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Original Article

Efficacy and placebo response of repetitive transcranial magnetic stimulation for primary insomnia

Binghu Jiang [a], Dongmei He [b], Zhiwei Guo [a], Qiwen Mu [a], Liwen Zhang [c, *]

[a] Imaging Institute of Rehabilitation and Development of Brain Function, Nanchong Central Hospital, The Second Clinical Medical College, North Sichuan Medical College, Nanchong 637000, Sichuan, China

[b] Department of Neurology, Nanchong Central Hospital, The Second Clinical Medical College, North Sichuan Medical College, Nanchong 637000, Sichuan, China

[c] Department of Neurology, BenQ Medical Center, the Affiliated BenQ Hospital of Nanjing Medical University, Nanjing 210019, China

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ABSTRACT

Background: Repetitive transcranial magnetic stimulation (rTMS) has been considered a promising technique for the treatment of primary insomnia. However, its efficacy and placebo response remains unclear due to limited clinical data. Therefore, we conducted a systematic review to examine the efficacy and placebo response of rTMS.

Methods: We performed a comprehensive literature search for clinical trials evaluating the efficacy of rTMS addressing primary insomnia. To pool effect size estimates (Hedges' *g*) of active rTMS and sham rTMS across studies for outcome measures, a meta-analysis was done according to the Cochrane guideline.

Results: In sum, rTMS significantly improved insomnia symptoms in the active rTMS group, and the pooled effect size of Pittsburgh Sleep Quality Index (PSQI) was −0.98 (95% CI: −1.28, −0.68) for treatment duration of 10 days, −1.16 (95% CI: −1.51, −0.82) for 20 days, and −2.14 (95% CI: −2.45, −1.83) for 30 days, respectively. However, the placebo response was also significant, reducing insomnia symptoms in the sham rTMS group. Furthermore, 73.5% (95% CI: 50.8%, 96.2%) of the effect size of active rTMS was actually produced by sham rTMS.

Conclusion: The rTMS was effective in the treatment of primary insomnia, yet, the placebo effect of sham stimulation was highly significant. This new evidence may alter rTMS regimen for insomnia from a clinical and methodological point of view. Finally, in future research more objective data and multicenter double-blinded controlled studies should be encouraged.

1. Introduction

Primary insomnia is defined by difficulties in falling asleep, maintaining sleep, and early morning awakening. Moreover, it is coupled with daytime consequences such as fatigue, attention deficits, and mood instability. These symptoms persist over a period of at least three months [1]. Furthermore, the diagnostic prevalence rises to almost 50% of the population, additionally, insomnia poses substantial risks for the development of cardiovascular, cancer, and mental disorders [2,3].

Approximately 40% of patients with primary insomnia do not reach sustained remission with the treatments of cognitive behavioral therapy, benzodiazepines, and benzodiazepine-receptor agonists [4]. Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive brain stimulation technique, which is useful in various neuropsychiatric and cognitive disorders [5,6]. Abnormal plasticity-related transcranial magnetic stimulation (TMS) phenomena have been demonstrated in obstructive sleep apnea syndrome, restless legs syndrome (RLS), insomnia, and sleep-deprived healthy subjects; moreover, TMS techniques may provide a further understanding on the role of neurotransmission pathways and plastic remodeling of neuronal networks involved in common sleep disorders [7,8]. Additionally, the placebo response to drugs for neuropsychiatric disorders is noticeable. For instance, the inactive placebos produced improvement that was 75% of the effect of the

* Corresponding author. Department of Neurology, BenQ Medical Center, Affiliated BenQ Hospital of Nanjing Medical University, 71 Hexi Street, Jianye District, Nanjing, Jiangsu 210019, China.
E-mail address: fskjbh@126.com (L. Zhang).

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active antidepressants and that of 64% in hypnotics [9–11]. Concerning insomnia trials, the proportion of the placebo (sham-rTMS) response to active-rTMS remains unclear.

Therefore, we performed a meta-analysis of clinical cohort trials of active-rTMS controlled by sham-rTMS to analyze the efficacy and placebo response of rTMS in patients with primary insomnia.

2. Materials and methods

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement was followed for this pooled analysis [12]. We searched PubMed, EMBASE, the Cochrane library, and China National Knowledge Infrastructure (CNKI) for sham-rTMS controlled clinical trials that examined the efficacy of rTMS for the treatment of primary insomnia through March 31, 2019 by using combination of “transcranial magnetic stimulation” or “repetitive transcranial magnetic stimulation” or “TMS” or “rTMS” and “primary insomnia” or “chronic insomnia”.

2.1. Inclusion and exclusion criteria

We included a study if: (1) participants had primary insomnia; (2) the active rTMS was used for treatment of primary insomnia, and sham rTMS was used for the control group; (3) objective or subjective outcome variables for determining effect size of active rTMS and sham rTMS were available. Studies were excluded if: (1) there was sample overlap; (2) a combination of drugs and rTMS; or (3) if the study was a case report.

2.2. Data extraction and quality assessment

Two independent raters (B.J. and D.H.) abstracted data using a standardized form, and disagreements were resolved by discussion. We extracted the following data: author, sample size and demographic characteristics of participants, characteristics of rTMS, treatment duration, and separate outcome measures before and after rTMS in active group and sham group. If the mean and standard deviation (SD) of the change scores were not directly extracted from the text, they were calculated by using the following formula recommended by the Cochrane Handbook for Systematic Reviews of Interventions [13]:

$$\text{Mean}_{\text{change}} = \text{Mean}_{\text{final}} - \text{Mean}_{\text{baseline}}$$

$$\text{SD}_{\text{change}} = \sqrt{\text{SD}^2_{\text{baseline}} + \text{SD}^2_{\text{final}} - (2{*}\text{Corr}{*}\text{SD}_{\text{baseline}}{*}\text{SD}_{\text{final}})}$$

The same two raters (B.J. and D.H.) independently assessed the quality of included studies using the Newcastle–Ottawa Quality Assessment Scale for Cohort Studies, which is recommended by the Cochrane Collaborative Group for the assessment of quality of nonrandomized studies [14]. Based on patient selection (four criteria), study-control group comparability (one criterion) and outcome assessment (three criteria), studies meeting ≥ 5 criteria were considered to be of a high quality.

2.3. Quantitative data synthesis

Data were pooled using the DerSimonian and Laird random effects model for efficacy of between-group outcome measures. We calculated separate and pooled within-group effect size for the continuous variables using Hedges' *g* and its 95% confidence interval (CI) in placebo and drug conditions. Hedges' *g* is a variation of Cohen's *d* that corrects for bias due to small sample sizes, and its magnitude can be interpreted small (0.20), medium (0.50), and large (0.80) [10,15]. The proportion of sham rTMS response to active rTMS response was calculated using a method described by Kirsch and Sapirstein [15]. Adverse events were also compared between groups.

We used the I^2 and Cochran-Q test to assess the heterogeneity. When significant heterogeneity was identified, subgroup analysis was considered to investigate the potential sources. Statistical analysis was performed with the Stata software version 15.0 (Stata, College Station, Texas). Two-tailed *p* value of less than 0.05 was considered to be significant.

3. Results

We identified nine studies [16–24] that met the inclusion and exclusion criteria (Fig. 1), including one English paper and eight Chinese papers. A total of 580 primary insomnia patients with mean age of 46.8 years were included, of which 56.6% of were female. There were 289 patients in active rTMS group, and 291 in sham rTMS group. We divided the treatment durations into three intervals: 10 days, ~20 days, and ~30 days. These studies were rated as being of good quality (Table 1).

3.1. Efficacy of rTMS

The active rTMS addressing primary insomnia was associated with reduced Pittsburgh Sleep Quality Index (PSQI), latency to onset of persistent sleep (LPS), and wakefulness after persistent sleep onset (WASO) compared with sham rTMS. The active rTMS was associated with increased total sleep time (TST) and sleep efficiency (SE) compared with sham rTMS, as well as more improved sleep phase (Table 2). In addition, the effect size of active rTMS for improving symptoms of insomnia seemingly increased with the increase of treatment duration within 30 days (Fig. 2).

3.2. Placebo response of the sham rTMS

The pooled within-group effect size estimates (Hedges' *g*) of the sham rTMS were significant to reduce the symptoms of primary insomnia in terms of PSQI (−1.39), SE (1.16), LPS (−1.5), TST (0.89), WASO (−1.67), NREM-1 (−4.27) and NREM-3 (4.22), respectively

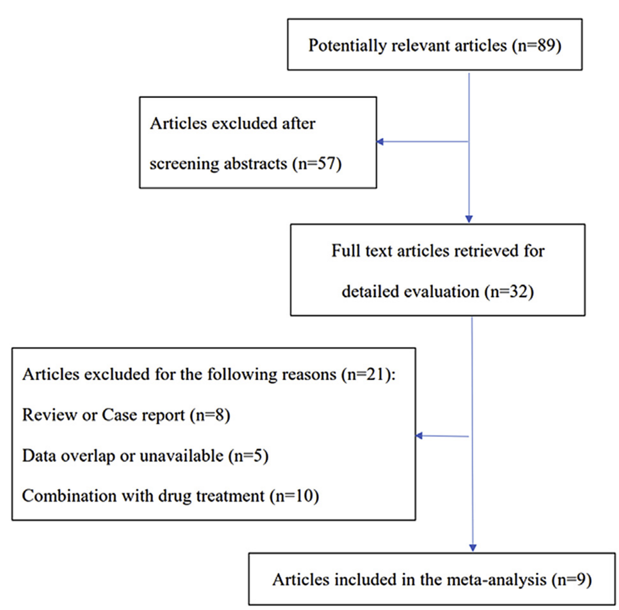

Fig. 1. Flow diagram of the reviewing process.

Table 1
Characteristics of included studies.

Study	Sample size	Age, y (SD)	Female, *n*	Criteria	Stimulation site	Intensity	Frequency	Duration	Sham	Quality
He-2009 [16]	82	37.1 (16.9)	55	DSM-IV	Right dorsolateral prefrontal cortex	100%	1 Hz	10 days	sham coil	4/1/2
Liu-2016 [17]	70	55.3 (10.3)	37	DSM-IV	Right dorsolateral prefrontal cortex	80%	1 Hz	4 weeks	coil tilted 180°	3/1/2
Mai-2016 [18]	60	42.5 (22.1)	31	ICD-10	Right dorsolateral prefrontal cortex	100%	1 Hz	2 weeks	sham coil	3/1/2
Feng-2017 [19]	80	44.5 (8.1)	54	ICD-10	Right dorsolateral prefrontal cortex	80%	1 Hz	10 days	coil tilted 90°	3/1/2
Meng-2017 [20]	60	46.3 (11.7)	30	ICD-10	Right dorsolateral prefrontal cortex	100%	1 Hz	4 weeks	sham coil	3/1/2
Hu-2018 [21]	34	75.5 (7.24)	13	DSM-V	Right dorsolateral prefrontal cortex	100%	1 Hz	4 weeks	coil tilted 90°	3/1/2
Shen-2018 [22]	98	41.0 (9.1)	56	ICD-10	Right dorsolateral prefrontal cortex	80–130%	0.5–1 Hz	4 weeks	20% intensity	3/1/3
Yuan-2018 [23]	60	52.5 (13.5)	34	ICD-10	Right dorsolateral prefrontal cortex	90–110%	1 Hz	4 weeks	coil tilted 180°	3/1/2
Huang-2018 [24]	36	45.1 (11.2)	18	DSM-IV	Right posterior parietal cortex	90%	1 Hz	10 days	sham coil	4/1/3

Table 2
Summary of pooled between-group effect size estimates.

Parameters	Hedges' *g* (95% CI)	*p*	I^2 (%)
PSQI	−1.44 (−1.63, −1.26)	<0.001	83.8
SE	0.57 (0.24, 0.91)	0.001	79.9
LPS	−0.95 (−1.25, −0.66)	<0.001	91.3
TST	0.49 (0.16, 0.82)	0.004	0.0
WASO	−0.65 (−0.93, −0.37)	<0.001	88.0
NREM-1	−0.68 (−1.08, −0.28)	0.001	98.8
NREM-2	0.10 (−0.23, 0.43)	0.538	59.4
NREM-3	0.49 (0.11, 0.87)	0.011	98.4
REM	0.77 (0.43, 1.11)	<0.001	66.5

CI, confidence interval; k, number of treatment conditions in the analysis; I^2, ratio (0–100%) indicating the proportion of the observed variance that reflects real differences in effect sizes (values of 25%, 50%, and 75% can be considered low, moderate, and high, respectively); SE, sleep efficiency; LPS, latency to onset of persistent sleep; TST, total sleep time; WASO, wakefulness after persistent sleep onset; REM, rapid eye movement; NREM, Non-REM.

(Table 3). The proportion of the sham rTMS response to the active rTMS response was 73.5% (95% CI: 50.8%, 96.2%), and it increased to 95.3% in NREM-3 but reduced to 3.7% in REM. Furthermore, the effect size of sham rTMS for improving symptoms of insomnia seemingly increased with the increase of treatment duration within 30 days (Fig. 3).

3.3. Safety

There were no severe adverse events reported during the treatment course. Some mild symptoms (eg, headache, neck pain, and numbness) were spontaneously relieved within half an hour. The relative risk of 1.55 (95% CI: 0.90, 2.67) was not significant ($p = 0.11$, $I^2 = 0.0\%$) between the two groups in adverse events.

4. Discussion

In the current study, we found that the active rTMS was effective in the treatment of primary insomnia, and the effect size increased with the increase of treatment duration within 30 days. However, the majority of effect size (73.5%) in active rTMS was actually produced by placebo condition (ie, sham rTMS). Notably, increased NREM-3 phase was attributed to placebo response (sham rTMS) that had no effect on REM phase.

The mechanisms underlying the rTMS stimulation for treating primary insomnia is unclear. It is currently believed that the cerebral cortex is in an hyperarousal state in patients with primary insomnia and insomnia secondary to RLS [25,26]. Barker et al. [27], originally evaluated motor cortex evoked potential using the rTMS by nerve cells depolarization/hyperpolarization. Low-frequency

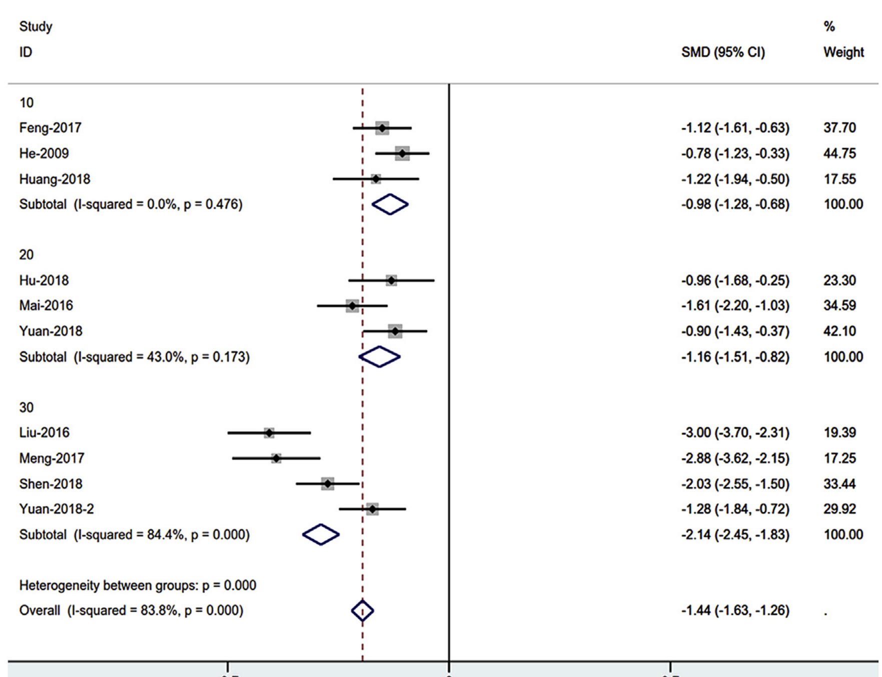

Fig. 2. Meta-analysis of the effect of active rTMS on PSQI. The pooled between-group effect size estimates (Hedges' *g*) of PSQI seemingly increased with the increase of treatment duration within 30 days. rTMS, repetitive transcranial magnetic stimulation; PSQI, Pittsburgh Sleep Quality Index; CI, confidence interval; SMD, standard mean difference.

Table 3
Pooled within-group effect size estimates and proportion of placebo response.

Outcome	Sham rTMS				Active rTMS				Placebo response (%)
	Hedges' *g*	95% CI	*p*	I^2 (%)	Hedges' *g*	95% CI	*p*	I^2 (%)	
PSQI	−1.39	−1.58, −1.21	<0.001	89.0	−2.51	−2.73, −2.28	<0.001	94.3	55.4
SE	1.16	0.79, 1.53	<0.001	77.4	1.53	1.17, 1.90	<0.001	0.0	75.8
LPS	−1.50	−1.81, −1.18	<0.001	62.0	−2.39	−2.74, −2.04	<0.001	74.0	62.8
TST	0.89	0.54, 1.24	<0.001	70.9	1.24	0.89, 1.59	<0.001	0.0	71.8
WASO	−1.67	−1.99, −1.35	<0.001	68.4	−2.21	−2.56, −1.87	<0.001	88.9	75.6
NREM-1	−4.27	−4.91, −3.63	<0.001	94.1	−5.56	−6.28, −4.84	<0.001	67.3	76.8
NREM-2	0.29	−0.05, 0.62	0.093	0.0	0.39	0.07, 0.72	0.018	87.2	74.4
NREM-3	4.22	3.60, 4.85	<0.001	91.8	4.43	3.82, 5.03	<0.001	36.5	95.3
REM	0.03	−0.31, 0.37	0.871	92.5	0.82	0.49, 1.16	<0.001	79.0	3.7

CI, confidence interval; k, number of treatment conditions in the analysis; I^2, ratio (0–100%) indicating the proportion of the observed variance that reflects real differences in effect sizes (values of 25%, 50%, and 75% can be considered low, moderate, and high, respectively); SE, sleep efficiency; LPS, latency to onset of persistent sleep; TST, total sleep time; WASO, wakefulness after persistent sleep onset; REM, rapid eye movement; NREM, Non-REM.

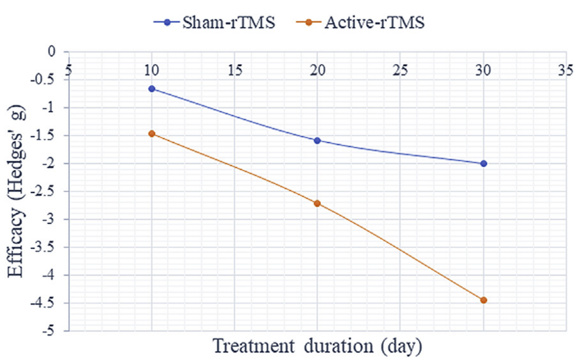

Fig. 3. Meta-analysis of the effect size of PSQI for separate active rTMS and sham rTMS. The pooled within-group effect size estimates (Hedges' g) of PSQI seemingly increased with the increase of treatment duration within 30 days. rTMS, repetitive transcranial magnetic stimulation; PSQI, Pittsburgh Sleep Quality Index.

rTMS (≤1 Hz) directly hyperpolarizes neural cells by pulsed magnetic field and inhibits the over-excited cerebral cortex. Therefore, reduction of excessive arousal level by low-frequency rTMS can effectively improve insomnia.

Jiang et al. [7], demonstrated that rTMS provided a new safe and effective means of physical therapy for chronic insomnia. In their study, the NREM-3 and REM sleep phases were more favorable and PSQI was lower in rTMS group compared with both medication and psychotherapy groups. In addition, rTMS more favorably decreased serum cortisol, hTSH, FT3, FT4, and ATCH levels, reflecting that hyperarousal levels declined more significantly following this treatment. Our results are consistent with the previous findings. Furthermore, low-frequency rTMS has also been found to be effective in RLS [28,29].

However, the new finding that a significant placebo response of rTMS for primary insomnia should be taken seriously. In previous studies, the placebo response is a major contributor to the efficacy of hypnotics addressing primary insomnia [10,30–32]. Winkler and Rief [10] reported that 63.6% of the response to the medications examined was a placebo response. Regarding antidepressant medication, Kirsch and Sapirstein [15] reported that the placebo response was constant (75%) across different types of medication, indicating the inactive placebos produced improvement that was 75% of the effect of the active drug. The data raise the possibility that the apparent drug effect is actually an active placebo effect, and the average placebo response rates in antidepressant trials have been stable for decades [9]. Our finding is consistent with that, showing 73.5% of the effect size of rTMS was a placebo response. That is important because a great proportion of the therapeutic effect could also be achieved by optimizing placebo mechanisms [33].

In addition to the overall stability of placebo response rates, our new finding showed that the placebo response might be associated with the treatment duration of rTMS, and there was a gradual increase in the placebo response before it reached a stable state. This new evidence should have an effect on the interpretation of the scientific literature, both from a clinical and methodological point of view.

The pathophysiology and neurochemistry underlying the placebo effect in sleep disorders should be further clarified. Based on the evidence available, the “placebo effect” may turn on or off a “switch” in the brain by some psychological anticipation to produce a positive or negative effect on the treatment process. To put it simply, false or simulated treatment process causes the patients to produce positive or negative psychological anticipation, which regulates the organism to produce endogenous substance, then the endogenous substance to achieve the effect of psychological anticipation [33,34]. Therefore, the placebo effect mechanism may involve multiple factors, such as neurotransmitter release to activate μ-opioid receptor system, dopaminergic nerve pathway, endogenous cannabinoid and serotonin signal system, synaptic remodeling and altered cerebral network connectivity [35–39]. To the sham rTMS effect, we speculate that psychological anticipation or expectation originating from cognitive networks can produce endogenous substances by acting on sleep-arousal networks, then reshape the body through the neuroendocrine system, ultimately visualize psychological expectations.

There are limitations in our study. First, we calculate the proportion of sham rTMS response to the active rTMS response by subtracting the effect size of sham rTMS condition from that of the active rTMS condition. This model depends on the hypothesis of the additivity of various effects being increasingly questioned. Second, the pooled sample size is relatively small, and most of the included studies are not of randomized, controlled, double-blind trials.

In conclusion, the active rTMS is effective in the treatment of primary insomnia, but the placebo effect of sham rTMS is highly significant. This new evidence may alter the rTMS regimen for insomnia from a clinical and methodological point of view. To disentangle the rTMS-induced placebo effect in primary insomnia, more objective data and outcome measures (eg, polysomnography). Moreover, multicenter double-blinded controlled studies, such as deceptive design, balanced design, open-hidden paradigm, and genome-wide association study (GWAS) of placebo effect related gene (namely placebo genomics), should be encouraged in the future research.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2019.05.008.

Conflict of interest

None.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.05.008.

References

[1] Chung KF, Yeung WF, Ho FY, et al. Cross-cultural and comparative epidemiology of insomnia: the Diagnostic and statistical manual (DSM), International classification of diseases (ICD) and International classification of sleep disorders (ICSD). Sleep Med 2015;16(4):477–82.

[2] Riemann D, Nissen C, Palagini L, et al. The neurobiology, investigation, and treatment of chronic insomnia. Lancet Neurol 2015;14(5):547–58.

[3] Irwin MR. Why sleep is important for health: a psychoneuroimmunology perspective. Annu Rev Psychol 2015;66:143–72.

[4] Qaseem A, Kansagara D, Forciea MA, et al. Management of chronic insomnia disorder in adults: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2016;165(2):125–33.

[5] George MS, Padberg F, Schlaepfer TE, et al. Controversy: repetitive transcranial magnetic stimulation or transcranial direct current stimulation shows efficacy in treating psychiatric diseases (depression, mania, schizophrenia, obsessive-complusive disorder, panic, posttraumatic stress disorder). Brain Stimul 2009;2(1):14–21.

[6] Bordet R, Ihl R, Korczyn AD, et al. Towards the concept of disease-modifier in post-stroke or vascular cognitive impairment: a consensus report. BMC Med 2017;15(1):107.

[7] Jiang CG, Zhang T, Yue FG, et al. Efficacy of repetitive transcranial magnetic stimulation in the treatment of patients with chronic primary insomnia. Cell Biochem Biophys 2013;67(1):169–73.

[8] Lanza G, Cantone M, Lanuzza B, et al. Distinctive patterns of cortical excitability to transcranial magnetic stimulation in obstructive sleep apnea syndrome, restless legs syndrome, insomnia, and sleep deprivation. Sleep Med Rev 2015;19:39–50.

[9] Furukawa TA, Cipriani A, Atkinson LZ, et al. Placebo response rates in antidepressant trials: a systematic review of published and unpublished double-blind randomised controlled studies. Lancet Psychiatry 2016;3(11):1059–66.

[10] Winkler A, Rief W. Effect of placebo conditions on polysomnographic parameters in primary insomnia: a meta-analysis. Sleep 2015;38(6):925–31.

[11] Atkin T, Comai S, Gobbi G. Drugs for insomnia beyond benzodiazepines: pharmacology, clinical applications, and discovery. Pharmacol Rev 2018;70(2):197–245.

[12] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.

[13] Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0. The Cochrane Collaboration; 2011. Available at, http://handbook-5-1.cochrane.org.

[14] The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses. Available at http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

[15] Kirsch I, Sapirstein G. Listening to Prozac but hearing placebo: a meta-analysis of antidepressant medication. Prev Treat 1998;1(2).

[16] He M, Wang X, Xu B, et al. Transcranial magnetic stimulation in the treatment of primary insomnia. Chin J Phys Med Rehabil 2009;31(11):763–6.

[17] Liu C, Wang T, Sun Z. Clinical observation of repetitive transcranial magnetic stimulation in the treatment of insomnia. Chin J Drug Depend 2016;25(2):206–8.

[18] Madina A, Nuerbiya M, Wang Q, et al. Efficacy of repetitive transcranial magnetic stimulation in the treatment of insomnia. World J Sleep Med 2016;3(5):275–9.

[19] Feng X, Gai H, Wang X. Repetitive transcranial magnetic stimulation in the treatment of primary insomnia. J Clin Psychiatry 2017;27(6):415–7.

[20] Meng H, Gao S, Bu C, et al. Clinical study of low frequency repetitive transcranial magnetic stimulation in treatment of insomnia. J Qi Uni Med 2017;38(8):895–7.

[21] Hu S, Shen Y, Gu X, et al. Repeated low-frequency transcranial magnetic stimulation can relieve insomnia. Chin J Phys Med Rehabil 2018;40(3):187–90.

[22] Shen X, Wang G. Curative effect of low-frequency repetitive transcranial magnetic stimulation on primary insomnia. J Med Southwest Chin 2018;20(1):28–32.

[23] Yuan J, Li X, Xu Y, et al. Randomized controlled trial of treatment with low-frequency repetitive transcranial magnetic stimulation for patients with primary insomnia. Chin Modern Med 2018;25(1):57–60.

[24] Huang Z, Li Y, Bianchi MT, et al. Repetitive transcranial magnetic stimulation of the right parietal cortex for comorbid generalized anxiety disorder and insomnia: a randomized, double-blind, sham-controlled pilot study. Brain Stimul 2018;11(5):1103–9.

[25] Riemann D, Spiegelhalder K, Feige B, et al. The hyperarousal model of insomnia: a review of the concept and its evidence. Sleep Med Rev 2010;14(1):19–31.

[26] Lanza G, Bachmann CG, Ghorayeb I, et al. Central and peripheral nervous system excitability in restless legs syndrome. Sleep Med 2017;31:49–60.

[27] Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. Lancet 1985;1(8437):1106–7.

[28] Lanza G, Lanuzza B, Arico D, et al. Impaired short-term plasticity in restless legs syndrome: a pilot rTMS study. Sleep Med 2018;46:1–4.

[29] Lanza G, Cantone M, Arico D, et al. Clinical and electrophysiological impact of repetitive low-frequency transcranial magnetic stimulation on the sensory-motor network in patients with restless legs syndrome. Ther Adv Neurol Disord 2018;11. 1756286418759973.

[30] McCall WV, D'Agostino Jr R, Dunn A. A meta-analysis of sleep changes associated with placebo in hypnotic clinical trials. Sleep Med 2003;4(1):57–62.

[31] Huedo-Medina TB, Kirsch I, Middlemass J, et al. Effectiveness of non-benzodiazepine hypnotics in treatment of adult insomnia: meta-analysis of data submitted to the Food and Drug Administration. BMJ 2012;345:e8343.

[32] Perlis ML, McCall WV, Jungquist CR, et al. Placebo effects in primary insomnia. Sleep Med Rev 2005;9(5):381–9.

[33] Enck P, Bingel U, Schedlowski M, et al. The placebo response in medicine: minimize, maximize or personalize? Nat Rev Drug Discov 2013;12(3):191–204.

[34] Bingel U, Wanigasekera V, Wiech K, et al. The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanil. Sci Transl Med 2011;3(70). 70ra14.

[35] Hall KT, Loscalzo J, Kaptchuk TJ. Genetics and the placebo effect: the placebome. Trends Mol Med 2015;21(5):285–94.

[36] Kaptchuk TJ, Kelley JM, Conboy LA, et al. Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome. BMJ 2008;336(7651):999–1003.

[37] Pecina M, Martinez-Jauand M, Hodgkinson C, et al. FAAH selectively influences placebo effects. Mol Psychiatry 2014;19(3):385–91.

[38] Jensen KB, Kaptchuk TJ, Chen X, et al. A neural mechanism for nonconscious activation of conditioned placebo and nocebo responses. Cereb Cortex 2015;25(10):3903–10.

[39] Schmid J, Theysohn N, Gass F, et al. Neural mechanisms mediating positive and negative treatment expectations in visceral pain: a functional magnetic resonance imaging study on placebo and nocebo effects in healthy volunteers. Pain 2013;154(11):2372–80.