

Repetitive Transcranial Magnetic Stimulation Combined with Antidepressants for the First Episode of Major Depressive Disorder

Benchalak Maneeton^{1,*}, Narong Maneeton¹, Pakapan Woottikul² and Surinporn Likhitsathian¹

¹Department of Psychiatry, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand; ²Psychiatric Nursing Division, Faculty of Nursing, Chiang Mai University, Chiang Mai, Thailand

Abstract: Objectives: The aims of this study were to systematically review the efficacy, acceptability, and tolerability of repetitive transcranial magnetic stimulation (rTMS) combined with antidepressants in the treatment of the first major depressive disorder (MDD) episode.

Materials and Methods: The primary efficacious outcome was the pooled mean-endpoint scores of the Hamilton Depression Rating Scale (HAMD). Rates of response, remission rate, overall discontinuation and discontinuation due to adverse events were also evaluated. Search in the Scopus, PubMed, CINAHL, and Cochrane Controlled Trials Register databases for interesting outcomes was carried out in March 2018.

Results: A total of 108 randomized patients of two randomized controlled trials were included in this study. The pooled mean- endpoint scores of the HAMD in one, two, and four weeks for rTMS plus antidepressants (citalopram or paroxetine) were greater than that of sham plus the antidepressants. The pooled rates of overall discontinuation and discontinuation rates due to adverse events were not different between the two groups.

Conclusion: According to a piece of limited evidence, the high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) could accelerate the antidepressant effect of SSRIs in young patients with a first-episode major depressive disorder. However, the acceptability and tolerability of HF-rTMS in the treatment of such patients are no better than an antidepressant alone. However, further well-defined and large sample-size studies of HF-rTMS combined with an antidepressant in MDD should be carried out to warrant these results.

Keywords: Citalopram, paroxetine, Hamilton depression rating scale, efficacy, acceptability, tolerability.

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1. INTRODUCTION

Major depressive disorder (MDD) is a recurrent, chronic mental illness and negatively impacts functioning and quality of life [1]. Although several antidepressants have displayed their efficacy in treatment in most of the MDD patients, including the first episode, [2,3] the delayed pharmacological antidepressant effects for the maximal or optimal improvement may require 6 to 12 weeks after administration, while some, including acutely suicidal patients, need a rapid response [4]. Additionally the delayed onset effect in MDD treatment is associated with several difficulties, including disability, reduced adherence to treatment, patient and family distress, economic consequences and increasing risk of suicidality [5-9]. The treatment option associated with rapid

onset antidepressant effect to achieve early improvement is necessary in those first episode MDD patients.

Several pieces of evidence indicated that repetitive transcranial magnetic stimulation (rTMS) had displayed positive effects in the treatment of MDD patients [10-12]. In addition, numerous clinical studies have determined the accelerated and augmentative antidepressant effects when combined with antidepressants. Most studies were investigated in the treatment-resistant depression group [13, 18]. Unfortunately, some clinical trials, especially in treatment-resistant depression, have not shown positive outcomes [14, 15, 19, 20]. Only a few studies evaluated the safety and efficacy of rTMS in accelerated and augmentative effects in the treatment of non-drug resistant depression patients, particularly in the first episode MDD patients [21, 22].

Although randomized controlled trials (RCTs) compared the efficacy and tolerability of rTMS plus antidepressant and antidepressant alone in the treatment of MDD, each RCT was a small study [21, 22]. Hence, a powerful method in

*Address correspondence to this author at the Department of Psychiatry, Faculty of Medicine, Chiang Mai University, 110 Intawaroros Road, Sriphum, Amphur Muang, Chiang Mai 50200, Thailand; Tel: +66 53 93 5422; Fax: +66 53 93 5426; E-mail: benchalak.maneeton@cmu.ac.th

estimation of the true effect size, a meta-analysis, is possibly applied for comparing the efficacy, acceptability and tolerability between rTMS plus antidepressant and antidepressant alone in the treatment of the first episode of MDD.

The aims of this study are to systematically review the efficacy, acceptability and tolerability of rTMS combined with antidepressants in the treatment of the first episode of MDD. The efficacious measurement was evaluated by calculating the pooled mean endpoint of standardized rating scales for depressive symptoms, response rate and remission rate. At the same time, acceptability and tolerability were estimated by using the overall discontinuation rate as well as the discontinuation rate due to adverse events. Only relevant RCTs were included in this systematic review.

2. MATERIALS AND METHODS

2.1. Types of Studies

This review synthesized all RCTs related to the rTMS combined with antidepressant treatments in MDD.

2.2. Types of Participants

Any patient categorized in the first episode of MDD by any set of diagnostic criteria was gathered in this review.

2.3. Types of Interventions

Any treatment of rTMS plus antidepressant compared with rTMS plus sham was included in this review. There was no restriction in the type and dosage form of the combined antidepressant, number of pulses per day, and the duration for rTMS treatment.

2.4. Types of Outcome Measures

2.4.1. Primary Outcome Measures

The primary outcome was the scores of the mean endpoint measured by the standardized depression rating scales.

2.4.2. Secondary Outcome Measures

The secondary outcomes included:

- a. Response rate.
- b. Remission rate.
- c. Discontinuation rates.
 - Overall discontinuation rate (acceptability).
 - Discontinuation rate due to adverse events (tolerability).

2.5. Information Sources

Scopus, PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and the Cochrane Central Register of Controlled Trials were the main databases for searching related articles. Since the publication of rTMS treatment in the PubMed occurred in 1991, a search of such articles was performed from January 1991 to July 2018. Searches were restricted to only human studies. The references of relevant studies were also inspected. Finally, ran-

domized controlled trials (RCTs) of MDD treated with rTMS, either combined with antidepressants or not, were included in this review. No language restriction was applied within the search tools.

2.6. Searches

To increase the sensitivity in optimal identification of the RCTs, the strategic search of the PubMed was carried out with the following words and phrases: [(Transcranial magnetic stimulation) OR (Repetitive transcranial magnetic stimulation) OR (TMS) OR (rTMS)] AND [(antidepress*) OR (Selective serotonin reuptake inhibitors) OR (Tricyclic antidepressant) OR (Serotonin and noradrenaline reuptake inhibitors) OR (Noradrenergic and specific serotonergic antidepressant) OR (Norepinephrine and dopamine reuptake inhibitors) OR (Monoamine oxidase inhibitors) OR (Vortioxetine) OR (Brexanolone) OR (Vilazodone) OR (Agomelatine) OR (Nefazodone) OR (Tianeptine) OR (Trazodone) OR (Reboxetine)] AND [(Major depressive disorder) OR (Major depression) OR (MDD)]. This similar search strategy was performed for the remaining databases.

2.7. Study Selection

Two reviewers (NM and BM) separately inspected all the titles and abstracts of articles collected from the electronic database searches. After obtaining the full-text version of the relevant articles, the two reviewers (NM and BM) individually re-evaluated them. When a disagreement between the reviewers occurred, the decision was made by consensus.

2.8. Data Collection Process

After important data of the eligible full-version articles were carefully extracted by the first reviewer, they were filled into the developed extraction form. They were re-checked again by the second reviewer (BM). In case of disagreement of the reviewers' point of view, a conclusion was also carried out by using consensus.

2.9. Data Items

The extracted outcomes, derived from each eligible study, consisted of the following: 1) data for quality assessments of individual study, 2) demographic characteristics of included patients, criteria for diagnosis, study designs, and criteria for eligibility/ineligibility 3) Forms, doses, and duration of antidepressant treatment, 4) stimulation parameters of rTMS, 5) Interesting findings and 6) intention-to-treat outcomes.

2.10. Risk of Bias in Individual Studies

The two reviewers (NM and BM) evaluated the internal validity (quality) of the included studies by using the Cochrane Collaboration's tool for assessing risk of bias, which includes the following: 1) random sequence generation (selection bias), 2) allocation concealment (selection bias), 3) Blinding of participants and personnel (performance bias), 4) blinding of outcome assessment (detection bias), 5) incomplete outcome data (attrition bias), 6) selective reporting (reporting bias), and 7) other biases [23] (Fig. 1).

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Huang 2012	●	●	?	?	+	●	+
Wang 2017	●	●	?	?	+	●	+

Fig. (1). Summary of risk of bias in randomized controlled trials of repetitive transcranial magnetic stimulation plus antidepressant or sham combined with antidepressants in the first episode of major depressive disorder. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

2.11. Summary Measures

The main outcomes were composed of the efficacy, acceptability, and tolerability. The efficacy was estimated by score of the mean endpoint measured by a standardized scale for MDD, and improvement, response and remission rate for MDD, defined by any set of measurements. Like previous meta-analysis, acceptability was estimated relying on the rate of overall discontinuation [24] and tolerability connected to adverse events [25] was estimated by the rate of discontinuation due to adverse events.

2.12. Statistical Analysis and Synthesis of Results

The present systematic review estimated either the weighted mean difference (WMD) or a standardized mean difference (SMD) with 95% CI based on the same or various measure scales applied across studies. If outcomes, such as standard deviation (SD), and the mean-endpoint scores were not present, the estimation could be achieved by using statistical methods or direct substitution [26]. An Inverse-Variance, weighing the effect of individual studies, was applied to determine the pooled scores of the mean endpoint with 95% CIs [23].

The dichotomous outcomes, including improvement, response and remission rates, were synthesized by estimating relative risk (RR) with 95% confidence interval (95% CI).

The Mantel-Haenszel approach was applied to estimate the pooled RRs of discontinuous outcomes with 95% CIs [23]. Based on the response rate, the number needed to treat (NNT) (95% CI) was also determined.

In general, the included studies in a systematic review are less likely to be completely identical ones, except comparatively homogenous studies. Thus, a random effect model, expected to show the true effect size differs across the studies, was reasonably used in the synthesis of all outcomes in this review. The synthesis of all the results was conducted by using the RevMan 5.1.

2.13. Risk of Bias Across Studies

If possible, evaluation of the reporting bias utilized the Egger’s test of funnel plot display a simple scatter plot of the intervention effect estimated from each study against a measure of each study’s size. If the plot resembles a symmetrical inverted funnel, an absence of bias is expected [27].

2.14. Test of Heterogeneity

As a rule, a test of heterogeneity could be applied to evaluate the homogeneity of clinical outcomes among eligible trials in a systematic review. When the test was conducted in the systematic review, it was hypothesized that the effect size had differences due to the various quality of

methodology in individual trials. The outcome of each study was examined based on whether it had greater differences from the anticipated result by chance alone. To determine those results, evaluation in the graph displays, as well as test of heterogeneity, was carried out. Significant heterogeneity of results was defined as an I^2 of 50% or more.

3. RESULTS

3.1. Study Selection

Searches of those databases found a total of 822 articles (SCOPUS=466, PubMed=102, Cochrane Controlled Trials Register=246, CINAHL=8) (Fig. 2). After discarding the duplicates, 617 articles persisted. Based on evaluating the titles and abstracts of those studies, 600 articles were excluded. After examining the full-text articles of those citations, fourteen were excluded from this review because they were not the first episode of MDD study [15, 16, 28-39] and

one was a protocol for clinical trial registration, which did not provide the results [40]. Consequently, a total of two articles were eligible in this review [21, 22]. However, a relevant or unpublished study, suitable in those eligible criteria, was not identified.

3.2. Study Characteristics

The duration of the included trials was four to eight weeks. The duration of the first included study was four weeks, including either high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) or sham combined with citalopram treatments for the first two weeks and citalopram treatment alone for two weeks afterward [21]. The last included study was of eight weeks, including either HF-rTMS or sham combined with paroxetine treatments for the first four weeks and paroxetine treatment alone for four weeks afterwards [22]. The participants randomly received either an antidepressant such as paroxetine or citalopram

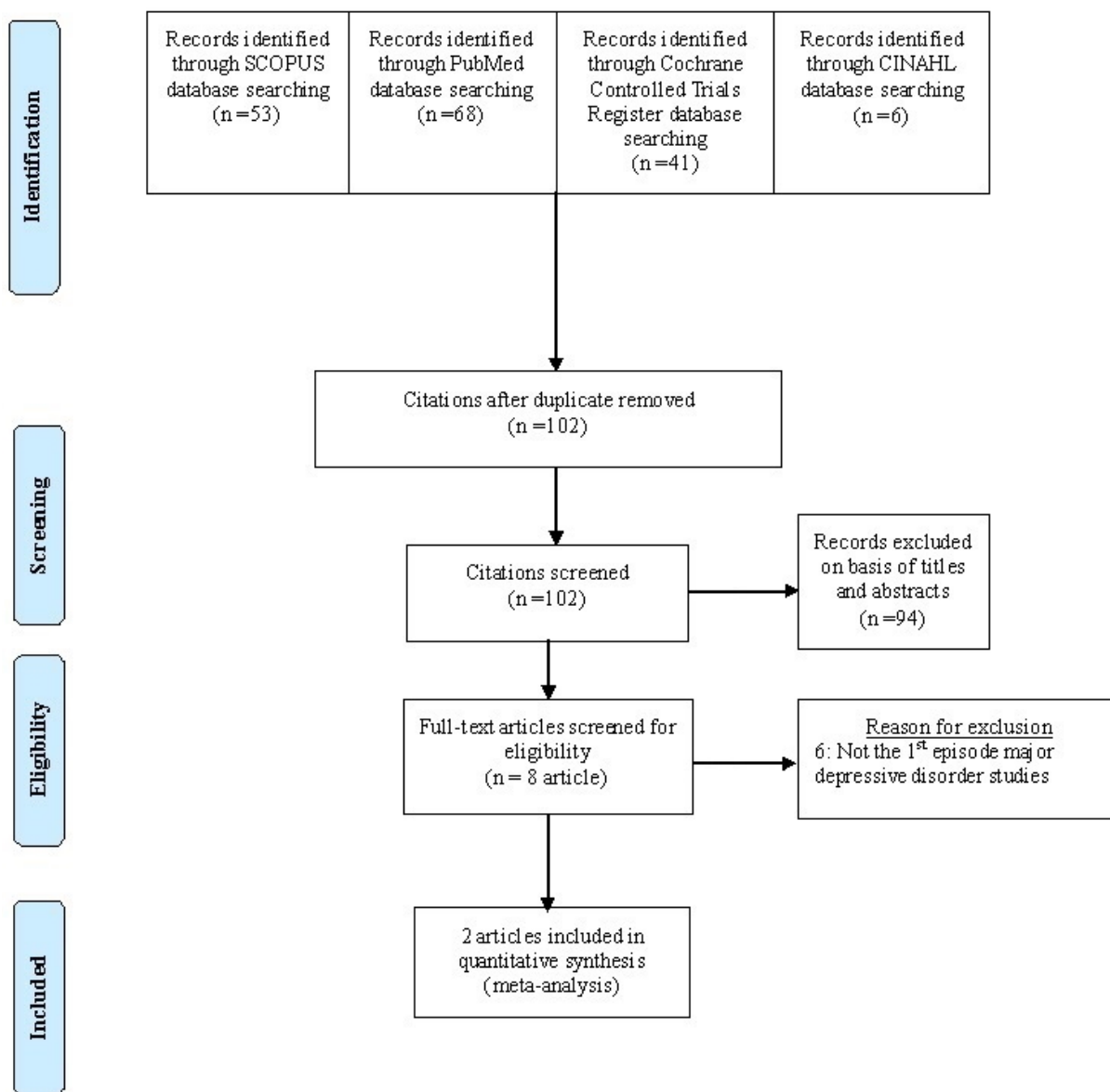


Fig. (2). Flow diagram of study. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

plus HF-rTMS or sham. The dose of paroxetine and citalopram ranged from 20 to 40 mg/day. According to HF-rTMS treatment, the target area for stimulation was the left dorsolateral prefrontal cortex (DLPFC), which is defined as the site 5-5.5 cm anterior in a sagittal plane from the site for motor threshold (MT) determination. A Magstim rapid stimulator with a figure-eight coil was used for treatment (The Magstim Company Ltd). The stimulation administered a total of 800 pulses per day with 10-20 sessions (five sessions a week). The demographic and clinical characteristics of both treated groups were generally compatible across the studies. A summary of eligible studies was illustrated in Table 1.

A total of 108 randomized subjects from each study were assembled in this systematic review. All eligible patients were diagnosed in the first episode of MDD by using the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV). Each patient, age 18-45 years, were independently randomized to obtain the treatment protocol of either antidepressant plus HF-rTMS or plus sham (Table 1).

Since the 17-item Hamilton Depression Rating Scale (HAMD-17) or 24-item Hamilton Depression Rating Scale (HDRS-24) was used in the evaluation of the severity of depressive symptoms in each RCT, the SMDs of the mean-endpoint scores were applied for calculating and synthesizing those outcomes. The rates of early improvement, response and remission were included in the first study [21], while the last study provided response and remission outcome [22]. As the dorsolateral prefrontal cortex was the target stimulation area, the first study assessed three frontal

executive function outcomes as well (the Wisconsin Card Sorting Test [WCST], Trail Making Test [TMT] and Stroop Color-Word Test [SCWT]). All studies presented the overall discontinuation and discontinuation rates due to adverse events.

3.3. Risk of Bias within Studies

Both studies did not discourse the random sequence generation, allocation concealment and selective reporting. However, they presented incomplete outcome data and other bias. The remaining risks in bias were unclear (Fig. 1). All studies applied the Intention-to-Treat analysis.

3.4. Synthesis of Results

3.4.1. Efficacy

According to the continuous outcomes, heterogeneity was not significantly found in the pooled mean-endpoint scores of HAMD-D. The pooled mean-endpoint scores of the HAMD-D in one, two and four weeks for HF-rTMS plus antidepressant (citalopram and paroxetine) were greater than that of sham plus the antidepressant with SMD (95% CI) of -0.54 (-0.93, -0.14), $I^2 = 0\%$, -0.84 (-1.24, -0.43) $I^2 = 0\%$ and -1.23 (-2.36, -0.11), $I^2 = 85\%$, respectively (see Figs. 3-5). However, mean endpoint scores of HAMD in 8 weeks between two groups were not significantly different [22].

Considered in dichotomous outcomes, early improvement rate (a 20% reduction of HAMD-17 scores) in the HF-rTMS plus citalopram-treated group was significantly greater than that of sham plus citalopram-treated group [21]. The response and remission rates of the HF-rTMS plus paroxet-

Table 1. The basic characteristics of randomized, controlled trials of repetitive transcranial magnetic stimulation combined with antidepressants or sham combined with antidepressants for first episode of major depressive disorder.

Study (Authors, Years)	Number of Randomized Patients	Age of Included Subjects (Years)	Study Duration (Weeks)	Drug/Dose	Diagnosis Criteria	Early Improvement	Response Criteria	Remission Criteria	Outcome Measures
Huang ML et al., 2012	60	18 - 45	4 weeks Week 1 - 2: rTMS/sham + citalopram Week 3 - 4: Only citalopram	- Citalopram (20 - 40 mg/day) - rTMS at DLPFC (800 pulses/day of 10 Hz rTMS at 90% of the motor-evoked potential threshold, each train lasted 4 s with a 56-s inter-train pause)	DSM-IV for MDD	20% decrease from baseline in HAMD-17	50% decrease from baseline in HAMD-17	HAMD-17 = 7 scores	- HAMD-17 - MADRS - TMT - SCWT - WCST
Wang YM et al., 2017	48	18 - 45	8 weeks Week 1 - 4: rTMS/sham + paroxetine Week 5 - 8: Only paroxetine	- Paroxetine (20 - 40 mg/day) - rTMS at DLPFC (800 pulses/day of 10 Hz rTMS at 80% of the motor-evoked potential threshold, each train lasted 2 s with a 28-s inter-train pause)	DSM-IV for MDD	-	50% decrease from baseline in HDRS-24	HDRS-24 = 8 scores	- HDRS-24

Abbreviations: DLPFC, Dorsolateral prefrontal cortex; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; HAMD-17, 17-item Hamilton Depression Rating Scale; HDRS-24, 24-item Hamilton Depression Rating Scale; MADRS, Montgomery- Åsberg Depression Rating Scale; MDD, Major depressive disorders; rTMS, Repetitive transcranial magnetic stimulation; s, second; SCWT; Stroop Color-Word Test; TMT, Trail-Making Tests; WCST, Wisconsin Card Sorting Test.

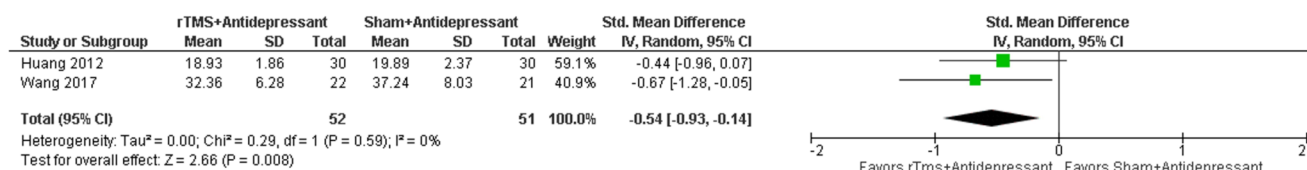


Fig. (3). Forest plot of comparison of the mean endpoint in depressive scores (95% confidence interval) of repetitive transcranial magnetic stimulation plus antidepressant or sham plus antidepressant in the first episode of major depressive disorder at 1week treatment. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

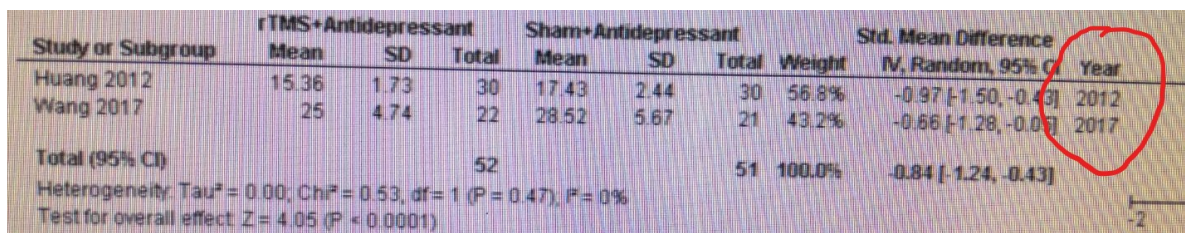


Fig. (4). Forest plot of comparison of the mean endpoint in depressive scores (95% confidence interval) of repetitive transcranial magnetic stimulation plus antidepressant or sham plus antidepressant in the first episode of major depressive disorder at 2week treatment. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

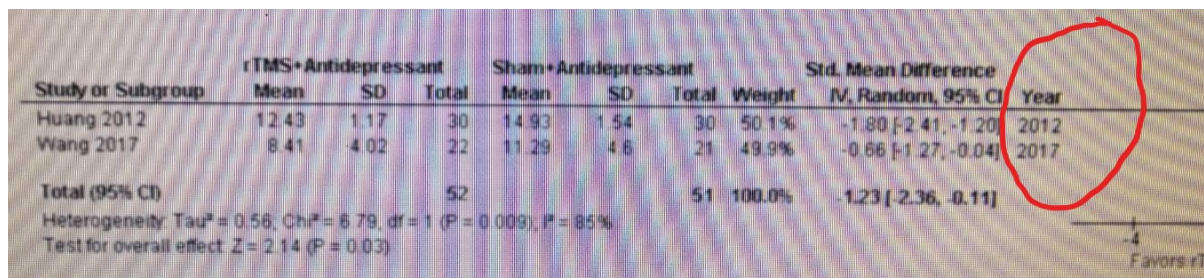


Fig. (5). Forest plot of comparison of the mean endpoint in depressive scores (95% confidence interval) of repetitive transcranial magnetic stimulation plus antidepressant or sham plus antidepressant in the first episode of major depressive disorder at 4week treatment. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

ine-treated were significant higher than a control group in 4 weeks treatment, but not in 8 weeks treatment [22]. However, a significant difference in response and remission rates between the two treated groups was found in the HF-rTMS plus citalopram study [21]. The executive function, measured by Wisconsin Card Sorting Test, Trail Making Test and Stroop Color-Word Test also had no significant difference between the two groups [21].

3.4.2. Main Adverse Event

None of the participants complained of significant adverse events and the treatments were well tolerated. The common side effects included headache and scalp pain in both groups, which significantly decreased after stopping those treatments. Additionally, the executive function, measured by Wisconsin Card Sorting Test (WCST), Trail-Making Test (TMT) and Stroop Color-Word Test (SCWT) also had no significant differences between the two groups [21].

3.4.3. Discontinuation Rate

3.4.3.1. Overall Discontinuation Rate (Acceptability)

Significant heterogeneity was not detected in the overall discontinuation. The pooled rate of overall discontinuation

was not different between the two groups with RR (95% CI) of 1.20 (0.34, 4.23), I² = 0%.

3.4.3.2. Discontinuation Rate Due to Adverse Events (Tolerability)

Significant heterogeneity was not found in the discontinuation rate due to adverse events. The pooled rate of discontinuation rates due to adverse events had no differences between the two groups with RR (95% CI) of 0.97 (0.21, 4.60), I² = 0%.

3.4.4. Risk of Bias Across Studies

When the included studies in a systematic review are less than ten, evaluation of the publication bias by using the display of the Egger’s test of funnel plot should not be conducted since it is not sufficiently powerful in determination of the chances of real asymmetry occurring due to the included results [27]. Hence, the Egger’s test of funnel plot was not carried out because this review comprised of only two RCTs.

4. DISCUSSION

The results in this review have shown that depressive symptoms improved more abruptly in HF-rTMS plus

antidepressant than antidepressants alone in young patients with the first episode of MDD. Additionally, its acceptability and tolerability in such patients was comparable to antidepressant.

As is known, rTMS has proved its efficacy in patients with the treatment of depressive disorders [41, 42]. Additionally, a previous study showed that rTMS was able to significantly accelerate the improvements in depressive symptoms of MDD patients [16]. The study of twice-daily HF-rTMS in MDD patients with the treatment-resistant depression found that the number of patients defined as response and remission was 55.6 and 37% after two weeks of the rTMS administration [43]. Similarly, the previous review also suggests that HF-rTMS could accelerate the clinical response to antidepressants in MDD patients [44]. The evidence supports the present systematic review. Although the final outcomes of clinical depressive improvements are not better than the antidepressant treatment alone, a combination of HF-rTMS with antidepressants may be useful in MDD patients who need abrupt improvement, including the groups with a high risk for suicide.

According to the safety of rTMS, several studies have promised that it is a safe treatment, with a few tolerable side effects, such as reported pain at the stimulation area, which was similar to the present review [43, 44]. Considering the adverse events regarding cognitive functions in the MDD patients, the present review did not report differences between HF-rTMS plus antidepressant treatment and antidepressant treatment alone. Additionally, the previous study in Parkinson's disease patients with concurrent depression suggests that both HF-rTMS and fluoxetine can improve the cognition of those patients [45]. Based on such evidence, HF-rTMS may be a safe treatment for MDD patients.

In this review, the acceptability of the HF-rTMS plus antidepressant treatment, measured by the overall discontinuation rate, was not different than that of the antidepressants alone. Similarly, the tolerability of the HF-rTMS plus antidepressant treatment, measured by the discontinuation rate due to adverse events was also comparable to antidepressants alone, which was similar to previous studies [44,46]. Although HF-rTMS combined with antidepressant are well-tolerated, the acceptability is comparable to antidepressants alone; the use of the combination of such treatments should be preserved for particular MDD patients who need early improvement.

Several limitations were found in the present systematic review. Firstly, although a meta-analysis can be conducted with at least two studies and a systematic review can be performed without any included study [47], the limited numbers of included RCTs with a small sample size in this review may decrease the power to estimate the effect of intervention [48]. Additionally, heterogeneity of the mean-endpoint scores between two studies was also found in 4 week treatment. Altogether, those limitations may restrict the real contribution of a meta-analysis. Secondly, since the rTMS regimen applied in those eligible studies was a lower number of pulse and sessions than the current consensus guidelines [49], it possibly affected the overall efficacy of MDD treatment. Thirdly, since all included trials were conducted in Chinese

patients, those findings may not be generalized to a wider population. Finally, according to biasing risk, there were some potentially high risks in many aspects, including the random sequence generation, allocation concealment and selective reporting, and the Egger's test of funnel plot display to determine asymmetry could not be conducted because of limited eligible trials [27], publication bias, therefore, could not be ruled out.

CONCLUSION

HF-rTMS can accelerate the antidepressant effect of in the combined HF-rTMS plus antidepressants treatment of young patients with the first episode of MDD. The acceptability of HF-rTMS plus antidepressant treatment is comparable to antidepressants alone. However, despite their safety and tolerability, further well-designed studies should be carried out to verify these outcomes.

CONTRIBUTIONS OF AUTHORS

All the authors conceptualized the idea, developed the review protocol, prepared the manuscript for publication, and affirmed the manuscript in its current form. NM and BM searched for articles from the databases, extracted the data, and analyzed the data.

DISCLOSURE STATEMENT

BM received honoraria and/or travel reimbursement from Lundbeck, Pfizer and Servier. NM received travel reimbursement from Lundbeck and Pfizer. PW had no potential conflicts of interest. SL received honoraria and/or travel reimbursement from Janssen-Cilag, Lundbeck, Daiichi Sankyo and Pfizer.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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