General Psychiatry

Efficacy and safety of repetitive transcranial magnetic stimulation for generalised anxiety disorder: A meta-analysis

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ABSTRACT

Background Pharmacological and conventional non-pharmacological treatments are only moderately effective in treating generalised anxiety disorder (GAD). Recently, repetitive transcranial magnetic stimulation (rTMS) has attracted interest because of its potential therapeutic value.

Aim To investigate the efficacy and safety of rTMS treatment for GAD.

Methods Literature studies published in English or Chinese were screened in 10 electronic databases up to 5 December 2018. The included studies' bias risk was assessed using Cochrane risk of bias assessment tool. Meta-analysis was performed to compute the standardised mean difference (SMD) and risk ratio (RR) along with its 95% CIs through using RevMan V.5.3. Heterogeneity was inspected by I^2 and the χ^2 test. We performed subgroup analysis and meta-regression to investigate heterogeneity. We used funnel plot to assess publication bias. We used the GRADE approach to assess the whole quality of evidence.

Results Twenty-one studies, with a total sample size of 1481, were analysed. The risk of bias in most studies included is moderate, the majority of which are lacking of blinding methods of treatment allocation. The treatment had beneficial effects in the rTMS group compared with the control group in mean anxiety score (SMD=−0.68; 95% CI −0.89 to −0.46). None of the 21 studies included here reported severe adverse events. As for dropout rates, there are no statistically significant differences between the two groups (RR 1.14, 95% CI 0.72 to 1.82) or adverse events (RR 0.95, 95% CI 0.77 to 1.18). No particular influence on the heterogeneity of any variable was observed. The risk of publication bias was low. According to the GRADE approach, the evidence levels of primary outcome (treatment effects) and secondary outcomes (acceptability and safety) were rated as 'medium'.

Conclusion The use of rTMS combined with medication treatment may have a significant positive anti-anxiety effect on patients with GAD. However, we should interpret the results cautiously due to the relatively high heterogeneity of the meta-analysis. Future high-quality clinical trials are needed to confirm our results.

INTRODUCTION

Generalised anxiety disorder (GAD) has the characteristics of chronic, overwhelming anxiety and worry.[1] In China, GAD has a lifelong prevalence of approximately 3.2%.[2] The anxiety, worry or physical symptoms cause impairment in important functionings such as occupational and social functionings, and cost much medical resource.[3] Standard first-line treatments for GAD include pharmacotherapy and psychotherapy.[4] However, treatment effects of the standard therapies are not as good as what we have expected, with approximately 50% of patients remain having residual symptoms.[5] Therefore, seeking novel treatment options for GAD is of great importance.[6]

Repetitive transcranial magnetic stimulation (rTMS) neuromodulation has merits because it is non-invasive, well tolerated, safe and so forth. There is a growing number of studies in various mental disorders.[7–11] During the rTMS treatment, the rTMS coil is placed on the scalp, and at the meantime the coil is electrified so that a magnetic field is produced which could penetrate the skull to induce effects.[12] The modulation effect of rTMS depends on the frequency, either decreasing or increasing cortical excitability.[13] The prevailing hypothesis is that the aftereffects of high-frequency (usually 5 Hz or greater) stimulation are excitatory while those of stimulation with low frequency (1 Hz or less) are inhibitory.[14] The US Food and Drug Administration has approved the high-frequency rTMS stimulation over the left dorsolateral prefrontal cortex (DLPFC) in treating resistant major depressive disorder (MDD).[15] The anxiety symptoms have also been improved in patients with MDD following the rTMS, suggesting that rTMS may be a potential treatment for anxiety disorder.[16]

Previous rTMS studies have shown the potential beneficial effects of rTMS in patients with GAD. Some studies like Bystritsky *et al*'s open-label study[17] and Diefenbach *et al*'s randomised controlled trial (RCT)[18] demonstrate fair anxiety reduction using low-frequency rTMS stimulation in GAD, whereas another study also shows a therapeutic effect using high-frequency rTMS.[19] Although the above studies found positive results of rTMS intervention in patients with GAD, they are varied in rTMS parameters and sample sizes are small. Therefore, it is difficult to get consistent conclusions in view of these studies. Recently, quite a few studies, mostly using low-frequency stimulation parameters, have been reported in China.[20–37] However, the meta-analysis of efficacy and safety of rTMS for GAD is seldom reported, and there is a need for updates.[38]

METHODS

Search strategy and methods

We searched for objective studies before 5 December 2018. The search terms were "generalized anxiety disorder", "anxiety", "transcranial magnetic stimulation", "TMS" and "rTMS". The Cochrane Library, PubMed, ISI Web of Knowledge, EMBASE and PsycInfo were retrieved. The Chinese search terms were '重复经颅磁刺激', '磁刺激', '经颅磁刺激', '跨颅磁刺激', '广泛性焦虑障碍' and '焦虑症'. We searched the following Chinese data libraries: Wanfang Data, Chinese National Knowledge Infrastructure, VIP Information, Huayi-Taiwan data and SinoMed.

Studies were included in accordance with PICOS (Participants, Intervention, Comparison, Outcomes and Study design) inclusion criteria: (1) participants: have a diagnosis of GAD according to one of the following diagnostic criteria: the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV),[39] the 10th revision of the International Classification of Disease (ICD-10),[40] the third edition of the Chinese Mental Illness Diagnostic Standard (CCMD-3)[41] or the MINI-international Neuropsychiatric Interview (MINI);[42] (2) intervention: used rTMS intervention; rTMS could be combined with drug therapy; (3) comparison: the control group used sham rTMS or received no intervention; (4) outcomes: the primary outcome was rTMS efficacy in decreasing the anxiety symptoms of patients with GAD; the secondary outcomes were acceptability and safety of rTMS; (5) study design: RCT. Studies such as case reports, case series, observational studies, meta-analyses and systematic reviews were not included in this study.

Literature search and data extraction

Two reviewers (HC and LJ) independently performed the literature search using the same search strategy. All retrieved literature was managed using the EndNote X7 software. Literature screening and data extraction were performed as follows: (1) duplicates of retrieved studies were excluded. (2) The studies were screened by checking the titles together with their abstracts and studies found to be inappropriate were excluded. (3) As for the remaining

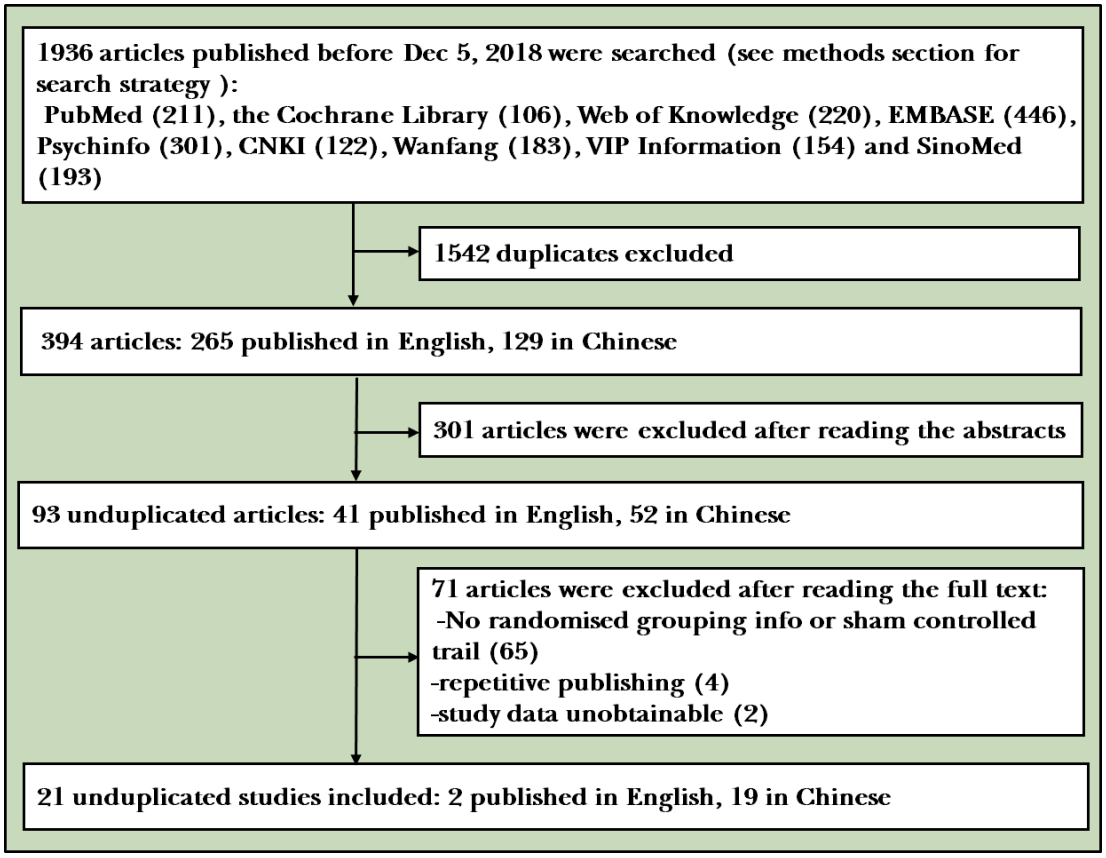

Figure 1 Flowchart of the literature screening.

Table 1 Basic characteristics of the included studies

Number	Studies	Diagnostic criteria	Blind method	Sample size (M/F) for rTMS group	Sample size (M/F) for control group	Age (M (SD)) for rTMS group	Age (M±SD) for control group	Stimulation site	Stimulation frequency Stimulation intensity (%MT)	Treatment frequency Number of pulses	Sham stimulation
1	Diefenbach 2016[18]	MINI	Double blind	13 (2/11)	12 (4/8)	44.00 (11.95)	44.58 (14.75)	R-DLPFC	1 Hz 90%	30 times 900 pulses	Sham coil
2	Dilkov 2017[19]	MINI	Double blind	15 (9/6)	25 (12/13)	34 (7)	38 (10)	R-DLPFC	1 Hz 110%	25 times NA	90°
3	Zhang 2010[20]	CCMD-3	NA	34 (12/22)	32 (13/19)	36.1 (9.6)	36.84 (8.1)	R-DLPFC	1 Hz 90%	12 times 1200 pulses	NA
4	Zhu 2011[21]	CCMD-3	NA	35 (7/28)	35 (9/26)	45.4 (9.5)	45.9 (8.7)	L-DLPFC	10–15 Hz NA	10 times NA	NA
5	Li 2012[22]	DSM-IV	NA	22 (12/10)	20 (14/6)	43.0 (13.3)	44.4 (10.6)	R-parietal lobe	1 Hz 90%	10 times 500 pulses	Sham coil
6	Zhang 2012[23]	CCMD-3	NA	42 (23/19)	42 (22/20)	12.8	13.7	R-DLPFC	1 Hz 80%	10 times NA	NA
7	Xiao 2014[24]	CCMD-3	NA	35 (17/18)	33 (15/18)	37.36 (13.72)	36.84 (14.36)	R-DLPFC	1 Hz 90%	10 times 600 pulses	NA
8	Guo 2015[25]	CCMD-3	NA	56 (29/27)	57 (32/25)	30.85 (8.12)	31.17 (7.24)	L-PFC	1 Hz 80%	20 times 2400 pulses	180°
9	Hou 2015[26]	CCMD-3	NA	30 (16/14)	30 (18/12)	34.86 (7.21)	35.24 (7.39)	L-DLPFC	1 Hz 80%	30 times 2400 pulses	NA
10	Qu 2015[27]	ICD-10	NA	28 (12/16)	30 (11/19)	38.1 (9.7)	39.0 (9.0)	R-DLPFC	1 Hz 80%	20 times NA	Sham coil
11	Wang1 2015[28]	DSM-IV	Single blind	20 (9/11)	20 (11/9)	40.15 (10.1)	39.3 (12.5)	R-DLPFC	10 Hz 90%	24 times 500 pulses	Sham coil
12	Wang2 2015[28]	DSM-IV	Single blind	20 (10/10)	20 (11/9)	39.1 (11.6)	39.3 (12.5)	R-DLPFC	1 Hz 90%	24 times 500 pulses	Sham coil
13	Wu 2015[29]	DSM-IV	NA	20 (11/9)	20 (12/8)	41.05 (10.3)	42.81 (9.85)	R-DLPFC	1 Hz 100%	10 times 600 pulses	NA
14	Zhang 2015[30]	ICD-10	NA	30 (13/17)	30 (11/19)	31.7 (9.3)	33.2 (10.8)	R-DLPFC	1 Hz 100%	30 times NA	90°
15	Liu 2016[31]	ICD-10	NA	30 (11/19)	30 (12/18)	44.1 (12.04)	43.77 (9.24)	R-DLPFC	1 Hz 100%	30 times NA	NA

Continued

Table 1 Continued

Number	Studies	Diagnostic criteria	Blind method	Sample size (M/F) for rTMS group	Sample size (M/F) for control group	Age (M (SD)) for rTMS group	Age (M±SD) for control group	Stimulation site	Stimulation frequency Stimulation intensity (%MT)	Treatment frequency Number of pulses	Sham stimulation
16	Ren 2016[32]	CCMD-3	NA	84 (50/34)	81 (48/33)	34.15 (12.12)	35.62 (12.33)	R-DLPFC	1 Hz 90%	21 times 600 pulses	NA
17	Wang 2016[33]	CCMD-3	NA	30 (13/17)	30 (14/16)	46.8 (6.3)	46.8 (6.3)	R-DLPFC	1 Hz 90%	20 times NA	NA
18	Wu 2016[34]	ICD-10	Single blind	36 (16/20)	28 (13/15)	38.6 (7.3)	38.1 (6.8)	L-PFC	1 Hz 80%	30 times 2400 pulses	90°
19	Wu 2017[35]	ICD-10	Single blind	33 (18/15)	37 (14/23)	44.7 (8.36)	43.19 (10.06)	R-DLPFC	1 Hz 90%	20 times NA	90°
20	Zhai1 2017[36]	CCMD-3	NA	28 (13/15)	28 (12/16)	67.13 (4.36)	67.22 (4.13)	R-DLPFC	1 Hz 90%	20 times NA	NA
21	Zhai2 2017[37]	ICD-10	NA	100 (62/38)	100 (59/41)	39.62 (10.1)	38.9 (9.8)	R-DLPFC	1 Hz 80%	20 times NA	Sham coil

CCMD-3, third edition of the Chinese Mental Illness Diagnostic Standard; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th ed; F, female; ICD-10, 10th revision of the International Classification of Diseases; L-DLPFC, left dorsolateral prefrontal cortex; M, male; MINI, MINI-international Neuropsychiatric Interview; MT, motor threshold; NA, no data or not described; R-DLPFC, right dorsolateral prefrontal cortex.

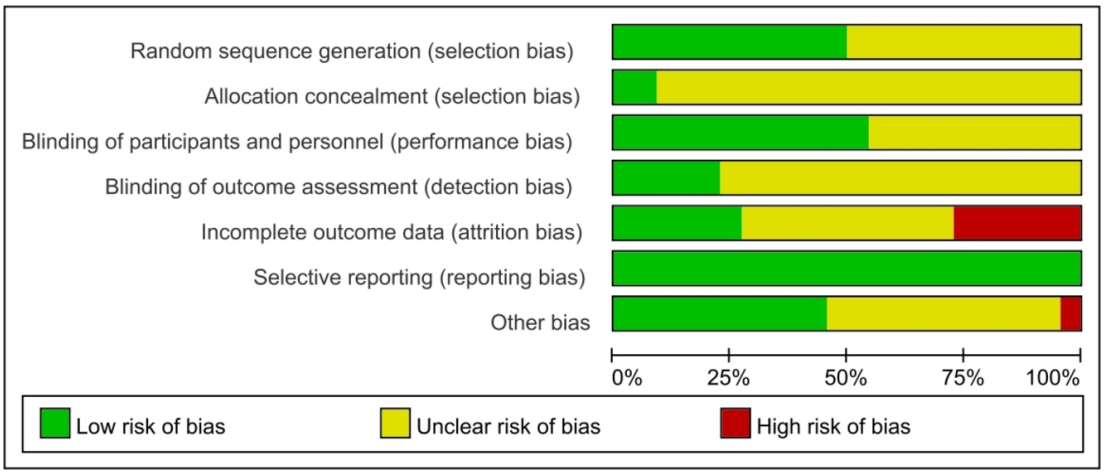

Figure 2 Risk of bias graph: in the form of percentage of each bias risk in all included studies.

literature, full text was checked to confirm their eligibility for inclusion. If the two search results were different, the two researchers reviewed the literature together and analysed the reasons for differences. If the opinions were still inconsistent, a third researcher (HL) would examine the literature and make a final decision. The literature screening process of this study is shown in figure 1.

The extraction form for included information was developed by HC. Two researchers (LJ and JZ) extracted the relevant data independently. The extracted data included the following items: study author, year of publication, diagnostic criteria, blind method, sample characteristics, stimulation site, stimulation frequency, stimulation intensity based on resting motor threshold, treatment regimen and sham rTMS methods. HRC checked the extraction results.

Quality evaluation of literature

In accordance with the criteria of bias risk given by the Cochrane handbook, two researchers (HL and WL) independently evaluated the risk of bias. When there was discrepancy between the evaluations of the two researchers, the conclusion would be determined by a third researcher (JP). The specific contents included the following: (1) random sequence generation (selection bias); (2) allocation concealment (selection bias); (3) blinding of subjects and researchers (performance bias); (4) blinding of outcome data (detection bias); (5) incomplete outcome data (attribution bias); (6) selective reporting (reporting bias); (7) other bias. When the assessment information was lacking, we contacted the corresponding author via email.

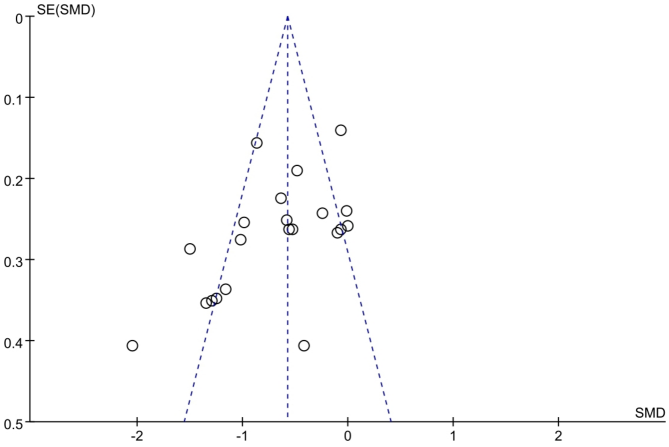

Figure 3 Funnel plot to assess potential publication bias in 21 included studies. SMD, standardised mean difference.

Outcome measures

The primary outcome of this study was rTMS efficacy in decreasing the anxiety symptoms of patients with GAD, which was measured using the reductions of anxiety symptoms assessed by the Hamilton Anxiety Scale (HAMA).[43]

The secondary outcomes: (1) acceptability, which was measured using the dropout rates during the treatment courses. (2) Safety, which was assessed using the number of adverse events like nausea, headache, syncope, insomnia, epilepsy or burned by electrode.

We used Review Manager (RevMan) V.5.3 to compute the combined effects of relative risk (RR), standardised mean deviation (SMD) and CIs. I^2 test was used to estimate heterogeneity level (I^2=25% meant low-level heterogeneity, 50% medium and 75% high).[44] A fixed-effects model was used when there was no significant heterogeneity (I^2<50%, p≥0.1), while a random-effects model was selected when heterogeneity was significant (I^2≥50%, p<0.1).

Subgroup analysis and meta-regression analysis

Subgroup analyses were conducted in the left hemisphere versus right hemisphere studies, high frequency (>1 Hz) versus low frequency (≤1 Hz) studies, and high treatment times (>20 times) versus low treatment times (≤20 times) studies.

The sources of heterogeneity were explored using meta-regression analysis. Meta-regression analysis was performed using Stata V.15.0 statistical software.[45]

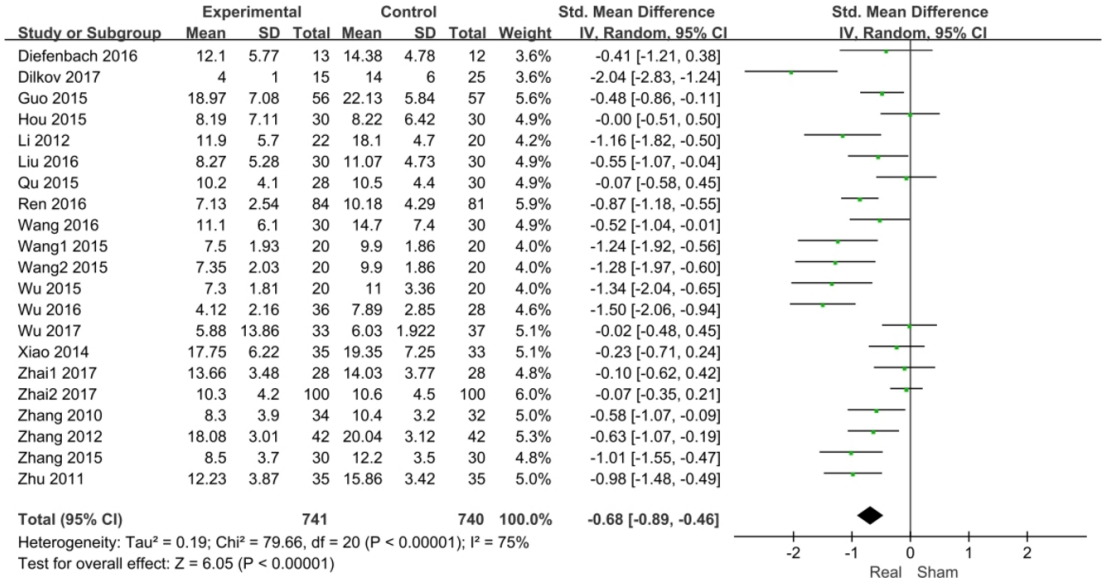

Figure 4 Forest plot illustrating efficacy of repetitive transcranial magnetic stimulation group compared with control group in the treatment of generalised anxiety disorder. Random-effects models were used.

Assessment of reporting biases and sensitivity analysis

The Cochrane funnel plot was used to detect potential publication bias. The planned sensitivity analyses: (1) open-label RCTs will be excluded. (2) The international studies will be excluded.

GRADE assessment

Quality of evidence was assessed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method.[46] The quality of evidence grades were as follows: (1) high quality, further study was difficult to affect the reliability of the efficacy evaluation results; (2) medium quality, further study was easy to affect the reliability of the efficacy evaluation results and was very likely to change the outcome of the evaluation; (3) low quality, further research was very easy to affect the reliability of the efficacy evaluation results and the evaluation outcome was very likely to change; (4) extremely low quality, the results of any efficacy evaluation were uncertain. Two authors (YW and WL) independently used the GRADE method to rate the overall evidence quality.

RESULTS

Extracted data of included studies

In total, 1481 subjects from 21 studies were included in our meta-analysis, which had 732 men and 749 women. One of the 21 studies included only male subjects.[47] All GAD subjects had to fulfil the diagnostic criteria listed as follows: MINI, ICD-10, CCMD-3 or DSM-IV. In 17 studies, the rTMS treatment was applied to the right hemisphere, including 16 studies where treatment was applied to the right DLPFC and one study to the right parietal lobe. Two studies used high-frequency stimulation,[21 28] while the other 19 studies used 1 Hz low-frequency stimulation. The range of stimulation intensity of all included studies was from 80% to 110% (of resting motor threshold). As

Table 2 Summary of the quality grade rating of different outcome indicators for the efficacy of rTMS for GAD

Outcome indicator	Number of included cases	Heterogeneity		Model of analysis	Group effect value		Esimated value	95% CI	GRADE
		I^2	p		Z	p			
Treatment effects: reduction of anxiety symptoms using HAMA	1481	75%	<0.001	Random effect	10.61	<0.001	−0.68 (SMD)	−0.89 to -0.46	Moderate
Acceptability: drop-outs for any reason, no of drop-outs	1339	0%	0.57	Fixed effect	0.57	0.57	1.14 (RR)	0.72 to 1.82	Moderate
Safety of rTMS: adverse effects, no of adverse events	1073	0%	0.49	Fixed effect	0.43	0.67	0.95 (RR)	0.77 to 1.18	Moderate

GAD, generalised anxiety disorder; GRADE, Grading of Recommendation Assessment, Development and Evaluation; HAMA, Hamilton Anxiety Scale; RR, relative risk; rTMS, repetitive transcranial magnetic stimulation; SMD, standardised mean difference.

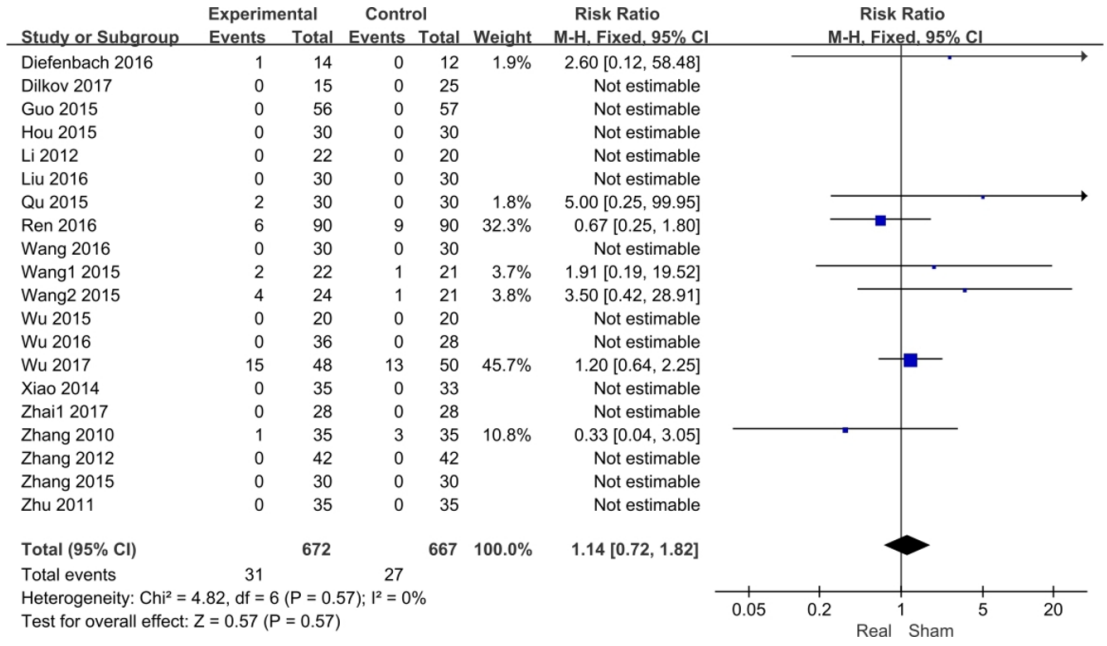

Figure 5 Forest plot illustrating acceptability of repetitive transcranial magnetic stimulation group compared with control group in the treatment of generalised anxiety disorder. Fixed-effects models were used.

for treatment times, the range varied from 10 times to 30 times. As for sham rTMS methods, six studies used sham coils. Four studies rotated the coil by 90° and one study rotated it by 180° to achieve the effect of sham therapy. However, 10 studies did not specify how the sham stimulus was provided. Both 'Wang1 2015' and 'Wang2 2015' were from two studies in Wang's master thesis[28] (table 1).

Risk of bias in included studies

The results of risk of bias are shown in figure 2. As for random sequence generation selection bias, 10 studies were rated as 'low risk'.[18 19 21 26 28 29 31 35–37] For allocation concealment selection bias, only two studies reported allocated details rating as 'low risk'.[18 19] For binding of subjects and researchers performance bias, there were six studies reporting binding details and were rated as 'low risk'.[18 19 28 34 35] There were six studies that reported incomplete data due to drop-out and adverse effects,[22 23 30 32–34] and they were rated as 'high risk'. For selective reporting bias, all 21 included studies got 'low risk' for none of them reporting results selectively. 'Unclear risk' was given to studies which had unclear information (figure 2).

Furthermore, the funnel plot was quite symmetrical, which suggested the publication bias for included studies was low risk (figure 3).

Effects of interventions

Efficacy of rTMS treatment

All 21 included studies assessed the efficacy of the rTMS using the HAMA scale (the primary outcome measure).

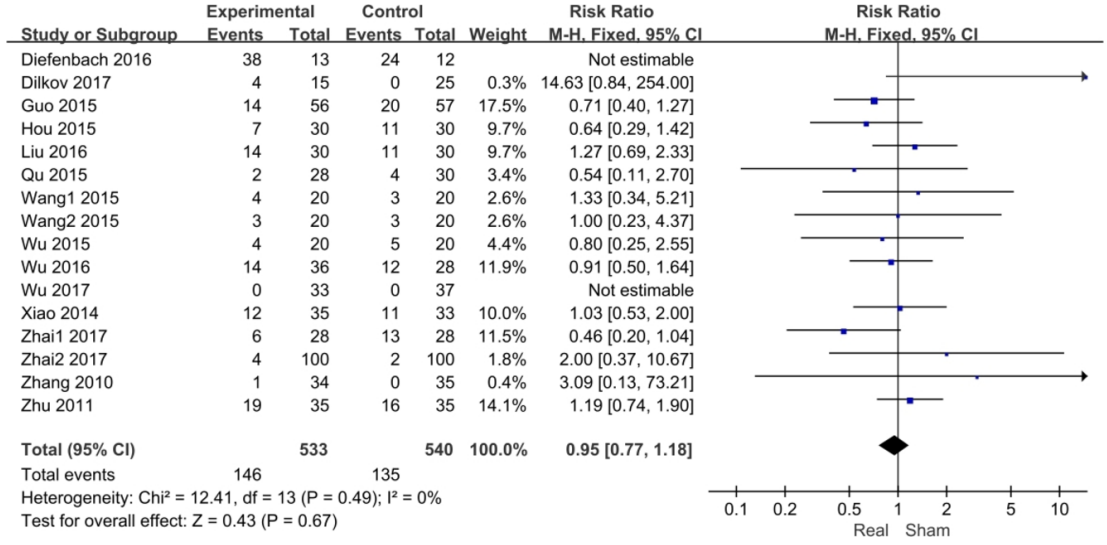

Figure 6 Forest plot illustrating adverse effects of repetitive transcranial magnetic stimulation group compared with control group in treating generalised anxiety disorder. Fixed-effects models were used.

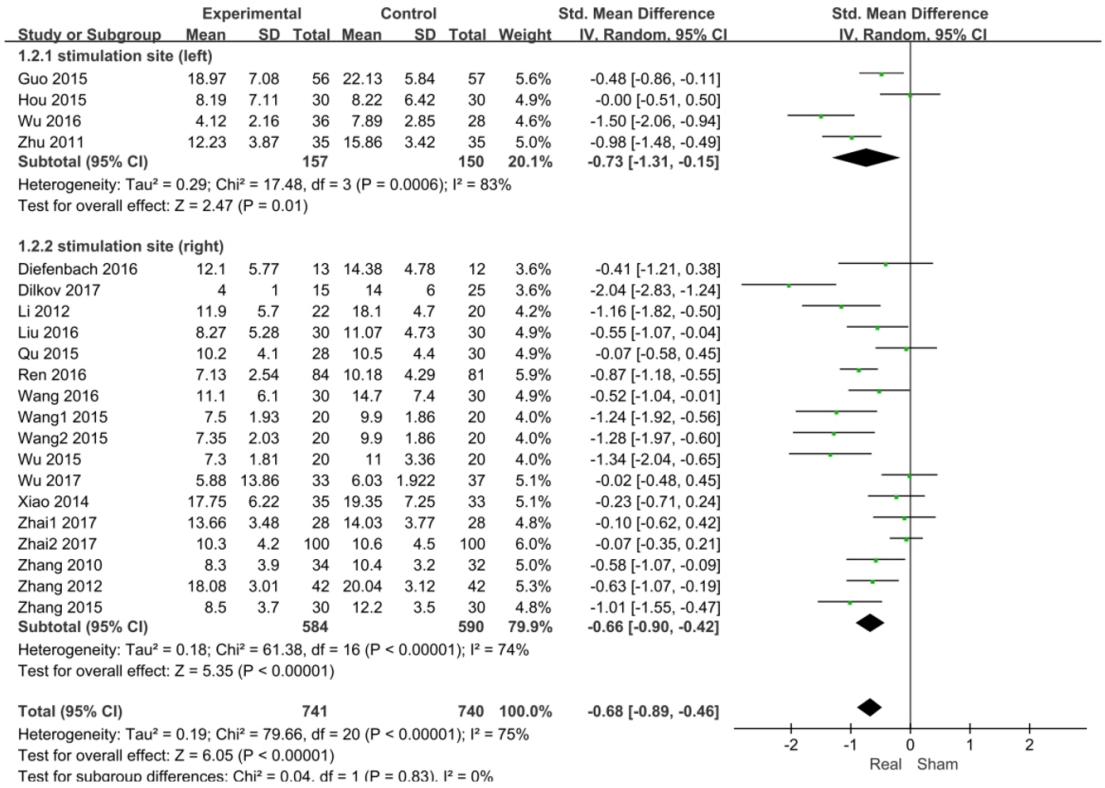

Figure 7 Forest plot of subgroup analysis illustrating efficacy of repetitive transcranial magnetic stimulation group compared with control group in treating generalised anxiety disorder: left hemisphere vs right hemisphere. Random-effects models were used.

The heterogeneity of the included studies was high, that was, χ^2=79.66, I^2=75%, and random effects model was selected here. Comparisons of the post-treatment HAMA scores indicate that rTMS was an effective treatment in improving anxiety symptoms of GAD (SMD=−0.68, 95% CI −0.89 to −0.46), and the difference between treatment group and control group was statistically significant (Z=6.05, p<0.001) (figure 4). The overall quality of the evidence of the improvement of anxiety symptoms is 'moderate', according to the GRADE evaluation criteria (table 2).

Acceptability of rTMS treatment

We analysed the drop-out data from 20 studies which reported drop-outs. The fixed-effects model was selected because of no heterogeneity (χ^2=4.82, I^2=0%). The analysis results found RR was 1.14% and 95% CI was 0.72 to 1.82. There were no significant differences between the rTMS treatment group and control group (Z=0.57, p=0.57) (figure 5). The GRADE evidence quality of the outcome was rated as 'moderate' (table 2).

Adverse effects of rTMS treatment

There were 16 studies that reported adverse effects with a total sample size of 1073. They reported mild headaches, dizziness, pain in the stimulated area, insomnia and facial spasm. There were no reports of severe adverse events in any included study. The meta-analysis showed that there were no significant differences between the rTMS treatment group and control group (RR 0.95, 95% CI 0.77 to 1.18, Z=0.43, p=0.67). The heterogeneity was quite low; therefore, a fixed-effects model was applied (χ^2=12.41, I^2=0%) (figure 6). As shown in table 2, the GRADE evidence quality was rated as 'moderate'.

Subgroup analysis

The result of the subgroup analysis for rTMS-stimulated sites (left or right hemisphere) was calculated. No significant difference of the effect size of rTMS for GAD was observed betweenthe left hemisphere subgroup (χ^2=17.48, I^2=83%, Z=2.47, p=0.01) and right hemisphere subgroup (χ^2=61.38, I^2=74%, Z=5.35, p<0.001) (figure 7).

Subgroup analysis of stimulated frequency was performed between the subgroup with frequency higher than 1 Hz (high frequency) and subgroup with frequency lower ≤1 Hz (low frequency). Subgroup analysis showed that no significant difference of the effect size was observed between high frequency subgroup (χ^2=0.36, I^2=0%, Z=5.23, p<0.001) and low frequency subgroup (χ^2=72.92, I^2=75%, Z=5.42, p<0.001) (figure 8).

Subgroup analysis was performed according to the number of treatments, that were the high number of treatments subgroup (>20 times) and low number of treatments subgroup (≤20 times). This subgroup analysis revealed a significant difference (p=0.03) between the high number subgroup (χ^2=29.85, I^2=73%, Z=5.18, p<0.001) and low number subgroup (χ^2=30.87, I^2=64%, Z=4.06, p<0.001) (figure 9).

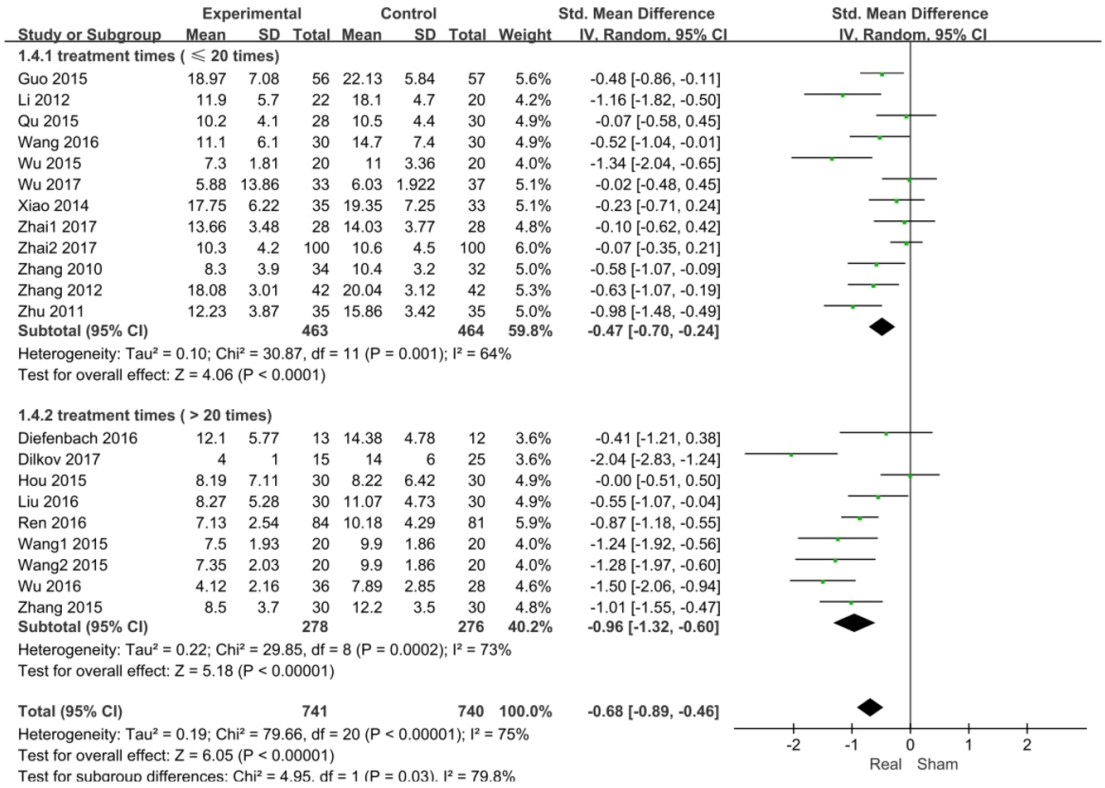

Figure 9 Forest plot of subgroup analysis illustrating efficacy of repetitive transcranial magnetic stimulation group compared with control group in treating generalised anxiety disorder: treatment regimen ≤20 times vs treatment regimen >20 times. Random-effects models were used.

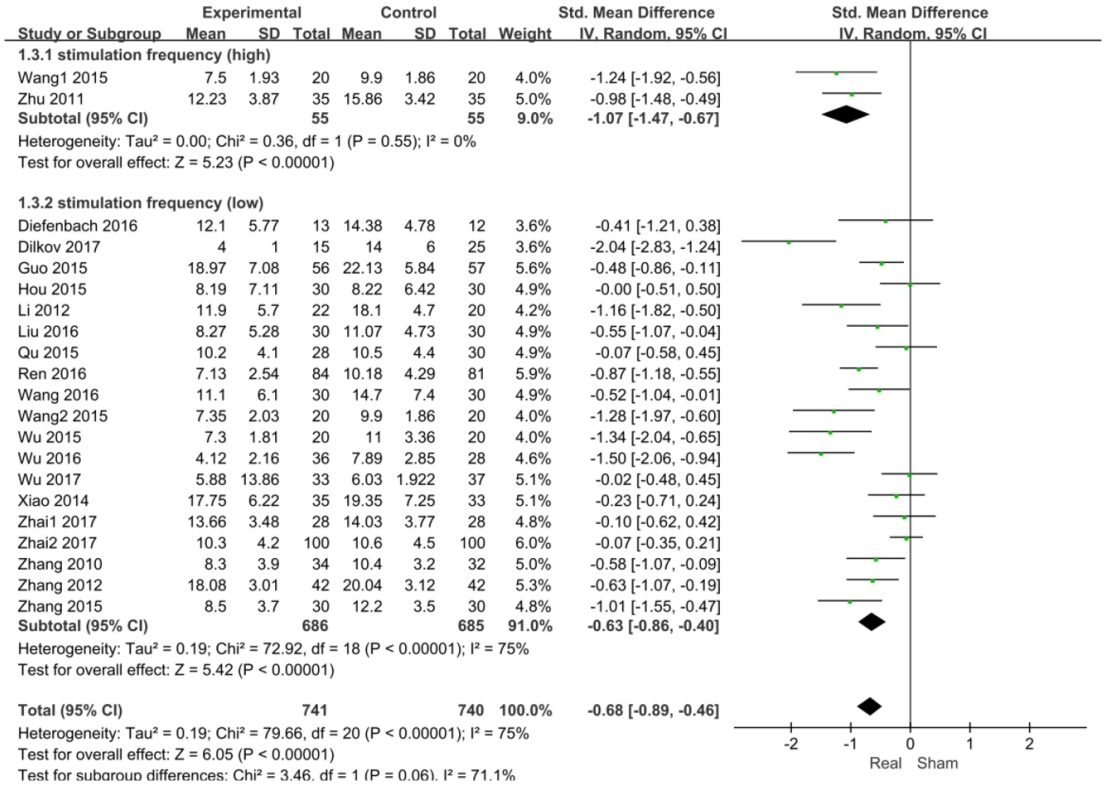

Figure 8 Forest plot of subgroup analysis illustrating efficacy of repetitive transcranial magnetic stimulation group compared with control group in treating generalised anxiety disorder: high frequency stimulation vs low frequency stimulation. Random-effects models were used.

Meta-regression analysis

The heterogeneity of results may be due to differences between studies with respect to patients' baseline symptoms, age and differences in rTMS regimens. However, the meta-regression analysis results indicated that these three variables did not contribute to heterogeneity (table 3).

Sensitivity analysis

Results of sensitivity analyses demonstrate that the effects and conclusions remained stable when excluding open-label studies, or international studies, indicating that our results were statistically robust (online supplementary figures S1 and S2).

DISCUSSION

Main findings

By integrating Chinese and international research, this meta-analysis has a relatively large sample size of 1481 subjects from 21 studies. Our results suggest that the effect of rTMS plus drug therapy may be better than drug therapy alone in decreasing the anxiety symptoms of GAD.

This meta-analysis found that rTMS might be an effective therapy in decreasing the anxiety symptoms of GAD, which was consistent with other studies.[19 38 48] Moreover, the therapy effects of rTMS still existed in subgroup comparisons in terms of stimulation sites, frequencies and number of treatments with rTMS. In any case, the positive results may be beneficial to improving people's attitudes towards mental illness in the long run.[49]

Furthermore, subgroup analysis by treatment number showed that rTMS had significantly better effects in the high number subgroup than low number subgroup, which suggests the number of rTMS sessions is important to therapeutic effects. However, if the rTMS dosing is too intensive, some patients would refuse and leave. Therefore, developing the optimal, acceptable and feasible dosing treatment of rTMS is of great importance.[18]

In terms of acceptability and adverse effects, rTMS had good acceptability, and no serious adverse effects were found. Moreover, rTMS could be effective for at least two ethnicities since included subjects in our study were from both Western and Asian countries. Therefore, rTMS appears to be an effective, safe intervention in treating patients with GAD. However, as is well illustrated by this meta-analysis, we need more high-quality studies to contribute to the optimal parameter settings in the future. Note that the overuse of rTMS should be avoided due to the uncertainties about its exact neural mechanism.[50–52]

All studies claimed that they used randomised methods in their studies; however, only two papers reported detailed allocation concealment. As a result, the risk of selection bias is quite high here (figure 2). On the basis of the risk of bias assessment of every study, the evidence quality GRADE rating of the primary outcome indicator (treatment effects) was 'moderate', meaning that the outcome indicator result was a medium recommendation for supporting the use of rTMS intervention. High-quality studies are needed to substantiate the findings in this study.

Table 3 Meta-regression of the included studies

Factor	Coefficient	SE	t	P>|t|	95% CI
Baseline HAMA score	−0.15	0.48	−0.31	0.76	−1.12 to 0.86
Age	−0.08	0.12	−0.71	0.49	−0.33 to 0.16
Treatment times of rTMS	−0.19	0.15	−1.21	0.24	−0.51 to 0.14

HAMA, Hamilton Anxiety Scale; rTMS, repetitive transcranial magnetic stimulation.

Limitations

We should pay attention to some limitations of this meta-analysis. One limitation is the small sample size existing in some of the included studies, which may lead to statistical bias. Another limitation is that our included studies recruited different subjects and adopted different treatment parameters. The differences were reflected in the age and baseline anxiety levels of patients with GAD, and in the rTMS parameters (eg, stimulation site, frequency and regimen). Although all these differences are not sources of heterogeneity based on the subgroup analysis and meta-regression, the existance of robust heterogeneity suggests that we must be cautious about the current conclusion. Moreover, the latest ideas suggest we could use connectivity-based targeting[53] or neuronavigation[54] to help optimise rTMS' effects. However, none of the Chinese studies included in this meta-analysis use the aforementioned methods to promote the effects of rTMS.

Implications

This meta-analysis evaluated the effect of rTMS intervention plus drug therapy in treating GAD and found that the use of rTMS had a relative effect on the improvement of anxiety symptoms. Although it had good acceptability and safety, the treatment might induce adverse effects such as dizziness and headache, among others. For patients with GAD who were resistant to traditional treatments, the use of rTMS might be considered clinically. However, we should interpret the results cautiously due to the high heterogeneity of this study.

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