, and the number of chains is 4. The potential scale reduced factor (PSRF) reflects convergence. If the PSRF is close to 1, the convergence is good, and the consistency of the homogeneity model means a high confidence interval. Then, a rank-ordering figure is generated.

This study is dichotomous, so the odds ratio (OR) and its 95% confidence intervals (CIs) are used to represent the effect size. Then, 95% CIs were calculated, and $p < 0.05$ was regarded as significant. The inconsistency test was evaluated according to Bayesian P values ($p < 0.05$ is considered to be of significant inconsistency). The I^2 test was analysed ($I^2 > 50\%$ is considered to be of significant heterogeneity) to verify homogeneity; 95% CIs were calculated, and $p < 0.05$ was regarded as significant.

3. Results

3.1. Screening result

A total of 1268 literature searches were retrieved from the databases, time span from the inception of the databases to 26 December 2017, including 544 literature searches in databases of PubMed, 52 in Embase, 0 in Cochrane Library, 218 in CNKI, 156 in Wanfang. After data rejection, 220 literature searches of duplication were rejected, and 37 literature searches of review were rejected. One animal study was rejected, 459 of none-tinnitus were rejected, Not treated with acupuncture 501 of not treated with acupuncture were rejected, 34 literature searches with evaluation results cannot be extracted were rejected, and 29 literature searches with low quality were rejected. In the end, 40 studies were included in the Bayesian analysis after the filtering process. All of those studies are in Chinese. A total of 3657 patients were included in the study (Fig1).

3.2. Basic information to be included in the study

All 40 studies were RCTs, which included a total of 3657 patients. Among them, 18 studies examined treatment by traditional

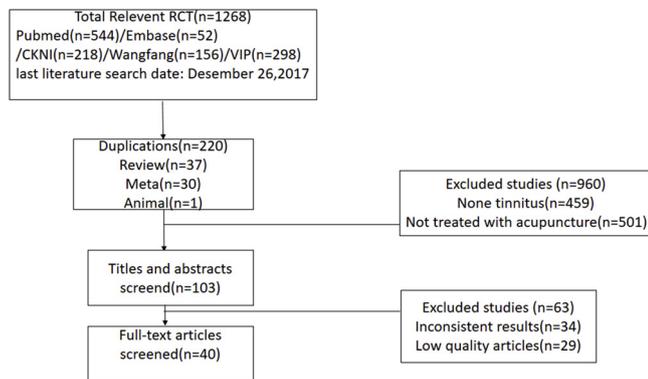


Fig. 1. Literature retrieval process.

acupuncture with supplementary medicine in the experimental group and by medicine in the control group; 3 studies examined treatment by moxibustion acupuncture in the experimental group and by traditional acupuncture in the control group; and 6 studies examined treatment by electroacupuncture with supplementary medicine in the experimental group and by medicine in the control group.

Three studies examined treatment by electroacupuncture in the experimental group and by traditional acupuncture in the control group; 3 studies examined treatment by electroacupuncture in the experimental group and by medicine in the control group; 2 studies examined treatment by moxibustion acupuncture with supplementary medicine in the experimental group and by medicine in the control group; 1 study examined treatment by electroacupuncture and moxibustion acupuncture in the experimental group and by electroacupuncture in the control group; 1 study examined treatment by moxibustion acupuncture in the experimental group and by traditional acupuncture in the control group; and 3 studies examined treatment by traditional acupuncture in the experimental group and by medicine in the control group. All studies showed effective responses, and no adverse reactions have been reported. (Table 1)

3.3. Diagnostic standards

We only selected studies that examined neurological tinnitus, and the diagnostic standards were based on recommendations from the following sources: "Guiding principles of clinical research on the treatment of tinnitus", "Clinical study on otolaryngology of traditional Chinese medicine", "Practical otolaryngology", "Otology", "Practical otolaryngology", "Diagnosis of otolaryngology", "Clinical study on otolaryngology of traditional Chinese medicine", "Therapeutics of otorhinolaryngology and otorhinolaryngology of TCM", "Diagnostic criteria of ophthalmology, otolaryngology and laryngitis", "Diagnostic criteria of TCM syndrome", "Chinese and Western medicine combined with otolaryngology", the "Practice of otorhinolaryngology head and neck surgery", the 2014 U.S. report "Clinical practice guideline: tinnitus", "Traditional Chinese medicine otolaryngology", "Diagnostic criteria of TCM diseases", "Diagnosis of otolaryngology", "Otorhinolaryngology therapeutic", and "Otorhinolaryngology and head and neck surgery". The diagnosis of neuromuscular tinnitus is similar across different types of the condition and organs.

The detailed diagnostic standards are as follows: (1) level 0: no tinnitus; (2) level 1: ringing sound is minimal and mostly unnoticeable; (3) level 2: tinnitus is mild but can be heard in a quiet environment and has no effects on normal life (such as sleep) and work; (4) level 3: the tinnitus is noticeable, can be heard in a normal environment but has no obvious interference with normal life and work; (5) level 4: tinnitus can be heard in any environment and affects sleep, resulting in lack of concentration and slight interference with work; (6) level 5: tinnitus is very loud and noisy, seriously affects sleep and work, and begins to lead

to mild irritability, anxiety, depression and other mental health symptoms; (7) level 6: tinnitus is extremely loud, equivalent to the loudest ambient sound experienced by the patient (such as the sound of a plane taking off); the patient is plagued by tinnitus all the time, cannot sleep, cannot work at all, and has obvious irritability, anxiety, psychiatric symptoms, such as depression.

3.4. Outcomes

The effectiveness of acupuncture in the treatment of neurological tinnitus also has standards. The detailed level standards are correlated with the diagnostic standards: (1) total recovery from tinnitus: tinnitus disappeared; (2) remarkable recovery: tinnitus decreased by more than 2 levels (including 2 levels); (3) effective: tinnitus decreased by 1 level; (4) invalid: tinnitus did not change.⁴⁹ The efficacy of different mechanisms and versions in the treatment of neuromuscular tinnitus was roughly the same.

3.5. MeSH meta-analyses

The following MeSH (Medical Subject Headings) meta-analysis of the relationship between interventions is generated by using Stata 14.0 with command lines of (*network setup m, study (ID) trt (t) numcodes, network convert pairs*) and (*network map*), as shown in Fig. 2. The solid line in the figure indicates direct comparison; the numbers in the picture are the numbers of RCTs for a direct comparison. Unconnected dots indicate that there is no direct comparison of RCTs, which can be indirectly accessed and compared by MeSH meta-analysis. On the diagram, a larger dot indicates a larger sample size of the intervention. Thicker lines between point connections are a result of a greater number of research studies related to the comparison of two treatment method interventions. (Fig. 2)

3.6. Research methodological quality evaluation

All 40 studies mentioned "randomized grouping"; 20 studies described specific methods to apply randomization, 8 of which were randomized according to the order of visits; and the other 12 studies described the randomized approach. One study used a double-blind approach. None of the studies described allocation. One study described follow-up bias and provided a detailed explanation of the exclusion criteria, and other studies did not mention follow-up bias. None of the included studies mentioned reporting bias or other biases. Overall, the study could only be ranked as medium to low quality. Specific results are shown in Figs. 3 and 4.

3.7. Comparison of the effectiveness of different interventions in the treatment of tinnitus

A total of 40 studies reported positive effects. According to the Monte Carlo simulation on iterations, the parameter PSRF moves close to 1, indicating satisfactory convergence. The following analysis is performed under the consistency model. First, compared with only medicine, the following methods can significantly improve the effectiveness of tinnitus treatment: electroacupuncture [OR = 5.55, 95% CI (2.88, 9.73), $P < 0.05$], moxibustion acupuncture [OR = 10.60, 95% CI (3.53, 31.68), $P < 0.05$], electroacupuncture and medicine [OR = 3.38, 95% CI (1.73, 6.11), $P < 0.05$], moxibustion acupuncture and medicine [OR = 4.72, 95% CI (1.63, 13.00), $P < 0.05$], and electroacupuncture and moxibustion acupuncture [OR = 10.96, 95% CI (2.47, 45.92), $P < 0.05$]. Compared with traditional acupuncture, the following methods can significantly improve the effectiveness of tinnitus treatment: electroacupuncture [OR = 3.00, 95% CI (1.75, 5.05), $P < 0.05$], moxibustion acupuncture [OR = 5.70, 95% CI (2.46, 15.36), $P < 0.05$], acupuncture and medicine [OR = 2.51, 95% CI (1.37, 5.38), $P < 0.05$], and electroacupuncture and moxibustion

Table 1
Baseline characteristics of studies included in the bayesian analysis.

Studies	Year	Follow-up time	Testing scheme (T/C)	Course of disease	Patient characteristics (years)T/C	Mean Age	Diagnostic basis of neurogenic tinnitus	Intervention measures		Main points
								Test group	Control group	
Chen Chuli ⁹	2013	Not mentioned	30/30	0.5–120months	20–60		Not mentioned	⑥	④	Tinghui(GB2),Yifeng(TE17),Ermen(TE21),Tinggong(SI19)
Chen Yili ¹⁰	2012	Not mentioned	32/30	(14days - 30years)/(15days - 33years)	(21 - 65) / (30 - 65)		①	③	①	Baihui(DU20),SI19,GB2,TE17,Fengchi(GB20),Hegu(LI4)
Dong Haiyan ¹¹	2013	2010.02–2011.12	33/30	(40.24 ± 20.52)/(39.49 ± 21.05)months	(48.85 ± 13.59)/(50.20 ± 13.84)		③	③	③	SI19, GB2, SJ17, GB20, Fengfu(DU16), Wangu(GB12) Zhigou(TE6), Zhongdu(TE3)DU20,
Fan Yushan ¹²	2013	2011.07-2012.06	30/30	(3weeks-9years)/(5weeks-10years)	25-56/35-60		④	⑦	④	Ermen(SJ21), SI19, GB2
Gao Lili ¹³	2015	2013.10-2015.05	55/55	(2.4 ± 0.2)/(2.5 ± 0.1)years	(49.0 ± 2.1)/(48.3 ± 2.0)		Not mentioned	④	④	Jiaji(EX-B2), GB2, Jixi(GB43), TE3, GB20 , SI19, TE21, Neiguan(PC6)
Guo Hui ¹⁴	2014	2012.09–2013.09	58/58	not mentioned	50.2 ± 0.6		Not mentioned	③	④	Taixi(KI3) , Zhaohai(KI6), SI19
Jiang Bin ¹⁵	2010	2007-2009	75/76	(2.70 ± 1.75)/(2.99 ± 2.32)years	(69.97 ± 7.90)/(70.88 ± 7.93)		Not mentioned	①	④	Not mentioned
Jiang Guiyun ¹⁶	2017	2009.01-2015.10	38/38	(5-70)/(7-72)days	32.6/33.4		③	③	③	TE21, GB2, SI19, TE3, TE17, Taichong(LR3), Ganshu(BL18), Shenshu(BL23)
Jin Ze ¹⁷	2015	Not mentioned	20/20	(13.88 ± 4.87)/(12.75 ± 5.65)months	(39 ± 5)/(40 ± 6)		①	④	①	TE21, SI19, GB2, TE17, TE3
Li Hongxing ¹⁸	2013	Not mentioned	76/50	1.78/1.40years	(55.51 ± 16.93)/(52.23 ± 17.91)		②	④	④	TE21, SI19, GB2, TE17
Li Ling ¹⁹	2016	2013.10-2014.06	40/40	(4 - 36)/(4-36)months	(37-68)/(35-66)		Not mentioned	③	④	TE21, GB2, SI19, Yongquan(KI1), TE17
Liu Minjuan ²⁰	2015	August, 2013 to December, 2014,	75/76	(6days-9years)/(7days-8.5years)	(44.6 ± 5.4)/(44.6 ± 4.6)		⑦	③	③	TE17, SI19, GB2, TE21, GB20
Liu Qiang ²¹	2015	2015.01-2015.07	30/30	Median17days/18days	42/60		③③	③	③	TE21, SI19, GB2, TE17, Wangu(GB12)
liu Xiuping ²²	2014	2011.11 - 2013.11	40/40	(10.65 ± 1.52)years	(51.03 ± 1.67)		①	③	①	SI19, Baihui(DU20), TE17, GB2, Hegu(LI4), GB20
Li Yang ²³	2010	2006-2009	45/45	(1month-11years)/(1month-10.5years)	not mentioned		⑥	⑧	②	DU21, TE17, TE6, TE3, BL23, Shixuan(EX-UE11)
Li Yinghao ²⁴	2015	2013.06–2014.08	34/34	(3.5 ± 1.5)/(5.4 ± 1.7)months	(47 ± 15)/(46 ± 16)		③②	⑥	④	DU20, TE21, SI19, GB2, TE17, TE3, LI4, LR3, GB43
Qin Guiying ²⁵	2011	2009.01-2010.12	50/50	(2.0 ± 0.4)/(2.1 ± 0.3)years	(43.0 ± 3.20)/(42.3 ± 3.10)		Not mentioned	②	④	GB2, SJ21, SI19, TE17, TE3
Ren Jianbing ²⁶	2014	2012.03-2013.10	44/42	(10.2 ± 5.4)/(9.7 ± 6.5)days	(42 ± 18)/(40 ± 15)		③	③	③	TE21, SI19, GB2, TE17, TE3
Shi Guoche ²⁷	2012	2011.08–2012.08	30/30	(1.5 ± 0.31)/(1.7 ± 0.42)years	(44.12 ± 3.32)/(42.30 ± 3.20)		③②	③	③	DU20, TE21, SI19, GB2, TE17, GB12, Shuaigu(GB8), TE3, LI4, Waiguan(TB5), LR3 , GB43, KI3
Song Pu ²⁸	2017	2012.11-2014.12	38/41	(5.2 ± 0.9)/(5.4 ± 0.7)months	(44.9 ± 10.8)/(45.2 ± 10.5)		Not mentioned	③	④	TE21, GB2, KI3, SI19
Tan Hui ²⁹	2016	Not mentioned	40/40	1month ~ 1year	40-60		②	③	③	TE17, SI19, GB2, LI4, Yanglingquan(GB34), Sanyinjiao(SP6), LR3, DU20, GB20, TB5, BL18, Pishu(BL20), BL23, Chenshan(BL57)
Wang Bing ³⁰	2005	Not mentioned	30/30	(7days-25years)/(1month-20years)	53/21		Not mentioned	③	①	GB8, SI19, TE17
Wang Lin ³¹	2013	2011.01-2011.05	30/30	(2.1 ± 0.1)/(2.2 ± 0.2)weeks	(50 ± 4)/(51 ± 5)		Not mentioned	⑥	④	TE21, SI19, GB2, TE17
Wang Zhaoling ³²	2013	Not mentioned	36/36	7d-3years	21-70		③	③	①	BL23, TE17, TE3, Qihai(RN6), BL18 , SI19, Guanyuan(BL26), KI3
Wang Zhengpeng ³³	2016	Not mentioned	40/40	(10.36 ± 1.47)/(9.88 ± 12.04)years	(42.52 ± 3.24)		Not mentioned	⑥	④	GB2, Wangu(GB12), TE17, TE21, SI19, GB8, Zhigou(TB6), TE3
Xu Yongzhu ³⁴	2017	2011.08-2016.08	76/68	(0.8 ~ 20.5)/(1.1 ~ 21)years	(44.9 ± 6.8)/(45.6 ± 7.1)		①	③	④	Zhongwan(RN12), Xiawan(RN10), RN6, BL26, TE21, SI19, GB2, GB12, TE17
Yang Hongfei ³⁵	2011	Not mentioned	54/36	(7days-10years)/(6days-7.75)years	45		③②	①	④	TE21, SI19, GB2, TE17, TE3, GB43, GB20, PC6, EX-B2

(continued on next page)

Table 1 (continued)

Studies	Year	Follow-up time	Testing scheme (T/C)	Course of disease	Patient characteristics		Diagnostic basis of neurogenic tinnitus	Intervention measures		Main points
					Mean Age (years)T/C	Mean Age (years)T/C		Test group	Control group	
Yang Ping ³⁶	2015	2012.09-2014.09	30/30	6.0 ± 2.3/6.2 ± 2.2	(52.3 ± 2.5)/(54.5 ± 4.0)	③	④	④	Not mentioned	Not mentioned
Yang Wanling ³⁷	2015	2009.02-2012.12	40/40	(2.56 ± 0.33)years	(42.52 ± 3.24)	①	④	④	GB2, GB12, TE17, TE21, SI19, GB8, SJ6, TE3	GB2, GB12, TE17, TE21, SI19, GB8, SJ6, TE3
Yao Qingren ³⁸	2017	2015.06-2016.12	80/80	2.75 ± 0.9/2.65 ± 0.91)years	(46.63 ± 6.79)/(46.05 ± 7.02)	③③	④	④	Not mentioned	Not mentioned
Zhang Donglin ³⁹	2015	2013.01—2015.02	100/100	2.4 ± 0.1/2.3 ± 0.3)years	(49.3 ± 2.1)/(48.9 ± 2.3)	Not mentioned	④	④	EX-B2, GB43, GB2, TE3, GB20, TE21, TE17, SI19, PC6	EX-B2, GB43, GB2, TE3, GB20, TE21, TE17, SI19, PC6
Zhang Fengju ⁴⁰	2016	2014.06-2015.07	49/49	0.5-23)years	47.2-11.4	③⑦	④	④	TE21, SI19, GB2, TE17, GB20, SP6, GB12	TE21, SI19, GB2, TE17, GB20, SP6, GB12
Zhang Xinhong ⁴¹	2012	2008.02-2011.06	32/30	2weeks-27)years/2weeks-29)years	(33.18 ± 12.58)/(35.23 ± 13.31)	③⑦	④	④	TE21, SI19, GB2, TE17, GB20, TE3	TE21, SI19, GB2, TE17, GB20, TE3
Zhao Yan ⁴²	2016	2014.09-2015.09	35/35	(1.67 ± 0.56)/1.53 ± 0.44)years	(57 ± 14)/(59 ± 12)	③	④	④	TE21, TE17, DU20, KI3, TB5, Xuanzhong(GB39)	TE21, TE17, DU20, KI3, TB5, Xuanzhong(GB39)
Zhao Yan ⁴³	2013	2010.10-2012.10	48/48	Not mentioned	(37.2 ± 4.9)/(38.1 ± 5.2)	③	④	④	SI19, GB2, TE17, GB20	SI19, GB2, TE17, GB20
Zhong Qu ⁴⁴	2014	Not mentioned	20/20	(7.56 ± 13.06)/(8.48 ± 12.36)	(43.14 ± 10.35)/(40.51 ± 12.37)	①	④	④	SI19, GB2, GB20, TE17, Fenglong(ST40)	SI19, GB2, GB20, TE17, Fenglong(ST40)
Zhou Ling ⁴⁵	2015	2014.11-2015.11	35/35	Not mentioned	Not mentioned	①	⑦	⑦	SI19, Sishencong(EX-HN1), TE17, TE3, Zusanli (ST36), GB2, DU20, BL26	SI19, Sishencong(EX-HN1), TE17, TE3, Zusanli (ST36), GB2, DU20, BL26
Zhou Youwu ⁴⁶	2014	2010.01-2013.12	80/80	Not mentioned	(52.1 ± 13.0)/(51.2 ± 12.7)	②	④	④	SI19, GB2, TE21, GB20, GB12, TB5	SI19, GB2, TE21, GB20, GB12, TB5
Zhu Mengdie ⁴⁷	2017	2015.08-2016.08	30/30	(1days-24)months)/(3days-22)months	(47.4 ± 14.2)/(46.3 ± 14.5)	⑥	④	④	TE21, SI19, GB2, TE17	TE21, SI19, GB2, TE17
Zhu Tianxiang ⁴⁸	2016	2013.09-2015.09	100/100	(4.37 ± 0.12)/(4.26 ± 0.28)years	(45.34 ± 1.13)/(44.25 ± 1.07)	⑩	④	④	RN6, BL26, RN10, BL26	RN6, BL26, RN10, BL26

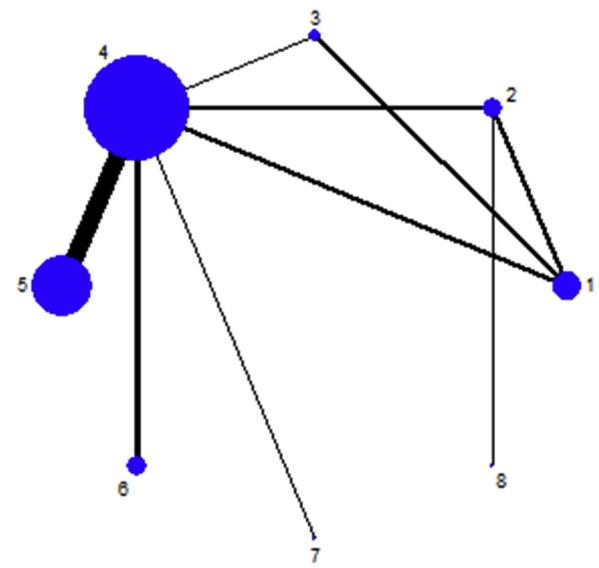


Fig. 2. Network plot for included studies. The nodes in the figure represent the following interventions: 1) acupuncture, 2) electroacupuncture, 3) moxibustion acupuncture, 4) medicine, 5) acupuncture and medicine, 6) electroacupuncture and medicine, 7) moxibustion acupuncture and medicine, and 8) electroacupuncture and moxibustion acupuncture.

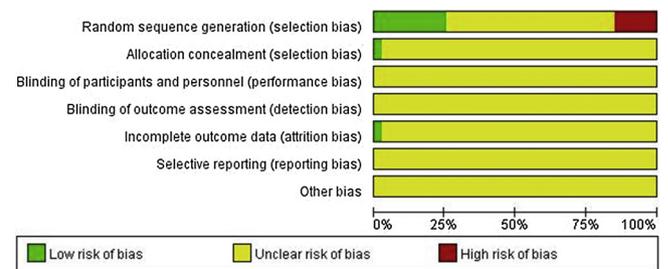


Fig. 3. Rise bar graph of bias.

acupuncture [OR = 5.90,95% CI (1.52, 29.73), P < 0.05]. The remaining paired comparisons showed no significant differences in treatment effectiveness (Table 2).

3.8. The list of the effectiveness of different interventions on the treatment of tinnitus

Based on the MCMC theory for probability evaluation, the ordering of the probability of treatment effects from high to low shows that moxibustion acupuncture has the most favourable results, followed by moxibustion acupuncture combined with electroacupuncture, moxibustion acupuncture combined with supplementary medication, traditional acupuncture combined with supplementary medication, electroacupuncture combined with supplementary medication, electroacupuncture, traditional acupuncture, and medication-only treatment(Fig. 5).

The convergence diagnostic plot drawn according to the Gelman-Rubin-Brooks diagnostic method suggests that the median value of the reduction factor and 97.5% tend to be stable after 25,000 iterations, and the Bayesian model iterates 25,000 calculations. The PSRF value is 1, indicating that the iterative convergence is better (Table 3). The consistency analysis was performed using the node analysis model. The P values of all the comparison groups after the split were greater than 0.05, indicating that the direct results were consistent with the indirect results (Table 4).

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Chen Chuli	?	?	?	?	?	?	?
Chen Yilu	●	?	?	?	?	?	?
Dong Haiyan	●	?	?	?	+	?	?
Fan Yushan	+	?	?	?	?	?	?
Gao Lili	?	?	?	?	?	?	?
Guo Hui	+	?	?	?	?	?	?
Jiang Bin	+	?	?	?	?	?	?
Jiang Guiyun	+	?	?	?	?	?	?
Jin Ze	?	?	?	?	?	?	?
Li Hongxing	●	?	?	?	?	?	?
Li Ling	?	?	?	?	?	?	?
Liu Minjuan	+	?	?	?	?	?	?
Liu Qiang	+	?	?	?	?	?	?
liu Xiuping	?	?	?	?	?	?	?
Li Yang	+	?	?	?	?	?	?
Li Yinghao	?	?	?	?	?	?	?
Qin Guiying	?	?	?	?	?	?	?
Ren Jianbing	?	?	?	?	?	?	?
Shi Guochen	+	?	?	?	?	?	?
Song Pu	?	?	?	?	?	?	?
Tan Hui	?	?	?	?	?	?	?
Wang Bing	?	?	?	?	?	?	?
Wang Lin	?	?	?	?	?	?	?
Wang Zhaoling	?	?	?	?	?	?	?
Wang Zhengpeng	?	?	?	?	?	?	?
Xu Yongzhu	?	?	?	?	?	?	?
Yang Hongfei	●	?	?	?	?	?	?
Yang Ping	?	?	?	?	?	?	?
Yang Wanjiang	+	?	?	?	?	?	?
Yao Qinggen	+	?	?	?	?	?	?
Zhang Donglin	?	+	?	?	?	?	?
Zhang Fengju	●	?	?	?	?	?	?
Zhang Xinhong	?	?	?	?	?	?	?
Zhao yan	?	?	?	?	?	?	?
Zhao Yan	●	?	?	?	?	?	?
Zhong Qu	?	?	?	?	?	?	?
Zhou Ling	?	?	?	?	?	?	?
Zhou Youwu	?	?	?	?	?	?	?
Zhu Mengdie	?	?	?	?	?	?	?
Zhu Tianxiang	?	?	?	?	?	?	?

Fig. 4. Potential risk of bias of each included study.

4. Discussion

Tinnitus often occurs with other symptoms, such as irritability,

insomnia, and inattention, which have serious adverse effects on patients' daily work and life. The pathogenesis of tinnitus is complicated, and there is no objective and accurate quantitative method for detecting the presence of tinnitus. Some studies have suggested that intracellular calcium ions play an important role in regulating the balance of inward and outward currents of neurons and hair cells. Excessive glutamate neurotransmitters can cause neuronal dendrites to swell in the auditory nerve fiber capsule, leading to tinnitus.^{50,51} Some studies have also suggested that changes in synaptic input signals lead to short-term or long-term secondary changes in neurostimulation or excitability, resulting in reorganization of the auditory system, leading to tinnitus.⁵² Studies have also shown that the posterior nucleus of the cochlear nerve is the integration site of proprioception and vestibular and auditory information. When the afferent nerve of the proprioceptive system transmits head and neck signals, stimulation of the trigeminal ganglion can cause the activation of the posterior nucleus of the cochlear nerve, resulting in the generation of the neuronal potential of the auditory neurons, resulting in tinnitus.^{53,54} Therefore, in western medicine, treatments often include vasodilators and neurotrophic drugs, the effects of which are not certain.

In traditional Chinese medicine, it is believed that tinnitus is caused by a deficiency in the liver and kidney, which causes a lack of blood supply to the head and neck. Therefore, the treatment should be based on blood-activating and kidney-tonifying therapies. Acupuncture is the main method of treatment of tinnitus in traditional Chinese medicine, and it can strengthen the patient's body qi. The circulation of blood, in return, achieves the effects of replenishing the kidney and spleen, promoting Qi and improving blood circulation. Acupuncture treatment has achieved certain effects. Acupuncture and moxibustion treatment of tinnitus has been discussed as early as in Huangdi Neijing, and the key to treatment is the organic combination of disease differentiation, syndrome differentiation, and meridian differentiation.⁵⁵

In the treatment of tinnitus acupuncture, the selection of acupoints is important and skilled. For instance, Ji⁵⁶ believed that the press-sensitive acupoints distribute principally in the Gallbladder Meridian of Foot-Shaoyang and below the knee-joint in tinnitus patients, while Wangu (GB 12) and Yifeng (SJ 17) were found to be the most sensitive acupoints. Chen⁵⁷ et al pointed selection and matching of acupoints in acupuncture treatment of tinnitus should be base on syndrome differentiation. Except for the basic acupoints, such as SI19, GB2 and SJ17, the patients with wind-heat invasion could add HN8 and LI4, while the patients with liver-fire flaming were preferable with LR3 and GB40. Based on basic acupoints SI19, GB2, and SJ17, Zhang et al⁵⁸ proposed a more detailed syndrome differentiation to guide the selection of acupoints in patients with tinnitus, such as excessive heat of liver-gallbladder with LR3, GB40, LR6, exogenous wind-heat with LI4, SJ5, syndrome of phlegm-fire blocking orifices with ST40, SP9, LR3, GB40, deficiency of kidney yin with KI3 and SP6. Zhang et al.⁵⁹ selected main points of SI19, GB2, SJ21, and DU20, with acupoints SJ17 and LR6, to treat tinnitus. In addition, the supplementary syndrome differentiation and acupoint matching were as followed: attack of exogenous evils with GB20 and SJ5; Wetness-Heat of Liver and Gallbladder with LR3, GB40; phlegm and fire Stagnation with ST40 and LI11.

Combined with literature research and statistical analysis, we found that tinnitus patients improved more when they were in the therapy of moxibustion acupuncture than when they were only taking acupuncture treatment. Moxibustion acupuncture is a combination of acupuncture and moxibustion.⁶⁰ After the acupuncture needle is punctured and left at a proper depth, moxa velvet fixed on the other end of needle handle is ignited until moxa velvet is burned out. As the heat is conducted into body through the needle to achieve therapeutic purposes, moxibustion acupuncture has the function of warming meridians, activating qi and activating blood circulation. Shizhen Li, a famous ancient Chinese physician, highly appraised the therapeutic effect of Moxibustion in Compendium of Materia Medica: "Moxibustion is to penetrate the various meridians and treat more than hundreds of

Table 2

Network meta-analysis of the therapeutic efficacy of different intervention measures on tinnitus. The values in the lower-left part of the table represent the OR of the column index compared with that of the row index, and the values in the upper-right part of the table represent the OR of the row index compared with that of the column index. The OR > 1.00 of the lower-left and upper-right parts of the table indicate the high effectiveness of the intervention measures listed in the figure: 1) acupuncture, 2) electroacupuncture, 3) moxibustion acupuncture, 4) medicine, 5) acupuncture and medicine, 6) electroacupuncture and medicine, 7) moxibustion acupuncture and medicine, and 8) electroacupuncture and moxibustion acupuncture.

1	3.00 (1.75, 5.05)	5.70 (2.46, 15.36)	0.54 (0.31, 1.07)	2.51 (1.37, 5.38)	1.80 (0.80, 4.60)	2.54 (0.91, 8.97)	5.90 (1.52, 29.73)
0.33 (0.20, 0.57)	2	1.92 (0.69, 6.33)	0.18 (0.10, 0.35)	0.85 (0.46, 1.71)	0.61 (0.27, 1.51)	0.86 (0.27, 2.99)	1.92 (0.56, 9.12)
0.18 (0.07, 0.41)	0.52 (0.16, 1.45)	3	0.09 (0.03, 0.28)	0.42 (0.14, 1.38)	0.34 (0.08, 1.12)	0.40 (0.10, 1.97)	0.94 (0.18, 6.27)
1.86 (0.93, 3.22)	5.55 (2.88, 9.73)	10.60 (3.53, 31.68)	4	4.64 (3.66, 5.95)	3.38 (1.73, 6.11)	4.72 (1.63, 13.00)	10.96 (2.47, 45.92)
0.40 (0.19, 0.73)	1.18 (0.59, 2.16)	2.36 (0.73, 7.09)	0.22 (0.17, 0.27)	5	0.76 (0.36, 1.34)	1.00 (0.35, 2.90)	2.29 (0.54, 9.56)
0.56 (0.22, 1.25)	1.64 (0.66, 3.74)	2.95 (0.89, 12.61)	0.30 (0.16, 0.58)	1.32 (0.75, 2.81)	6	1.32 (0.42, 4.51)	2.97 (0.65, 14.86)
0.39 (0.11, 1.10)	1.16 (0.33, 3.64)	2.51 (0.51, 10.17)	0.21 (0.08, 0.61)	1.00 (0.35, 2.85)	0.76 (0.22, 2.41)	7	2.27 (0.37, 12.87)
0.17 (0.03, 0.66)	0.52 (0.11, 1.78)	1.07 (0.16, 5.69)	0.09 (0.02, 0.41)	0.44 (0.10, 1.84)	0.34 (0.07, 1.54)	0.44 (0.08, 2.72)	8

The values in the lower-left part of the table represent the OR of the column index compared with that of the row index, and the values in the upper-right part of the table represent the OR of the row index compared with that of the column index. The OR > 1.00 of the lower-left and upper-right parts of the table indicate the high effectiveness of the intervention measures listed in the figure: 1) acupuncture, 2) electroacupuncture, 3) moxibustion acupuncture, 4) medicine, 5) acupuncture and medicine, 6) electroacupuncture and medicine, 7) moxibustion acupuncture and medicine, and 8) electroacupuncture and moxibustion acupuncture.

diseases and pathogens.⁶¹ That moxibustion acupuncture is more effective in treating patients with tinnitus is consistent with clinical experience. On one hand, acupuncture treatment dredges meridians and regulates or correct the flow of “Qi” to restore health through stimulating acupuncture points. On the other hand, moxibustion could help to enhance the thermal effect through the meridians and collaterals to dredge channel of Qi (vital energy) and blood. Therefore, when the moxibustion combined with acupuncture treatment, they harmonize the Qi, blood, Yin and Yang to achieve the efficacy of preventing and treating disease and preserving health.

In this study, we evaluate some of the most commonly applied tinnitus acupuncture treatments in a network meta-analysis. The statistical analyses and direct and indirect effect comparison on eight methods, including traditional acupuncture, electroacupuncture, moxibustion acupuncture, acupuncture with added drugs, acupuncture and drug combination therapy, combined treatment of electroacupuncture and drugs, combined treatment of moxibustion acupuncture and drugs, unveiled the treatment results. We conducted that the eight interventions are all effective in the treatment of neurological tinnitus, of which moxibustion acupuncture seems to be a better trend treatment for tinnitus. However, though moxibustion acupuncture is helpful, the smoke may have an impact on the environment. Therefore, general moxibustion places should set up smoke purifier or smoke extraction system to prevent emission and pollution of moxibustion smoke. In addition, to further clarify the better treatments to the tinnitus patients, more researches with high grade evidence and greater sample sizes are needed.

Table 3
The PSRF value.

Parameter	PSRF
d.1.2	1.03
d.1.3	1.02
d.1.4	1.02
d.2.8	1.02
d.4.5	1.01
d.4.6	1.01
d.4.7	1.01
sd.d	1.01

Therefore, we still need to update the literature to incorporate higher quality studies in the future to find more effective interventions for tinnitus.

5. Conclusion

The therapeutic effect of acupuncture on patients with tinnitus is worthy of affirmation, as the eight therapeutic methods discussed in this paper are all effective in the treatment of neurological tinnitus. The ordering of clinical effect from high to low shows as follows: moxibustion acupuncture, moxibustion acupuncture combined with electroacupuncture, moxibustion acupuncture combined with supplementary medication, traditional acupuncture combined with supplementary medication, electroacupuncture combined with supplementary

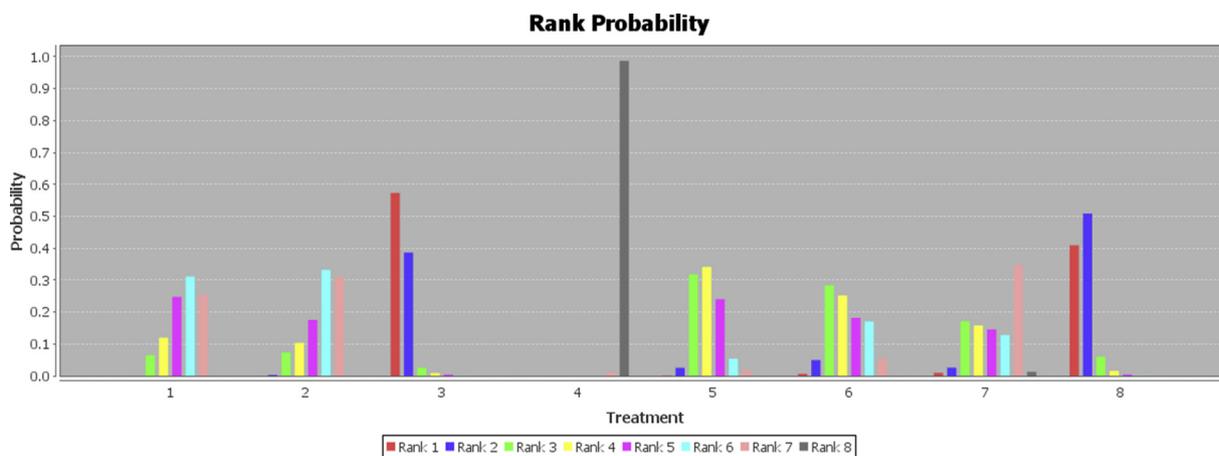


Fig. 5. The probability of effectiveness in different treatment methods. 1) traditional acupuncture, 2) electroacupuncture, 3) moxibustion acupuncture, 4) medicine, 5) traditional acupuncture with supplementary medication combination therapy, 6) electroacupuncture and supplementary medication combination therapy, 7) moxibustion acupuncture and supplementary medication combination therapy, and 8) electroacupuncture combined with moxibustion acupuncture.

Table 4

The P values of all the comparison groups. 1) traditional acupuncture, 2) electroacupuncture, 3) moxibustion acupuncture, 4) medicine, 5) traditional acupuncture with supplementary medication combination therapy, 6) electroacupuncture and supplementary medication combination therapy, 7) moxibustion acupuncture and supplementary medication combination therapy, and 8) electroacupuncture combined with moxibustion acupuncture.

Name	Direct Effect	Indirect Effect	Overall	P-Value
1, 2	-0.43 (-1.24, 0.49)	0.42 (-0.46, 1.32)	N/A	0.2
1, 3	1.82 (0.85, 3.08)	0.09 (-1.95, 2.26)	N/A	0.14
1, 4	-1.22(-1.90,-0.61)	-1.11 (-2.19, 0.10)	N/A	0.83
1, 8	1.46 (0.57, 2.35)	0.63 (-0.93, 2.07)	N/A	0.36
2, 4	-1.35 (-2.22, -0.50)	-0.97 (-1.91, 0.04)	N/A	0.54
2, 8	0.74 (-0.73, 2.17)	1.55 (0.44, 2.67)	N/A	0.4
3, 4	-1.45 (-3.48, 0.54)	-3.16 (-4.49, -1.98)	N/A	0.14

Note : 1) traditional acupuncture, 2) electroacupuncture, 3) moxibustion acupuncture, 4) medicine, 5) traditional acupuncture with supplementary medication combination therapy, 6) electroacupuncture and supplementary medication combination therapy, 7) moxibustion acupuncture and supplementary medication combination therapy, and 8) electroacupuncture combined with moxibustion acupuncture.

medication, electroacupuncture, traditional acupuncture, and medication-only treatment. Therefore, moxibustion acupuncture seems to be a better trend treatment for tinnitus.

Author contributions

P Pang, YC Shi, HC Xu, L Deng, and SZ Wu searched the literature. P Pang, YC Shi, HC Xu and XY Chen collected and analysed the data and wrote the paper. All authors read and approved the final manuscript.

Conflict of interest

The authors declare that they have no competing interests.

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