

Transcutaneous auricular vagus nerve stimulation in treating major depressive disorder

A systematic review and meta-analysis

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Abstract

Background: Transcutaneous auricular vagus nerve stimulation (taVNS), as a noninvasive intervention, has beneficial effects on major depressive disorder based on clinical observations. However, the potential benefits and clinical role of taVNS in the treatment of major depressive disorder are still uncertain and have not been systematically evaluated. Therefore, we performed a systematic review and meta-analysis to evaluate the effectiveness and safety of taVNS in treating major depressive disorder.

Methods: Four electronic databases, namely, Embase, MEDLINE, the Cochrane Library and PsycINFO, were searched for all related trials published through May 1, 2018. We extracted the basic information and data of the included studies and evaluated the methodological quality with the Cochrane risk of bias tool and the nonrandomized studies-of interventions (ROBINS-I) tool. A meta-analysis of the comparative effects was conducted using the Review Manager 5.3 software.

Results: A total of 423 citations from the databases were searched, and 4 studies with 222 individuals were included in the meta-analysis. The taVNS technique could decrease 24-item HAMD scores more than the sham intervention (MD: -4.23 , 95% CI: -7.15 , -1.31 ; $P = .005$) and was also more effective in decreasing Self-Rating Depression Scale scores ((MD: -10.34 , 95% CI: -13.48 , -7.20 ; $P < .00001$), Beck Depression Inventory scores (MD: -18.1 , -2.5 ; $P = .01$) and Self-Rating Anxiety Scale scores (MD: -6.57 , 95% CI: -9.30 , -3.84 ; $P < .00001$). However, there was no significant difference in the Hamilton Anxiety Rating Scale scores between the taVNS and sham taVNS groups (MD: -1.12 , 95% CI: -2.56 , 0.32 ; $P = .13$). No obvious adverse effects of taVNS treatment were reported in the included studies.

Conclusion: The results of the analysis preliminarily demonstrated that taVNS therapy can effectively ameliorate the symptoms of major depressive disorder, providing an alternative technique for addressing depression. However, more well-designed RCTs with larger sample sizes and follow-ups are needed in future studies to confirm our findings.

Abbreviations: BDI = Beck Depression Inventory, CANMAT = Canadian network for mood and anxiety treatments, DBS = deep brain stimulation, ECT = electroconvulsive therapy, GBD = Global Burden of Disease, HAMA = Hamilton Anxiety Rating Scale, HAMD = Hamilton Depression Rating Scale, iVNS = invasive nerve stimulation, MD = mean difference, MDD = major depressive disorder, ROBINS-I = risk of bias of nonrandomized studies-of interventions, SAS = Self-Rating Anxiety Scale, SDS = Self-Rating Depression Scale, taVNS = transcutaneous auricular vagus nerve stimulation (taVNS), VNS = vagus nerve stimulation.

Keywords: major depressive disorder, meta-analysis, systematic review, transcutaneous auricular vagus nerve stimulation

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1. Introduction

Major depressive disorder (MDD) is a mental disorder that does harm to the physical and psychological health of an individual and, even worse, may lead to suicide. The global prevalence of major depressive disorder was estimated to be approximately 216,047,000 people in 2015 according to the Global Burden of Disease (GBD) study, representing an increase of 17.8% from the measurement in 2005.^[1] MDD are characterized by the symptoms of low mood, sadness, isolation and accompanied by several psychophysiological changes that last at least 2 weeks. Although both bipolar depression and unipolar depression are associated with depressive symptoms and functional impairment, bipolar depression accompanies with the feature of mania or hypomania and is observed with more white matter abnormalities in the brain,^[2] which needs to be differentiated in order to treat properly. According to the Canadian network for mood and anxiety treatments (CANMAT) clinical guidelines for the management of major depressive disorder, there are many interventions for treating major depressive disorder, including pharmacotherapy, psychotherapy, neurostimulation, and complementary and alternative interventions.^[3] However, previous studies found that approximately 30% of patients would resist antidepressants, even though antidepressant medicines are widely used in clinical practice.^[4,5] Neurostimulation, such as vagus nerve stimulation (VNS), deep brain stimulation (DBS), or electroconvulsive therapy (ECT), has been recommended and is effective for treatment-resistant depression; however, these interventions also possess a certain risk of developing infections and other potential side effects due to surgical implantation.^[6-8] Therefore, it is necessary to find a safe and effective method to address major depressive disorder.

Transcutaneous auricular vagus nerve stimulation (taVNS), as a noninvasive method, has a good efficacy in treating neuropsychiatric disorders.^[9] Transcutaneous electrical stimulation of the concha or the lower half of the back ear (afferent vagus nerve distribution), can produce a similar modulatory effect to that of invasive nerve stimulation (iVNS).^[10] In recent years, several clinical trials were involved in exploring the therapeutic effects of taVNS for managing major depressive disorder; however, the potential benefits and clinical role of taVNS in the treatment of major depressive disorder are still uncertain and have not been systematically evaluated. Therefore, we performed a systematic review and meta-analysis to assess the efficiency and advantages of taVNS in the treatment of major depressive disorder.

2. Methods

2.1. Search strategy

Four electronic databases, namely, Embase (via OVID), MEDLINE (via OVID), the Cochrane Library/Central Register of Controlled Trials and PsycINFO (via OVID), were searched for all citations published through May 1, 2018. The combinations of medical subject heading terms (MeSH) and free text terms related to major depressive disorder, transcutaneous auricular vagus nerve stimulation and clinical trials were searched for potentially eligible citations. The specific search strategies of each database are listed in appendix 1, <http://links.lww.com/MD/C719>.

2.2. Selection and exclusion criteria

All clinical trials that met the following criteria were included in the meta-analysis: patients were diagnosed with major depressive disorder; transcutaneous auricular vagus nerve stimulation was

used as an intervention; placebo or other non-taVNS were used as a comparison; and randomized controlled trials or nonrandomized controlled trials were used as the study design.

Studies that reported insufficient data or nontarget outcomes were excluded. Conference abstracts, editorials, case reports, and letters were also excluded.

2.3. Data extraction and quality assessment

Data and relevant information were extracted by 2 reviewers (PHL and HLF) independently. Detailed information of the basic characteristics of each study's population, intervention, comparisons and outcomes was extracted. Another 2 reviewers (WTC and CXW) checked for the accuracy of the data and related information and then evaluated the methodological quality of the included studies according to the Cochrane risk of bias tool and the ROBINS-I bias tool.^[11,12] Any disagreement was resolved via discussion or was adjudicated by a third reviewer (LML) if necessary.

2.4. Outcomes

The primary outcomes of our study were depression scales, including the 24-item Hamilton Depression Rating Scale (HAMD), the Self-Rating Depression Scale (SDS), and the Beck Depression Inventory (BDI). The secondary outcomes were major depressive disorder-related scales, including the Hamilton Anxiety Rating Scale (HAM-A) and the Self-Rating Anxiety Scale (SAS).

2.5. Statistical analysis

The meta-analysis was conducted with Review Manager 5.3 (Cochrane Collaboration, Oxford, UK). The continuous outcomes were reported as the mean value and standard deviation and were analysed by using the mean difference (MD) with 95% CIs. I-square (I^2), as an index, was used to assess heterogeneity and to determine which statistical model to use to analyse the results. If I^2 exceeded 50% and the P -value was $<.1$, a random-effects model was selected; otherwise, a fixed-effects model was used to analyse the results. Moreover, if the pooled results showed clinical heterogeneity, a subgroup analysis or sensitivity analysis was conducted to solve this issue. Publication bias was estimated by funnel plots or Egger's test. If the number of included studies was <10 or if it was difficult to assess publication bias in a study, then Egger's test was performed. Conversely, funnel plots were used to evaluate publication bias.

3. Results

3.1. Study Identification and Selection

The titles and abstracts of a total of 423 citations from 4 databases were screened for initial review. After removing 61 duplicates and 327 studies with unrelated target topics, 35 articles remained for full-text reviews. Three studies ($n=222$) met the inclusion criteria and were eligible for further quantitative analyses. Figure 1 shows the specific screening procedure of the PRISMA flowchart.

3.2. Characteristics of the included studies

Among the 3 included studies, there was one randomized controlled trial and 2 nonrandomized controlled trials.^[13-15] The

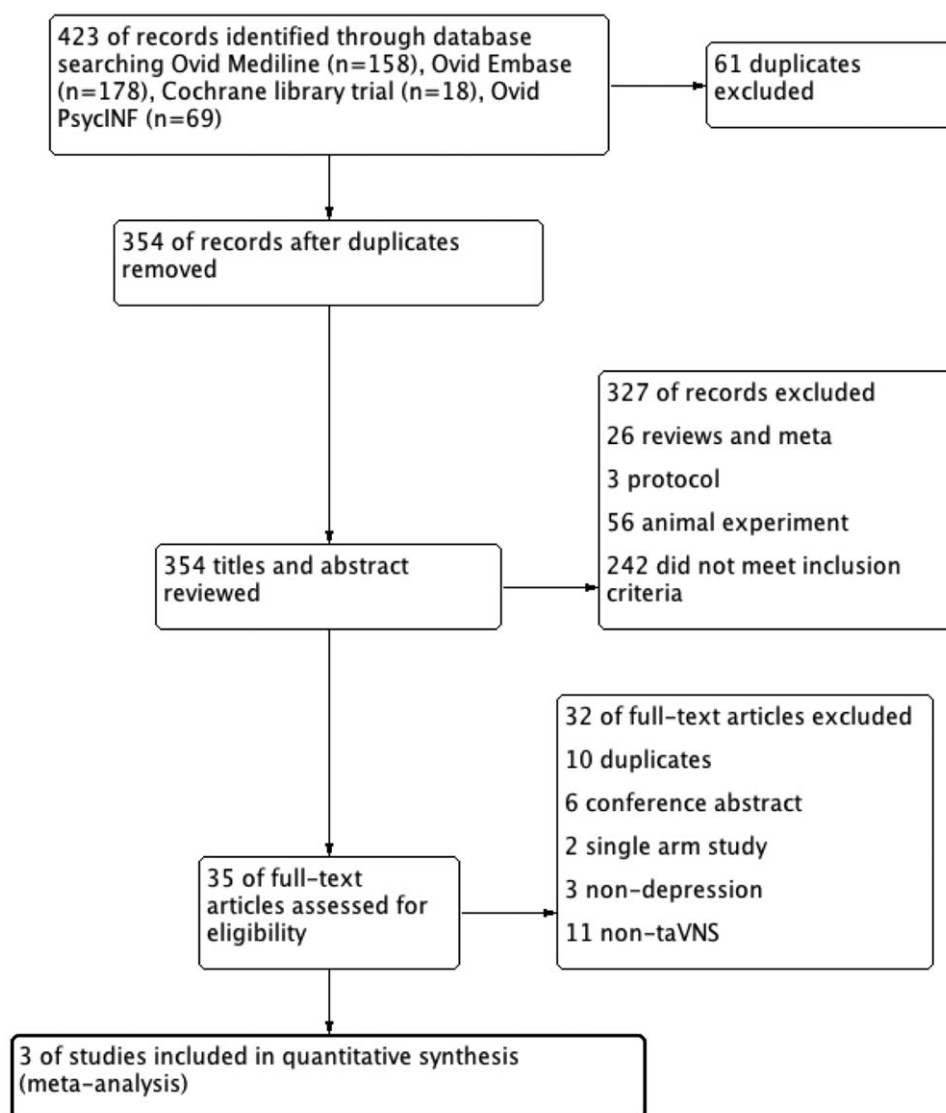


Figure 1. Screening procedure of the PRISMA flowchart.

4 included studies were published between 2013 and 2018. The clinical trials of the included studies were conducted in Germany and China. The sample sizes of the included studies ranged from 37 to 160 patients.

The population of the included studies were all major depressive disorder patients according to the ICD-10 (World Health Organization 1992), and the patients were all in a stable stage. The interventions used in the control groups were all sham taVNS.^[13–15] The therapy duration ranged from 2 weeks to 4 weeks. In addition, the frequency of treatment was mostly twice a day or at least 5 days a week. The specific characteristics of the included studies are presented in Table 1.

3.3. Quality assessment of the included studies

We assessed the quality of the included studies according to the Cochrane risk of bias tool and the risk of bias of nonrandomized studies-of interventions (ROBINS-I) tool. One randomized controlled trial^[13] reported adequate random sequence generation (selection bias), while concealment of allocation was unclear

in this RCT study. In addition, this RCT did not use blinding of either the participants or personnel. The attrition bias and reporting bias of this RCT were low risk. The other 2 clinical trials^[14,15] were evaluated with the ROBINS-I tool. All the non-RCT studies did not report confounding biases since the studies were not cohort studies. Two studies^[14,15] had a low risk of bias in the selection of participants for the study due to all the eligible subjects for the target trials being included in the study and the interventions being consistent from the start to the end of treatment. Since taVNS was a well-defined intervention in these 2 trials, the bias in classification of the intervention was low. The deviation bias from the intended intervention was low in all 2 studies, as all the studies used a blinding method to mask participants and to reduce the chance of an impact on the outcome. Two trials^[14,15] reported drop-out rates that had a low-risk bias of missing data. One study^[14] reported that the outcome assessments might not have been influenced by the knowledge of the participants, while the other one trials^[15] was unclear as to whether the outcome measures could have been influenced by knowledge of the intervention received by the participants,

Table 1**The characteristics of included studies.**

Author	Year	Patients	Intervention1	Intervention2	Outcome	Duration	Frequency	Study design
Hein, E. ^[13]	2013	Major depressive disorder	Transcutaneous auricular vagus nerve stimulation (taVNS) (n=18)	Sham taVNS (n=19)	24- item Hamilton Depression Rating Scale (HAM-D); Beck Depression Inventory (BDI)	2 weeks	15 min once (study 1) or twice a day (study 2)/ 5 days each week	Random clinical trial
Rong, P.J. ^[14]	2016	Major depressive disorder	Transcutaneous auricular vagus nerve stimulation (taVNS) (n=91)	Sham taVNS (n=69)	24- item Hamilton Depression Rating Scale (HAM-D); 14- item Hamilton Anxiety Rating Scale (HAM-A), the Self-Rating Anxiety Scale (SAS), Self-Rating Depression Scale (SDS)	4weeks, 8, 12weeks	30 min, twice a day;	Non-RCT
Tu, Y.H. ^[15]	2018	Major depressive disorder	Transcutaneous auricular vagus nerve stimulation (taVNS) (n=20)	Sham taVNS (n=21)	24- item Hamilton Depression Rating Scale (HAM-D); 14- item Hamilton Anxiety Rating Scale (HAM-A), Self-Rating Anxiety Scale (SAS), Self-Rating Depression Scale (SDS)	4weeks	30 min, twice a day; at least 5 days a week	Non-RCT (A single-blinded clinical trial)

resulting in a moderate risk of bias. All the non-RCT studies^[14,15] had a moderate risk of selection report bias. The detailed quality assessments of the RCT study and the non-RCT studies are presented in Tables 2 and 3.

3.4. Analysis of outcomes

3.4.1. Primary outcomes

3.4.1.1. 24-item Hamilton Depression Rating Scale (HAMD). Four studies used the 24-item HAMD as their primary outcome. Since the heterogeneity index, namely, I^2 , of the pooled results of the 3 studies was 64%, and P -value equalled .06, we selected a random-effects model to analyse the pooled results. The 24-item HAMD score decreased more in the taVNS group at the end of treatment than in the sham group (MD: -4.23 , 95% CI: -7.15 , -1.31 ; $P=.005$) (Fig. 2).

3.4.1.2. Self-Rating Depression Scale (SDS). Two studies used the Self-Rating Depression Scale (SDS) as a measured outcome. We selected a fixed-effects model since the heterogeneity index I^2

was 0%, and $P=.5$. The pooled results of the SDS score differed between the taVNS group and the sham group at the end of treatment (MD: -10.34 , 95% CI: -13.48 , -7.20 ; $P<.00001$) (Fig. 3).

3.4.1.3. Beck Depression Inventory (BDI). One study used the Beck Depression Inventory (BDI) as a measured outcome. The BDI score was significantly decreased in the taVNS group compared to that in the sham group (MD: -10.3 , 95% CI: -18.1 , -2.5 ; $P=.01$) (Fig. 4).

3.4.2. Secondary outcomes

3.4.2.1. Hamilton Anxiety Rating Scale (HAMA). Two studies reported the Hamilton Anxiety Rating Scale (HAMA) as a measured outcome. A fixed-effects model was chosen to analyse the pooled results due to the heterogeneity index I^2 being 0%, and $P=.47$. The pooled results showed that the HAMA score was lower (MD: -1.12 , 95% CI: -2.56 , 0.32 ; $P=.13$) in the taVNS

Table 2**Risk of bias summary for RCT study: review authors' judgements about each risk of bias item for each included study.**

STUDY TYPE: RCT study							
Author (Year)	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
Hein, E. 2013 ^[13]	Low risk of bias Use a randomized controlled design	Unclear risk of bias No related information	High risk of bias Patients in tvNS and sham tvNS did not use blinding.	Unclear risk of bias No related information	Low risk of bias no patient dropped out at the end of treatment	Low risk of bias The outcome measurements were clearly defined and both internally and externally consistent; and there was no indication of selection of the reported analysis from among multiple analyses; and there was no indication of selection of the trial for analysis and reporting on the basis of the results.	Unclear risk of bias No related information

Table 3

Risk of bias summary for non-RCTs studies: review authors' judgements about each risk of bias item for each included study.

Study Type: non-RCTs studies

Author (Year)	Bias due to confounding	Bias in selection of participants into study	Bias in classification of interventions	Bias due to deviations from intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Rong,P.J. 2016 ^[14]	NI No information	Low risk of bias (i) All participants who would have been eligible for the target trial were included in the study; (ii) For each participant, start of follow up and start of intervention coincided.	Low risk of bias taVNS is a well-defined intervention	Low risk of bias sham taVNS was used to blind the participants and there were no deviations from the intended interventions (in terms of implementation or adherence) that were likely to impact on the outcome.	Low risk of bias Seven participants from the taVNS group dropped from the study; Fifteen participants from the sham taVNS group withdrew from the study.	Low risk of bias The methods of outcome assessment were comparable across intervention groups; and the outcome measure was unlikely to be influenced by knowledge of the intervention received by study participants	Moderate (i) The outcome measurements are clearly defined and both internally and externally consistent;(ii) There is no indication of selection of the reported analysis from among multiple analyses;(iii) There is no indication of selection of the trial for analysis and reporting on the basis of the results.
Tu,Y.H. 2018 ^[15]	NI No information	Low risk of bias (i) All participants who would have been eligible for the target trial were included in the study; (ii) For each participant, start of follow up and start of intervention coincided.	Low risk of bias taVNS is a well-defined intervention	Low risk of bias sham taVNS was used to blind the participants and there were no deviations from the intended interventions (in terms of implementation or adherence) that were likely to impact on the outcome.	Low risk of bias Reported 3 patients in taVNS group and one patients in sham taVNS group dropped out at the end of treatment	Moderate The methods of outcome assessment were comparable across intervention groups; while the outcome measure was unclear whether it would be influenced by knowledge of the intervention received by study participants or not	Moderate (i) The outcome measurements are clearly defined and both internally and externally consistent; and (ii) There is no indication of selection of the reported analysis from among multiple analyses;(iii) There is no indication of selection of the trial for analysis and reporting on the basis of the results.

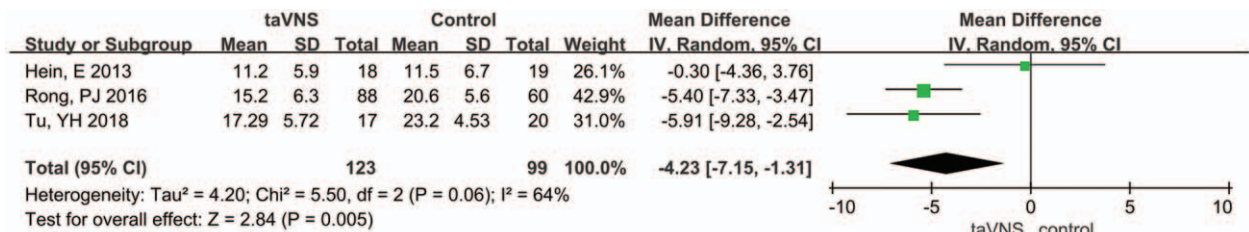


Figure 2. Forest plot of comparison for transcutaneous vagus auricular nerve stimulation (taVNS) versus sham treatment (HAMD outcome). CI=confidence interval, IV=inverse variance, SD=standard deviation.

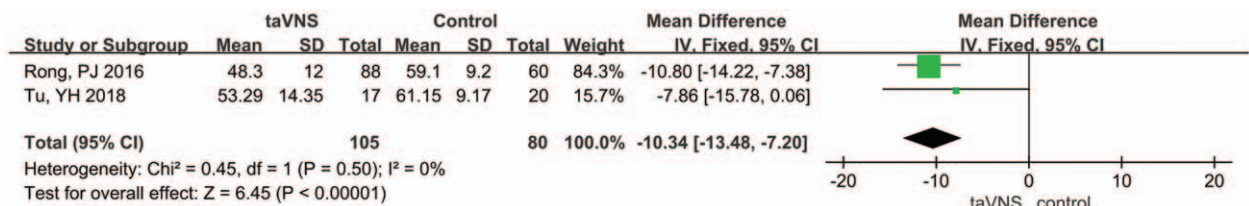


Figure 3. Forest plot of comparison for transcutaneous vagus auricular nerve stimulation (taVNS) versus sham treatment (SDS outcome). CI=confidence interval, IV=inverse variance, SD=standard deviation.

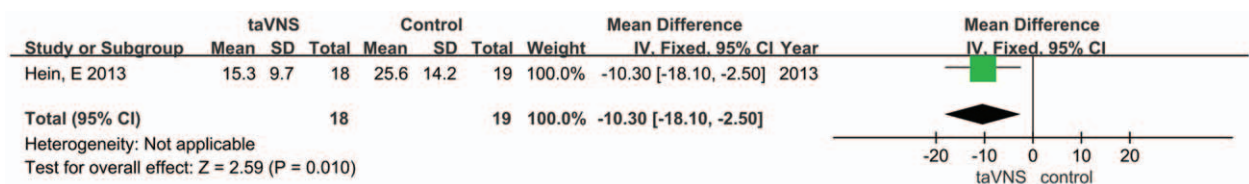


Figure 4. Forest plot of comparison for transcutaneous vagus auricular nerve stimulation (taVNS) versus sham treatment (BDI outcome). CI=confidence interval, IV=inverse variance, SD=standard deviation.

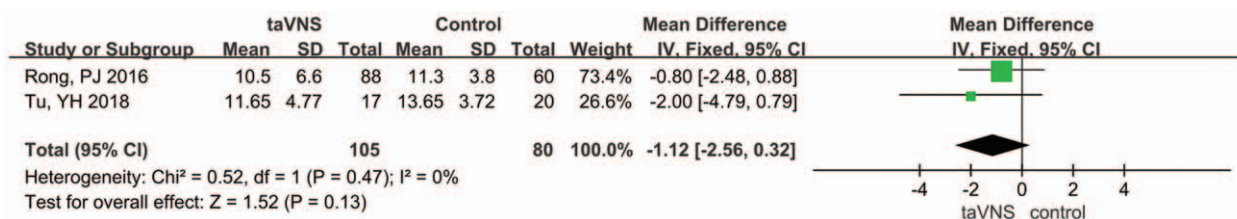


Figure 5. Forest plot of comparison for transcutaneous vagus auricular nerve stimulation (taVNS) versus sham treatment (HAMA outcome). CI=confidence interval, IV=inverse variance, SD=standard deviation.

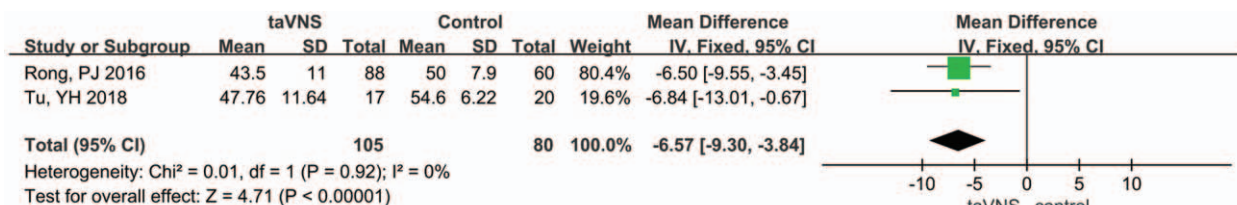


Figure 6. Forest plot of comparison for transcutaneous vagus auricular nerve stimulation (taVNS) versus sham treatment (SAS outcome). CI=confidence interval, IV=inverse variance, SD=standard deviation.

group post-intervention than in the sham group. While there were no significant differences between the taVNS and sham taVNS (Fig. 5)

3.4.2.2. Self-Rating Anxiety Scale (SAS). The Self-Rating Anxiety Scale (SAS) was used as an assessment outcome in 2 studies. The heterogeneity index I² was 0%; thus, we selected a fixed-effects model. After combining the results, the pooled results showed that there was a significant difference between the taVNS group and the sham group at the end of treatment (MD: -6.57, 95% CI: -9.30, -3.84; P < .00001) (Fig. 6).

3.5. Publication bias

Due to the small number of included studies, a funnel plot did not allow assessment of the publication bias. Therefore, we used Egger’s test to evaluate the publication bias. There was no obvious publication bias in included studies when performing Egger’s test (P = .773). The specific Egger’s tests are shown in Table 4.

3.6. Adverse outcomes

One studies recorded the side effects of transcutaneous auricular vagus nerve stimulation in treating major depressive disorder but did not report the adverse outcomes.^[15] One study reported that 2 patients who underwent taVNS and 3 patients who underwent sham taVNS had mild tinnitus side effects but recovered quickly after cessation of the taVNS intervention.^[14] Another study reported that there were no adverse side effects after the taVNS intervention.^[13]

4. Discussion

4.1. Summary of findings

We conducted this meta-analysis by mainly comparing transcutaneous auricular vagus nerve stimulation with sham taVNS. The analysis consisted of 2 study designs, namely, RCTs, and non-RCTs. Normally, RCTs are difficult to combine with other study designs in analysing the results. However, since taVNS is a new and non-invasive intervention for major depressive disorder and considering the ethical and safety concerns, there were few RCT studies involved in studying taVNS. Therefore, it seemed reasonable to combine the results of RCTs and non-RCTs together to explore the potential effects of taVNS on major depressive disorder. After performing a systematic review and meta-analysis, there were several findings as follows.

First, the pooled results of our meta-analysis demonstrated that taVNS could significantly reduce HAMD, SDS, SAS, and BDI scores. The HAMD is the most frequently used and is considered the gold standard for assessing depressive symptoms that includes evaluating the mood, suicide ideation, feelings of guilt, insomnia and other somatic symptoms of depression patients.^[16,17] The BDI scale mainly assesses depression patients from a psychodynamic perspective.^[18,19] These measured scales can comprehensively and typically evaluate the symptoms of depression. Therefore, the pooled results suggested that taVNS, as a noninvasive therapy, could alleviate the symptoms of major depressive disorder effectively. As the Hamilton Anxiety Rating Scale (HAMA) scores between the taVNS and sham taVNS groups were not significantly different, transcutaneous auricular

Table 4

Egger’s test of publication bias of all included trials comparing taVNS with control interventions Egger’s test.

Std_Eff	Coef.	Std. Err.	t	P> t	[95%Conf.Interval]	
slope	-1.148727	1.049177	-1.09	.471	-14.47979	12.18233
bias	1.588509	4.263738	0.37	.773	-52.58742	55.76444

vagus nerve stimulation might be less effective for ameliorating anxiety symptoms. Previous researchers demonstrated that vagus nerve stimulation was effective for refractory or medication-resistant depression.^[20,21] Transcutaneous auricular vagus nerve stimulation intervention also stimulates the auricular vagus nerve (afferent vagus nerve distribution) via transcutaneous auricular electric stimulation without surgical implantation. This intervention is safe and has few side effects compared to vagus nerve stimulation with surgical implantation. One researcher also analysed and summarized the treatment effects and potential mechanism of taVNS on major depressive disorder, indicating that taVNS had beneficial effects of reducing multiple symptoms of depression patients according to the changes of subscores of the 24-item HAMD scale.^[22] A portion of major depressive disorder patients may be resistant to antidepressants and may need a variety of therapies to address major depressive disorder.^[23,24] Therefore, based on our analysis results, health-care professionals could recommend that depressive patients select taVNS as an alternative intervention when confronted with resistant or refractory depression.

Second, the adverse events of taVNS intervention were mostly reported to be safe for individuals with major depressive disorder. Only one study^[14] reported that 2 patients in the taVNS group and 3 patients in the sham taVNS had tinnitus side effects, which fully recovered after self-adjustment. The side-effect reports of these studies demonstrated that taVNS was a safe therapy for major depressive disorder.

Third, the quality of the included studies showed that only one study used the random clinical trial design,^[13] while the other 2 trials used non-RCT designs, and we evaluated the quality using the ROBINS-I tool.^[14,15] The 2 non-RCT studies had a low risk of bias in the selection of the participants, classification of interventions, deviations, outcome assessments, and attrition and a moderate risk of reporting selection bias. In contrast, the confounding bias was not reported in any of these 2 trials.^[14,15]

4.2. Findings in relation to previous studies and reviews

To our knowledge, our current study was a first systematic review and meta-analysis that evaluated the effectiveness of transcutaneous auricular vagus nerve stimulation in the treatment of major depressive disorder. The previous meta-analyses mainly focused on assessing the effectiveness of vagus nerve stimulation via surgical implantation for managing major depressive disorder.^[25–27] Another review conducted a systematic review to assess auricular therapy, including ear buried seeds and transcutaneous vagus nerve stimulation, for treating major depressive disorder.^[28] Although this previous systematic review involved taVNS therapy, the review was not comprehensive and included few taVNS studies in the analysis. The above systematic reviews mainly focus on evaluating the effectiveness of vagus nerve stimulation (surgical implantation) or auricular therapy in treating depression, while studies in systematically estimating effectiveness and safety of transcutaneous auricular vagus nerve stimulation in addressing major depressive disorder were still lacking in the current. We only analysed one type of vagus nerve stimulation (transcutaneous auricular vagus nerve stimulation) for treating depression and did not combine with other therapies, thus allowing us to evaluate the clinical effects of taVNS accurately without other confounding factors.

4.3. Limitations

Several limitations in this meta-analysis need to be taken into consideration. First, most of the included studies were non-RCTs,

and only one RCT with a small sample size was included in the analysis, which may have weakened the strength of the evidence. Second, all the included studies only blinded patients and did not blind the therapists or the outcome assessors. Although it is difficult to blind the therapists, the outcome assessors could have been blinded to reduce detection bias. Third, only one study reported follow-up surveys, which may influence the evaluation of the long-term effectiveness of transcutaneous auricular vagus nerve stimulation in treating major depressive disorder.

4.4. Implications for clinical practice

We summarized the effectiveness of transcutaneous auricular vagus nerve stimulation for major depressive disorder and determined that taVNS could alleviate the symptom of depression, specifically reducing 24-item Hamilton Depression Rating Scale, Self-Rating Depression Scale, Self-Rating Anxiety Scale and Beck Depression Inventory scores, which may provide clinicians and patients with an alternative intervention for major depressive disorder. However, the evidence was not strong enough since the inclusion of only 3 studies into quantitative synthesis, which encouraged researchers to do more clinical research about taVNS in order to provide robust evidence. In addition, the current conditions and characteristics of taVNS in the treatment of major depressive disorder that we systematically reviewed are convenient for researchers to do in the future clinical research.

5. Conclusion

In conclusion, our systematic review and meta-analysis preliminarily demonstrated that transcutaneous auricular vagus nerve stimulation is an effective and safe method for treating major depressive disorder. The taVNS technique could alleviate the symptoms of depression, providing an alternative technique for patients who suffer a stable depressive disorder and are unwilling to select other invasive therapies. However, more well-designed RCTs with larger sample sizes and follow-ups are needed in future studies to confirm our findings.

Author contributions

TCZ, LLM participated in the study concept and design and manuscript authorization. WCX, LPH, FHL and CWT extracted the data and assessed studies. CSY and LLM analyzed the data. WCX wrote the manuscript and ensured the integrity of the data. All authors read and approved the final manuscript.

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Writing – review & editing: Liming Lu, Chunzhi Tang.

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