## <u>META-ANALYSIS</u>

# Repetitive Transcranial Magnetic Stimulation and Non-convulsive Electric Shock in the Treatment of Depression: A Meta-analysis

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## ABSTRACT

**Background** • Depression is an affective mental disorder that seriously endangers the physical and psychological health of human beings. This study attempted to systematically evaluate and compare the clinical efficacy and onset time of repetitive transcranial magnetic stimulation and non-convulsive electroshock in the treatment of Depression through the method of evidencebased medicine.

Methods • As of December 2022, we have selectively searched domestic and foreign databases by computer, including English databases PubMed, ScienceDir ETC (Elsevier), Embase, wiley, and Chinese databases HowNet (CNKI), Wanfang (WanFang), VIP (VIP), Chinese Medical Association, CBM (sinomed) Chinese biomedical literature database, etc., collected randomized controlled studies on repetitive transcranial magnetic stimulation and non-convulsive electric shock in the treatment of Depression, and included 21 documents in total. Two researchers independently screened the literature, comprehensively evaluated the retrieved literature according to the established inclusion and exclusion criteria, extracted valid data, and used Review Manager 5.4 software for quantitative statistical analysis. The clinical effective rate and Hamilton depression Rating scale

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## INTRODUCTION

Depression is a global mental health challenge that significantly impacts individuals and societies worldwide. According to the World Health Organization (WHO), depression is one of the leading causes of disability and (Hamilton depression scale, HAMD) and onset time were used as outcome indicators for evaluation.

**Results** • A total of 12 literatures were included in this study for Meta-analysis, involving a total of 678 subjects. The results of Meta-analysis showed that the HAMD score of the study group was higher than that of the control group after treatment, MD=2.01, 95%CI (0.59-3.68), P < .05; there was no statistically significant difference in clinical efficacy between the study group and the control group, OR = 0.88, 95%CI (0.31-1.92), Z = 1.16, P = .29; the onset time of the study group was shorter than that of the control group, MD = 2.01, 95%CI (0.59-3.68), Z = 3.31, P = .001. **Conclusion** • Repetitive transcranial magnetic stimulation is superior to non-convulsive electroconvulsive shock in the treatment of Depression. However, further research is needed to verify its long-term efficacy in the treatment of such diseases. Future studies could focus on investigating the sustainability of treatment effects, exploring potential predictors of treatment response, and comparing the costeffectiveness of rTMS and NCES in clinical practice. Such research would provide valuable insights for optimizing treatment strategies for depression. (Altern Ther Health *Med.* [E-pub ahead of print.])

affects more than 264 million people of all ages globally. Its prevalence has been steadily increasing, making it a critical public health concern.<sup>1</sup> Currently, most patients with Depression are receiving drug treatment, but the effect of using two or more antidepressants with different mechanisms is not significant in some patients with depression.<sup>2,3</sup> Convulsive electroconvulsive therapy (METC) belongs to the category of modified electroshock therapy, as a classic treatment in psychiatry,<sup>4</sup> convulsive electroconvulsive therapy is very effective in the treatment of treatmentresistant Depression (TRD), and can even prevent depression relapse. However, previous relevant data have shown that it has the risk of inducing seizures during anesthesia induction, and although it can improve the treatment effect of

Depression, it can also affect the cognitive function of patients. According to statistics, about one-third of depressed patients in clinical practice do not respond well to treatment with convulsive electroconvulsive therapy. ECT itself has adverse effects, including short-term effects on cognition, particularly memory, and other functions, which limit its use in some individuals.<sup>5,6</sup> Repetitive transcranial magnetic stimulation (rTMS) has emerged as a promising non-drug treatment modality for various psychiatric disorders, including depression. Unlike traditional pharmacological approaches, rTMS directly targets specific brain regions implicated in the pathophysiology of these conditions, offering a targeted and localized therapeutic intervention. rTMS utilizes electromagnetic pulses to induce electrical currents in the brain. This non-invasive procedure involves placing a coil over the scalp, through which brief magnetic pulses are delivered to the underlying brain tissue. These pulses can either stimulate or inhibit neuronal activity, depending on the parameters used. One of the key advantages of rTMS is its potential to modulate cognitive functions. Research suggests that rTMS can influence various cognitive domains, including attention, memory, and executive functions. By selectively stimulating specific brain regions involved in these cognitive processes, rTMS holds promise as a treatment option that not only alleviates depressive symptoms but also enhances cognitive function, which is particularly relevant for individuals with depression who may experience cognitive impairments. In contrast to rTMS, non-convulsive electroconvulsive shock (NCES) therapy, commonly known as electroconvulsive therapy (ECT), has been used for decades in the treatment of severe depression. While ECT can be effective in reducing depressive symptoms, it is associated with side effects such as memory loss and cognitive disturbances. These adverse effects have led to ongoing efforts to develop alternative treatments with improved tolerability and cognitive outcomes.7,8

It has shown its value both in the augmentation treatment of Depression and in the treatment of treatment-resistant Depression, and has been shown to improve cognitive function in patients.<sup>9</sup> Previous studies have shown that compared with no-convulsive electroconvulsive therapy, repetitive transcranial magnetic stimulation has little effect on patient cognition and can even improve cognition in patients with treatment-resistant Depression, so it is more likely to motivate patients.<sup>10</sup>

Evidence-based Medicine (EBM) plays a crucial role in modern medical practice, particularly when evaluating new treatment modalities such as rTMS. EBM emphasizes the integration of the best available evidence from research with clinical expertise and patient values to guide clinical decisionmaking. It offers a systematic and rigorous approach to evaluating the effectiveness and safety of medical interventions, ensuring that healthcare practices are based on reliable and up-to-date information. Currently, many studies have compared the effectiveness of non-convulsive electroconvulsive therapy and repetitive transcranial magnetic stimulation in Depression, but may be limited to small sample sizes, and current results are still controversial.

To date, several studies have investigated the comparative effectiveness of rTMS and non-convulsive electric shock therapies in the treatment of Depression. However, the existing literature remains limited and inconclusive, with variations in study design, sample sizes, and outcome measures. Therefore, there is a need for comprehensive and up-to-date evidence to guide clinical decision-making and inform treatment strategies for Depression.

In light of the rapidly evolving landscape of systemic treatment for Depression, it is essential to incorporate recent research findings into the discussion. Several noteworthy papers have been published, shedding light on the efficacy, safety, and long-term outcomes of rTMS and non-convulsive electric shock therapies. Furthermore, emerging evidence suggests the potential synergistic effects of combining rTMS or non-convulsive electric shock therapies with other treatment modalities, such as psychotherapy or pharmacotherapy.

In this study, we aim to contribute to the existing literature by conducting a meta-analysis of randomized controlled trials to evaluate and compare the clinical efficacy and onset time of rTMS and non-convulsive electric shock therapies in the treatment of Depression. By including recently published papers and considering the evolving landscape of systemic treatment for Depression, our analysis will provide comprehensive insights into the effectiveness of these interventions and their potential role in guiding clinical practice.

## MATERIALS AND METHODS

## Literature retrieval

In this study, the retrieval strategy was formulated according to the "PICOS principles" in the Cochrane Systematic Review Manual, and the literature databases retrieved were mainly Chinese databases and English databases. Among them, the sources of English databases mainly include PubMed, EMBASE, and the Cochrane Central Controlled Trials Registration System. The sources of Chinese databases mainly include the China National Knowledge Infrastructure (CNKI), Wanfang Database, and the China Biomedical Literature Service System (Sinomed). The search time was limited from the establishment of the database to December 2022. The keywords for the search strategy were developed by considering relevant terms related to the intervention (repetitive transcranial magnetic stimulation, non-convulsive electroshock) and the target condition (depression). These keywords were combined using Boolean operators (such as "AND" and "OR") to create search strings. Additional terms related to outcomes (clinical efficacy, onset time) and study design (randomized controlled trials) were also included. Filters for study type (randomized controlled trials) and language (English and Chinese) were applied to retrieve relevant studies.

## Literature selection

**Inclusion criteria:** 1) The medical records of the study are in line with the diagnostic criteria for depressive episodes of the American "Diagnostic and Statistical Manual, Fourth Edition, DSM-IV" 2) All are randomized controlled trials ( Randomized controlled trials, RCTs ) or a controlled trial; 3) no contraindications for ECT and rTMS treatment; 4) the research medical records are all older than 18 years old, provided informed consent, no metal implants, no dementia, no history of epileptic seizures and related family history; 5) There is no organic brain injury, no agitation or delirium, no substance abuse, alcohol or drug dependence in the research medical records, and no physical conditions that are not suitable for anesthesia.<sup>11</sup>

**Exclusion criteria**: 1) The medical records of the study were secondary Depression (such as vascular Depression) or a special subtype of Depression, as well as severe suicidal intentions or female pregnancy; 2) The type of research was case reports or reviews or animal experiments 3) Articles with obvious flaws, such as only one author, wrong random method, inconsistent data or inconsistent with reality; 4) The full text of the research cannot be obtained.

#### Method

A comprehensive literature search was first conducted in several of the most important medical databases, including English databases PubMed, ScienceDirect (Elsevier), Embase, wiley, and Chinese databases HowNet (CNKI), WanFang (WanFang), VIP (VIP), Zhonghua Medical Association, CBM (sinomed) Chinese biomedical literature database, and related website searches. In order to avoid the bias caused by limited literature language, this study conducted a search in both Chinese and English literature. For the Chinese and English databases, the search keywords are different. In the English database, free words such as "transcranial magnetic stimulation", "TMS", "electroconvulsive therapy", "ECT", and "depression" are combined with subject words, and the retrieval strategy is determined after multiple pre-searches. Search keywords such as "transcranial magnetic stimulation", "electric shock", "depression" and "randomized controlled trials" were used in the Chinese database. To avoid missing relevant studies, citations listed in conference abstracts and articles found in the search were also traced. At the same time, the references of meta-analysis related to the efficacy of repetitive transcranial magnetic stimulation and nonconvulsive electroconvulsive therapy in the treatment of Depression were searched manually.

And in this study, the research group refers to the patient group receiving repetitive transcranial magnetic stimulation, and the control group refers to the patient group receiving electroconvulsive therapy without convulsions.

#### Outcome measures

The Hamilton Depression Rating Scale (HAMD) was used for evaluation. Clinical efficacy: Evaluate the effective rate based on the HAMD score reduction rate, that is, effective = HAMD score reduction rate  $\geq$  50%. Onset time: The onset time after treatment of the two groups of patients was counted, and the HMAD score of the patients decreased to below 14 points, which indicated that the treatment was effective.

### **Quality Evaluation**

All data extraction processes were completed independently by two reviewers. First, read the title of the literature, then the abstract of the literature related to the content of this study, and further read the full text of the literature if it is a randomized controlled trial. The studies meeting the inclusion and exclusion criteria were classified, and evaluated, and data were extracted. If there is any disagreement between the two reviewers in screening literature and extracting data, the problem will be resolved through discussion within the group. To resolve such disagreements, a consensus-based approach is employed. This involves discussions between reviewers to clarify any discrepancies and reach a mutual agreement. In some cases, a third reviewer or an arbiter is involved to provide an unbiased perspective and facilitate resolution. Authors of studies for which detailed data were not available were contacted by e-mail or obtained by consulting the contents of literature citing the candidate study. The specific content of data extraction includes the first author, year of publication, country, experimental design, case characteristics, intervention methods, and outcomes (effective rate, remission rate, acceptability). The methods provided by the Cochrane Handbook were used to conduct a systematic review of the included randomized controlled trials, including randomization methods (sufficient, unclear, insufficient), allocation concealment (adequate, unclear, insufficient) and whether to use blind evaluation.<sup>12</sup>

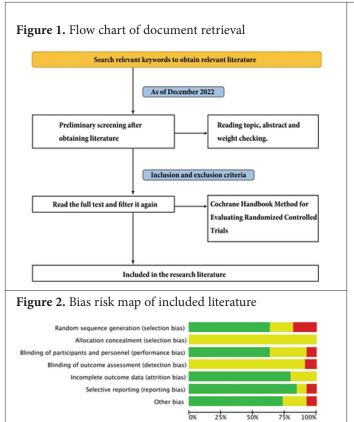
#### Statistical analysis

Statistical analysis of data adopts RevMan 5.4 software and Stata 15 software recommended by the Cochrane Collaboration Network. If P < .1 and  $I^2 > 50\%$ , it indicates that there is statistical heterogeneity among the trials, and the chisquare test is used to test the heterogeneity of the included studies, and the results of studies without heterogeneity are meta-analyzed using the fixed effect model; otherwise, A random effects model is used. The count data were expressed by odds ratio (odds ratio, OR), and the measurement data were expressed by mean difference (MD), both of which were expressed by 95% confidence interval (confidence interval, CI). Sensitivity analysis was performed by article-by-article exclusion. If the number of documents was sufficient, the inverted funnel plot was used to analyze whether there was publication bias in the included documents. The test level of Meta-analysis was uniformly set at  $\alpha = .05$ , and the results were presented in the form of forest plots.

## RESULT

## Search Results

For this study, 24 papers were obtained after reading the title, abstract, deduplication, and further reading. However,

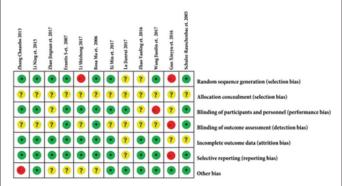


**Figure 3.** Summary chart of the risk of bias in the included literature

Unclear risk of bias

High risk of bias

Low risk of bias





according to the method of evaluating randomized controlled trials in the Cochrane Handbook, 3 of them did not achieve sufficient allocation concealment, and 8 contained controlled trials with flaws in randomization methods and experimental design, so they were not included; the other 2 studies were not included. The original data were the same, so only one of them was included. Finally, 12 articles were included, namely Zhang Chuanbo 2013, Li Ning et al. 2015, Zhao Jingnan et al. 2017, Erantis S et. 2007, Li Shizhong 2017, Rosa Ma et. 2006, Xi Min et al. 2017, Lu Jianrui 2017, Zhao Yanling et al. 2017, Guo Xinyu et al. 2016, Schulze-Rauschenbac et. 2005; 9 are Chinese literature, 3 are English literature, including 678 patients. All included studies reported cases lost to follow-up and performed intention-to-treat analysis. The complete screening process is shown in Figure 1:

#### **Basic Features**

The basic characteristics of the included literature are detailed in Table 1 :

## **Quality Evaluation**

The risk of bias assessment tool recommended by the Cochrane Collaboration was used to evaluate the methodological quality of the 12 included studies. Among them, 9 studies described using the random number table method to generate random sequence grouping, and 3 documents did not specify. All studies did not indicate whether the implementer and subjects were blinded (including single-blind and double-blind). It is not clear whether the outcome indicators have selective reporting bias or other biases; the baseline levels of the included literatures are all comparable. See Figure 2 and Figure 3 for details:

## HAMD score

A total of 6 studies used HAMD score as the outcome index, and the heterogeneity test results showed that  $I^2 = 5.9\%$ , P < .05, indicating that there was statistical heterogeneity among different studies, so a random effect model was used. The results of Meta analysis showed that MD=2.01, 95%CI (0.59-3.68), P < .05, the HAMD score of the study group was

				Gen		HAMD	score at		
	sample size	age		(Male/Female)		enrollment			
	(Study /	research	control	research	control	research	control		
included studies	Control)	group	group	group	group	group	group	drug use	outcome measures
Zhang Chuanbo 201313	40 / 40	46.85 ±4.66	46.40±4.65	14/26	12/28	25.23±4.43	25.77±4.67	Both use antidepressants venlafaxine (75-150mg / d) or mirtazapine (15-30 mg / d)	HAMD score, clinical efficacy
Li Ning et al. 201514	31/29	36±8	32±9	12/9	17/12	42.2±5.6	42.0±5.5	Both routinely use escitalopram (10-20 mg/d)	HAMD score, clinical efficacy
Zhao Jingnan et al. 201715	30/30	25.5±5.5	25.5±6.5	18/12	19/11	35±5.5	35±5.5	Both routinely use escitalopram (10-20 mg/d)	HAMD score
Erantis S et. 200716	24/22	63.6±17.3	68.0±13.4	-	-	23.9±7.0	24.8±5.0	-	Clinical efficacy
Li Shizhong 201717	38/38	35.86±5.47	38.52±5.71	19/19	20/18	-	-	Mirtazapine after meal (15mg/time, 15mg/time, increase to 30mg/time after 4 days )	Clinical efficacy
Rosa et al 200618	22/20	41.8±10.2	46.0±10.6	-	-	3.01±0.47	3.21±5.0	=	Clinical efficacy
Xi Min et al. 2017 <sup>19</sup>	21/19	44.61±5.83	44.62±6.70	11/10	10/9	33.57±4.64	34.11±3.57	Maintain the original therapeutic dose of antidepressants, and use benzodiazepines as appropriate	HAMD score, clinical efficacy
Lu Jianrui 2017 <sup>20</sup>	30/30	30.1±7.3	31.1±6.9	17/13	19/11	-	-	-	Clinical curative effect, onset time
Zhao Yanling et al. 2016 <sup>21</sup>	40/40	31.05±3.58	31.08±3.53	21/19	20/20	-	-	-	Clinical curative effect, onset time
Wang Jianlin et al. 2017 <sup>22</sup>	20/20	32.42±5.87	32.19±5.81	9/11	7/13	26.33±6.44	26.15±6.39	Venlafaxine (initial dose 75 mg /d, maximum dose 225 mg /d)	HAMD score, clinical efficacy
Guo Xinyu et al. 201623	32/32	27.5±5.4	27.5±5.4	18/14	18/14	27.74±6.65	27.85±6.70	-	HAMD score
Schulze-Rauschenbac et al. 2005 <sup>24</sup>	16/14	47.7±13.1	46.7±11.0	9/7	7/7	-	-	The effect of drug treatment is not good, it is not stated whether to use the drug	Clinical efficacy

Wang—Repetitive Transcranial Magnetic Stimulation and Nonconvulsive Electric Shock in the Treatment of Depression higher than that of the control group after treatment, and the difference was statistically significant. See Figure 4 for details:

## **Clinical efficacy**

A total of 10 studies reported the effectiveness of the two groups after treatment. The heterogeneity test results showed that  $I^2 = 4.9 \%$ , P = .071, indicating that there was no statistical heterogeneity among different studies, so the fixed effect model was adopted. The results of Meta-analysis showed that OR = 0.88, 95%CI (0.31-1.92), Z = 1.16, P = .29, and there was no statistically significant difference in clinical efficacy between the study group and the control group. See Figure 5 for details.

The lack of a statistically significant difference suggests that the intervention, in this case, did not show a substantial advantage in terms of clinical efficacy compared to the control group. However, it is important to consider the confidence interval, which spans from 0.31 to 1.92. The wide range indicates uncertainty in the estimate and suggests that further studies with larger sample sizes are needed to obtain more precise conclusions regarding clinical efficacy.

## Effective time

A total of 2 studies reported the onset time of the two groups after treatment, and the heterogeneity test results showed that  $I^2 = 46$  %, P = .043, indicating that there was statistical heterogeneity in different studies, so the random effect model was adopted. The results of Meta-analysis showed that MD = 2.01, 95%CI (0.59-3.68), Z = 3.31, P =.001, the onset time of the study group was shorter than that of the control group, and the difference was statistically significant. See Figure 6 for details:

This finding has clinical relevance as it suggests that the intervention in the study group led to a faster onset of therapeutic effects compared to the control group. A shorter onset time can be beneficial for patients, as it indicates a more rapid response to the treatment and potentially faster relief of symptoms. This finding has a significant impact on treatment choices, as interventions with shorter onset times can be preferred in clinical practice, particularly in situations where prompt symptom relief is crucial.

## **Bias analysis**

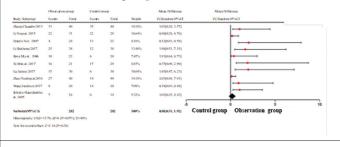
Use the funnel plot to evaluate the publication bias of the included literature. In the funnel plot, the dotted line perpendicular to the horizontal axis indicates the combined effect size. The results show that there are almost no scattered points at the top of the funnel, and most points are evenly distributed in the middle of the funnel, but there are still Some points outside the funnel, and the overall presentation is not completely symmetrical, suggesting that the included studies may have publication bias. It is considered that the reasons for bias may be related to factors such as small sample size, different doses, types, and courses of treatment of drugs used. See Figure 7 for details:

The observed publication bias may be attributed to several factors such as small sample sizes, variations in drug

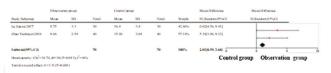
## **Figure 4.** Meta-analysis of HAMD scores in the two groups after treatment

	Observation group			Control ge	Control go up				Mean Difference					
Study Subproup	Mean	SD	Total	Man	50	Total	Waste	IV,Rander, 95%CI	IV/Random/95%CI					
Zhang Chuanho 2013	4.35	3,076	40	5.15	2,783	43	23,26%	1.88[0.35, 4.98]						-
Li Ninget, 2015	6.5	2.5	31	6.4	2.8	29	17.44%	2.51[0.91, 422]				-		
Zhao Jingtan et. 2017	6.65	2.35	30	6.44	2.25	50	17.44%	3,14[1.05, 5.13]				•		
Xi Minet. 2017	22.81	3.5	21	21.53	3.19	19	11.63%	0.54[-3,18,5.56]				-	•	
Wang Junin d. 2017	6.74	1.58	20	4.17	1.02	20	11.63%	-0.87[-2.55, 1.74]				-	•	
Gao Nityu a.2016	21.52 5.04 32			20.58 5	5.29	32	18.60%	0.94[-1.66, 3.51]				-		
									-	à	3	· .		_
Subtotal(95% CI) 174					178	100%	2.01[0.59, 3.68]	Control group			Observation group			
Heteropenety : Che <sup>2</sup> =26.81, df=11 (P=0.005 g 1 <sup>2</sup> =59%								C	ontro	group	Obse	rvation	grou	
Test for overall effect: Z	-2.75(2-0.0	97)												

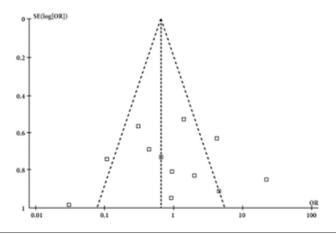
**Figure 5.** Meta-analysis of the effective rate of clinical treatment in the two groups after treatment



**Figure 6.** Meta-analysis of the onset time of the two groups after treatment



**Figure 7** Funnel plot of the publication bias analysis results of the included literature



doses, types, and treatment durations. Studies with significant results are more likely to be published, while those with nonsignificant findings may remain unpublished or be less likely to be included in the review. To mitigate the effects of publication bias, it is crucial to consider not only published studies but also unpublished or gray literature, such as conference abstracts or trial registries. Additionally, conducting a comprehensive search strategy, including multiple databases and sources, can help reduce the risk of publication bias. The potential impact of publication bias should be acknowledged when interpreting the results and should be considered when drawing conclusions.

## Sensitivity analysis

Sensitivity analysis was performed in this study, and the effectiveness of the two groups was analyzed again. The results showed that there was no statistically significant difference in the treatment results between the two groups [MD =0.84, 95%CI (0.44,1.62), Z = 0.64, P = .52], which is basically consistent with the preliminary results. The sensitivity analysis helps validate the stability and consistency of the results by reevaluating the data and applying different analytical approaches. In this case, the sensitivity analysis supports the initial findings and strengthens the confidence in the conclusion that there is no significant difference in treatment outcomes between the study group and the control group.

## DISCUSSION

Depression is a widespread mental health condition that affects millions of people worldwide.<sup>25</sup> It is characterized by persistent feelings of sadness, loss of interest or pleasure, changes in appetite and sleep patterns, and impaired concentration. Depression can significantly impact an individual's quality of life, relationships, and overall functioning.<sup>26</sup> Finding effective treatments for depression is of utmost importance to alleviate suffering and improve outcomes for those affected. While pharmacotherapy, such as antidepressant medications, has been the cornerstone of treatment for depression, it is not always effective for all individuals. Furthermore, pharmacotherapy may have limitations such as side effects, potential drug interactions, and a delayed onset of action. Therefore, it is crucial to explore alternative treatments that can complement or provide alternatives to pharmacotherapy.<sup>27-31</sup> With the development of modern medicine, repetitive transcranial magnetic stimulation (rTMS) has been increasingly recognized in clinical practice. Different transcranial magnetic stimulation pulse signals (single pulse, double pulse and repetitive pulse) can be used to study the facilitation and inhibition of different nerves, and different intensities, frequencies, stimulation sites and coil directions can be used for Depression in different patients to obtain the best treatment.<sup>32,33</sup> ECT, specifically modified electroconvulsive therapy (METC), has been widely used as a treatment for Depression, particularly treatment-resistant Depression (TRD). It has shown significant efficacy in improving depressive symptoms and even preventing relapse. However, ECT carries risks, including the induction of seizures during anesthesia induction and adverse effects on cognitive function, particularly memory. Moreover, about one-third of depressed patients do not respond well to ECT treatment.

rTMS is a non-pharmacological treatment option for depression that has shown promise in clinical practice. It is a relatively new physical therapy that has been used as an augmentation treatment and in the management of treatmentresistant depression. Compared to non-convulsive ECT, rTMS has several advantages. It has fewer cognitive side effects and may even improve cognitive function in individuals with treatment-resistant depression. In this study, the researchers employed an evidencebased medicine approach. They followed the RCT search strategy developed by the Cochrane Collaboration and conducted searches in multiple international and domestic databases to collect relevant literature on depression treatment with rTMS and non-convulsive electroconvulsive therapy. Meta-analysis was performed on the literature on depression. After multiple screenings, 12 articles, covering 678 subjects, were finally included. The overall quality of the literature was average, and the number of included studies and cases was small, which may have some impact on the results of this study.

The results of the meta-analysis showed that the HAMD score of the study group was higher than that of the control group after treatment, MD=2.01, 95%CI (0.59-3.68). This indicates that the study group, receiving rTMS, experienced a greater reduction in depressive symptoms compared to the control group. Furthermore, there was no statistically significant difference in clinical efficacy between the study group and the control group. This suggests that both rTMS and non-convulsive electroconvulsive therapy were similarly effective in reducing depressive symptoms. However, the onset time of the study group was shorter than that of the control group. This indicates that individuals receiving rTMS experienced a faster response to treatment compared to those receiving non-convulsive electroconvulsive therapy.

It is suggested that the therapeutic effect of rTMS is equivalent to that of non-convulsive electroconvulsive therapy, but rTMS has a faster onset time. Similar conclusions have been drawn by meta-analyses conducted by foreign who also believe that non-convulsive scholars, electroconvulsive therapy has a better effect. However, rTMS is more tolerable for patients. It may be due to differences in the definition of depression or variations in the number of included studies. Subsequently, a sensitivity analysis was conducted, which yielded results consistent with the preliminary findings. Finally, an assessment of publication bias was performed, and the results showed a relatively significant publication bias in this study, which may be related to differences in intervention measures, drug use, treatment duration, and sample sizes among the trials.

Indeed, to accurately compare the efficacy of rTMS versus non-convulsive electroconvulsive therapy for the treatment of depression, it would be ideal to have monotherapy without the interference of drug therapy, in order to avoid any potential influence on the results. However, six out of the nine included studies in this analysis involved concomitant drug treatment, indirectly suggesting that there is insufficient evidence to prove that repetitive transcranial magnetic stimulation is better tolerated.

The findings of the meta-analysis indicate that there is no significant difference in clinical efficacy between rTMS and non-convulsive ECT for depression treatment. This suggests that both interventions can be effective in reducing depressive symptoms. However, the meta-analysis also reveals a notable difference in the onset time of therapeutic effects. rTMS shows a significantly shorter onset time compared to non-convulsive ECT. The faster onset time of rTMS may have implications for treatment decisions. A quicker response to treatment is desirable as it allows for more immediate relief from depressive symptoms, potentially improving the patient's overall wellbeing and functioning. The rapid onset of rTMS may be attributed to its ability to directly modulate neural activity in specific brain regions implicated in depression. This targeted stimulation may lead to a more rapid normalization of brain function and improvement in depressive symptoms. The differential onset time between rTMS and non-convulsive ECT highlights the importance of individualizing treatment choices based on the patient's specific needs and preferences. For individuals who require a prompt response to treatment or have concerns about the side effects associated with ECT, rTMS may be a favorable option. On the other hand, nonconvulsive ECT might be considered for individuals who have not responded to other treatments or have severe and treatment-resistant depression.

It is important to acknowledge the limitations inherent in our analysis. These limitations may impact the interpretation and generalizability of our findings.

Firstly, one of the notable limitations is the heterogeneity of the included studies. Our meta-analysis incorporated studies with variations in study design, patient characteristics, treatment protocols, outcome measures, and follow-up periods. This heterogeneity can introduce potential sources of bias and affect the overall validity and robustness of the results. Although we used random-effects models to account for heterogeneity, it is important to interpret the findings with caution due to the inherent variability across studies.

Secondly, the number of included studies and the sample sizes were relatively small. While we made efforts to conduct a comprehensive literature search, the available evidence on the topic remains limited. The small number of studies and participants may limit the statistical power of our analysis and increase the risk of type II errors. Therefore, larger-scale studies with more substantial sample sizes are needed to provide more definitive conclusions on the clinical efficacy of rTMS and nonconvulsive electric shock therapies for Depression.

Furthermore, the quality of the included studies varied. Although we applied rigorous inclusion and exclusion criteria, some studies may still have inherent methodological limitations, such as inadequate blinding, high risk of bias, or incomplete reporting of outcomes. These factors can introduce potential biases and affect the overall strength and reliability of our results. Future studies should aim to adhere to rigorous methodological standards to improve the quality of evidence in this field.

Another limitation worth noting is the potential publication bias. Despite our efforts to search multiple databases and include both domestic and foreign studies, there is a possibility that studies with negative or nonsignificant findings may not have been published or may have been overlooked in our search. This publication bias may lead to an overestimation of the treatment effects observed in our analysis. Additionally, our analysis focused on short-term outcomes, primarily assessing the clinical efficacy and onset time of the interventions. Long-term outcomes, such as durability of response, relapse rates, and overall functional improvement, were not extensively evaluated due to the limited availability of data. Future studies with longer follow-up periods are needed to provide a comprehensive understanding of the sustained effectiveness and safety of rTMS and non-convulsive electric shock therapies for Depression.

In conclusion, based on the available literature, the evidence regarding the treatment of Depression with psychotic symptoms is limited. Currently, the most commonly recommended approaches involve a combination of antidepressant medications and antipsychotics or electroconvulsive therapy. The analysis results of this study suggest that the clinical efficacy of repetitive transcranial magnetic stimulation is higher than that of non-convulsive electroconvulsive shock in the treatment of Depression. However, further research is needed to verify its effectiveness in the treatment of such disease's long-term effects.

#### REFERENCES

- Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. Arch Intern Med. 2003;163(20):2433-2445. doi:10.1001/archinte.163.20.2433
- Alexopoulos GS. Depression in the elderly. Lancet. 2005;365(9475):1961-1970. doi:10.1016/ S0140-6736(05)66665-2
- Cui R. Editorial: A Systematic Review of Depression. Curr Neuropharmacol. 2015;13(4):480. doi :10.2174/1570159X1304150831123535
- Daskalakis, ZJ, et al., Confirmatory Efficacy and Safety Trial of Magnetic Seizure Therapy for Depression (CREST-MST): study protocol for a randomized non-inferiority trial of magnetic seizure therapy versus electroconvulsive therapy. Trials, 202 1): p. 786.
- Solomons K, Holliday S, Illing M. Non-convulsive status epilepticus complicating electroconvulsive therapy. Int J Geriatr Psychiatry. 1998;13(10):731-734. doi:10.1002/(SICI)1099-1166(1998100)13:10<731::AID-GPS831>3.0.CO;2-L
- Stumpf V, Narang P, Lippmann S. Electroconvulsive Therapy-Related Tardive Seizure. J ECT. 2019;35(2):e17. doi:10.1097/YCT.00000000000565
- Lefaucheur JP, Aleman A, Baeken C, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): an update (2014-2018). *Clin Neurophysiol.* 2020;131(2):474-528. doi:10.1016/j.clinph.2019.11.002
   McClintock SM, Reti IM, Carpenter LL, et al; National Network of Depression Centers rTMS
- McClintock SM, Reti IM, Carpenter LL, et al; National Network of Depression Centers rTMS Task Group; American Psychiatric Association Council on Research Task Force on Novel Biomarkers and Treatments. Consensus Recommendations for the Clinical Application of Repetitive Transcranial Magnetic Stimulation (rTMS) in the Treatment of Depression. J Clin Psychiatry. 2018;79(1):16cs10905. doi:10.4088/JCP.16cs10905
- Ameis SH, Blumberger DM, Croarkin PE, et al. Treatment of Executive Function Deficits in autism spectrum disorder with repetitive transcranial magnetic stimulation: A double-blind, sham-controlled, pilot trial. *Brain Stimul.* 2020;13(3):539-547. doi:10.1016/j.brs.2020.01.007
- Kim WJ, Rosselin C, Amatya B, Hafezi P, Khan F. Repetitive transcranial magnetic stimulation for management of post-stroke impairments: an overview of systematic reviews. J Rehabil Med. 2020;52(2):jrm00015. doi:10.2340/16501977-2637
- Brandt SJ, Oral HY, Arellano-Bravo C, Plawecki MH, Hummer TA, Francis MM. Repetitive Transcranial Magnetic Stimulation as a Therapeutic and Probe in Schizophrenia: Examining the Role of Neuroimaging and Future Directions. *Neurotherapeutics*. 2021;18(2):827-844. doi:10.1007/s13311-021-01046-1
- Liao X, Xing G, Guo Z, et al. Repetitive transcranial magnetic stimulation as an alternative therapy for dysphagia after stroke: a systematic review and meta-analysis. *Clin Rehabil.* 2017;31(3):289-298. doi:10.1177/0269215516644771
- Zhang C. Clinical Controlled Study of Repetitive Transcranial Magnetic Stimulation and Nonconvulsive Electroshock in the Treatment of First-episode Depression. *Chinese Journal of Physical Medicine and Rehabilitation*. 2013;35(10):819-821.
- Ning L, et al. A randomized controlled trial of repetitive transcranial magnetic stimulation and modified electroconvulsive shock on the onset time of first-episode Depression. *Chinese Journal* of Mental Health. 2015;(9):667-671.
- Zhao J, et al. A Randomized Controlled Trial of Repetitive Transcranial Magnetic Stimulation and Modified Non-convulsive Electric Convulsive Shock Treatment of Onset Time of Firstepisode Depression. *Contemporary Medicine*. 2017;23(30):99-101.
- Eranti S, Mogg A, Pluck G, et al. A randomized, controlled trial with 6-month follow-up of repetitive transcranial magnetic stimulation and electroconvulsive therapy for severe depression. Am J Psychiatry. 2007;164(1):73-81. doi:10.1176/ajp.2007.164.1.73
- Li S. Clinical comparative analysis of repetitive transcranial magnetic stimulation and nonconvulsive electroconvulsive shock in the treatment of first-episode depression. *China Medical Device Information*. 2017;23(24):84-85.
- Rosa, MA, et al., Comparison of repetitive transcranial magnetic stimulation and electroconvulsive therapy in unipolar non-psychotic refractory Depression: a randomized, single-blind study. Int J Neuropsychopharmacol, 2006. 9 (6): p. 667 76. doi:10.1017/S1461145706007127
- Min X, et al. A randomized controlled study of rTMS and MECT on the curative effect and cognitive function of treatment resistant Depression. *Neurous Diseases and Montal Hadilty* 2017;17(5):308-311
- function of treatment-resistant Depression. Nervous Diseases and Mental Health. 2017;17(5):308-311.
  Lu J. Comparing the onset time of repeated transcranial magnetic stimulation and modified electroconvulsive shock in the treatment of first-episode Depression. Electronic Journal of Clinical Medicine Literature. 2017;4(53):10336-10337.

- Zhao Y, Bi H, Wang X. Clinical Analysis of Onset Time of Repetitive Transcranial Magnetic 21. Stimulation and Modified Electric Shock Therapy for First-episode Depression. Chinese Continuing Medical Education. 2016;8(34):102-103.
- Wang J. Le Juner, and Wang Xudong, Observation on the clinical effect of non-convulsive electric 22. shock and repetitive transcranial magnetic stimulation assisted conventional drug regimens in the treatment of refractory Depression. China Basic Medicine. 2017;24(23):3655-3657.
- 23. Guo X, et al. Comparison of the clinical efficacy of non-convulsive electroshock and repetitive transcranial magnetic stimulation in the treatment of treatment-resistant Depression. Int J Psychiatry. 2016;43(2):245-248.
- Schulze-Rauschenbach SC, Harms U, Schlaepfer TE, Maier W, Falkai P, Wagner M. Distinctive 24. neurocognitive effects of repetitive transcranial magnetic stimulation and electroconvulsive therapy in major depression. Br J Psychiatry. 2005;186(5):410-416. doi:10.1192/bjp.186.5.410 Rakel RE. Depression. Prim Care. 1999;26(2):211-224. doi:10.1016/S0095-4543(08)70003-4 25.
- Hauenstein EJ. Depression in adolescence. J Obstet Gynecol Neonatal Nurs. 2003;32(2):239-26. 248. doi:10.1177/0884217503252133
- Seiffge-Krenke I. [Depression in children and adolescents: prevalence, diagnosis, etiology, gender 27. differences and therapeutic approaches]. Prax Kinderpsychol Kinderpsychiatr. 2007;56(3):185-205. doi:10.13109/prkk.2007.56.3.185
- Baldinger P, Lotan A, Frey R, Kasper S, Lerer B, Lanzenberger R. Neurotransmitters and 28. electroconvulsive therapy. J ECT. 2014;30(2):116-121. doi:10.1097/YCT.00000000000138
- Matz, O., et al., Cardiac stress after electroconvulsive therapy and spontaneous generalized convulsive seizures: A prospective echocardiographic and blood biomarker study. Epilepsy Behav, 29 2019. 101 (Pt A): p. 106565. doi:10.1016/j.yebeh.2019.106565
- Baeken C, Brem AK, Arns M, et al. Repetitive transcranial magnetic stimulation treatment for 30. depressive disorders: current knowledge and future directions. Curr Opin Psychiatry. 2019;32(5):409-415. doi:10.1097/YCO.0000000000000533
- 31.
- Konstantinou G, Hui J, Ortiz A, et al. Repetitive transcranial magnetic stimulation (rTMS) in bipolar disorder: A systematic review. *Bipolar Disord*. 2022;24(1):10-26. doi:10.1111/bdi.13099 Nardone R, Sebastianelli L, Versace V, et al. Repetitive transcranial magnetic stimulation in 32. traumatic brain injury: evidence from animal and human studies. *Brain Res Bull*. 2020;159:44-52. doi:10.1016/j.brainresbull.2020.03.016
- 33. Schambra HM. Repetitive Transcranial Magnetic Stimulation for Upper Extremity Motor Recovery: Does It Help? Curr Neurol Neurosci Rep. 2018;18(12):97. doi:10.1007/s11910-018-0913-8