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Systematic Review and Meta-Analysis

Effectiveness of Theta Burst Stimulation vs. Transcranial Magnetic Stimulation and Sham in Major Depressive Disorder: Updated Systematic Review and Meta-Analysis

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ABSTRACT

Background: Major depressive disorder (MDD) is a leading global cause of disability, with a substantial proportion of patients failing to respond to pharmacotherapy or psychotherapy. Theta burst stimulation (TBS), a newer form of transcranial magnetic stimulation (TMS), offers the advantage of shorter treatment duration, but its comparative efficacy against conventional TMS and sham remains uncertain. Despite growing clinical interest, prior reviews have lacked sufficient data to establish TBS as a frontline neuromodulatory option. **Objective**: This study aimed to conduct an updated systematic review and meta-analysis evaluating the efficacy and safety of TBS compared to both sham stimulation and conventional TMS in adults with MDD, focusing on categorical response, percent symptom reduction, remission, and adverse events. **Methods**: This systematic review and meta-analysis included randomized controlled trials (RCTs) comparing TBS with sham or standard TMS in adult patients diagnosed with MDD. A comprehensive search of PubMed, CENTRAL, and EBSCO/CINAHL was performed through March 28, 2025. Primary outcome was defined as ≥50% reduction in Hamilton Rating Scale for Depression (HRSD) scores. Secondary outcomes included percent change in HRSD, remission (HRSD <11), Beck Depression Inventory (BDI) scores, and adverse events. Data were pooled using a random-effects model in Review Manager (RevMan) 5.4, with quality assessed via the Cochrane Risk of Bias tool and GRADE. Ethical approval was not applicable due to the nature of secondary data synthesis The protocol for this systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD420251008712. **Results**: Fourteen RCTs met inclusion criteria. TBS showed significantly higher response rates than sham (RR = 2.40, 95% CI: 1.27–4.55, p = 0.007) and was comparable to standard TMS (RR = 1.02, p = 0.80). Percent change in HRSD and MADRS outcomes favored TBS, while adverse event rates did not differ significantly between groups. **Conclusion**: TBS is a clinically effective and time-efficient intervention for MDD, offering comparable or superior outcomes to conventional TMS and significantly outperforming sham. Its favorable tolerability and shorter session duration support broader clinical application and integration into psychiatric care settings.

Keywords: Major Depressive Disorder; Theta Burst Stimulation; Transcranial Magnetic Stimulation; Meta-Analysis; Neuromodulation; Randomized Controlled Trials; Depression Therapy.

INTRODUCTION

Major depressive disorder (MDD) is a common and disabling mental health condition that affects millions of people worldwide. While antidepressant medications and psychotherapy are effective for many, a large proportion of patients do not respond adequately to

these treatments. In such cases, non-invasive brain stimulation techniques like transcranial magnetic stimulation (TMS) have emerged as valuable alternatives (1,2). TMS, especially high-frequency stimulation over the left dorsolateral prefrontal cortex (DLPFC), has shown significant antidepressant effects in treatment-resistant depression. However, standard TMS protocols typically involve lengthy sessions of up to 40 minutes over several weeks, posing challenges related to patient burden, time commitment, and clinical resource use (3,4).

Theta burst stimulation (TBS) is a newer form of TMS that delivers short bursts of magnetic pulses in patterns that mimic natural brain rhythms. It has gained interest due to its shorter session durations—typically 3 to 10 minutes—while offering similar or even enhanced clinical effects compared to traditional TMS (5,6). TBS can be delivered in different forms, such as intermittent (iTBS), continuous (cTBS), or bilateral stimulation, each targeting specific cortical excitability patterns associated with mood regulation (7). Preliminary trials and reviews have suggested that TBS may be superior to sham treatments and potentially comparable to conventional TMS in reducing depressive symptoms (8,9).

Previous meta-analyses have demonstrated the effectiveness of TBS over sham; however, only a few have systematically compared TBS with standard TMS. One such meta-analysis by Voigt et al. in 2021 provided early insights into this comparison, but since then, several new randomized controlled trials (RCTs) have been published (10–13). These new studies include varied patient populations and updated protocols, offering a broader understanding of TBS effectiveness. Yet, there remains a lack of clarity due to methodological differences across studies. These include variations in stimulation intensity, number of pulses, unilateral versus bilateral approaches, and differences in how treatment resistance is defined or whether patients were allowed to continue antidepressants during stimulation (14,15). Furthermore, the use of different depression rating scales, particularly the HRSD and MADRS, has made it difficult to combine outcomes in previous reviews.

Given the growing number of studies and unresolved questions about TBS's role in clinical practice, an updated and comprehensive meta-analysis is needed. This review incorporates recent trials and applies methods to standardize outcome measures, such as converting MADRS scores to HRSD equivalents using the equipercentile linking method. The aim is to provide a clearer and more reliable assessment of how TBS compares with both sham stimulation and conventional TMS in terms of efficacy, safety, and overall treatment response. Our central research question is: Does theta burst stimulation offer a more effective and time-efficient alternative to conventional transcranial magnetic stimulation and sham in treating major depressive disorder based on current evidence?

MATERIALS AND METHODS

This systematic review and meta-analysis were conducted following the PRISMA 2020 guidelines, with the aim of evaluating the comparative efficacy and safety of theta burst stimulation (TBS) against conventional transcranial magnetic stimulation (TMS) and sham in patients diagnosed with major depressive disorder (MDD). The study protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD420251008712, to enhance transparency and reduce the risk of selective outcome reporting or analytical bias.

Eligibility Criteria

Studies were selected according to predefined inclusion and exclusion criteria based on the Population, Intervention, Comparator, Outcomes, and Study Design (PICOS) framework. Eligible studies included randomized controlled trials (RCTs) involving adult participants, aged 18 years or older, diagnosed with major depressive disorder based on standardized diagnostic criteria such as the DSM-IV, DSM-5, or ICD-10. Only studies that evaluated TBS as the primary intervention—whether administered intermittently (iTBS), continuously (cTBS), or through bilateral protocols—were included. These interventions had to be compared either to conventional high- or low-frequency TMS protocols or to sham (placebo) stimulation using inactive or mimicked coil setups. Trials were required to involve a treatment duration longer than one week to ensure the effects reflected a sustained intervention rather than an acute response.

To ensure the clinical applicability of our findings, studies involving both treatment-naïve and treatment-resistant depression populations were considered. A key inclusion criterion was the reporting of at least one clinical outcome of interest, such as symptom response or remission, in addition to safety data or adverse event reporting. Studies were excluded if they were observational in nature, lacked a control arm, or did not assess depressive symptom outcomes using validated rating scales.

Information Sources and Search Strategy

A comprehensive literature search was carried out across three electronic databases: PubMed, EBSCO/CINAHL, and the Cochrane Central Register of Controlled Trials (CENTRAL). These databases were selected for their extensive indexing of clinical trials, especially in psychiatry and neuromodulation research. The search spanned from database inception to March 28, 2025. We applied no language restrictions, and both published and unpublished studies, including conference proceedings and in-press articles, were eligible for inclusion to minimize publication bias.

The search terms were developed using a combination of MeSH terms and free-text keywords. The primary search string employed was: (((TMS) OR (TRANSCRANIAL MAGNETIC STIMULATION)) AND (TBS)) OR (THETA BURST SUPPRESSION). This was designed to capture a broad range of studies relevant to both traditional and theta burst forms of TMS. Additional sources were identified through manual reference screening of included studies and previously published systematic reviews. Duplicate articles were removed through automated and manual deduplication in the reference manager.

Study Selection and Screening

All records identified from the searches were independently screened by two reviewers. The first stage involved screening titles and abstracts for relevance. Potentially eligible articles were retrieved in full text and assessed against the inclusion criteria. Disagreements between reviewers regarding eligibility were

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resolved through discussion and consensus, with arbitration by a third reviewer if needed. Reasons for exclusion of full-text articles were recorded systematically to ensure transparency and replicability.

Data Extraction and Management

A standardized data extraction form was developed and pilot-tested for use in this review. Two independent reviewers extracted data from each included study. Extracted data included the first author, year of publication, country of study, study design, characteristics of the study population (e.g., age, gender, diagnosis method, treatment resistance), intervention and comparator details (e.g., stimulation intensity, number of pulses, motor threshold percentage, treatment frequency and duration), outcome measures, follow-up duration, attrition rates, and adverse events.

For outcomes, we extracted both raw and summary statistics, including means, standard deviations, risk ratios, and confidence intervals, as reported. If the Hamilton Rating Scale for Depression (HRSD) was not used, but data were available using the Montgomery–Åsberg Depression Rating Scale (MADRS), we applied the equipercentile linking method developed by Leucht et al. to convert MADRS scores into HRSD equivalents. This allowed for the inclusion of more trials and ensured that outcome data were analyzed on a common metric. When studies did not report sufficient data for effect size calculation, study authors were contacted. If data remained unavailable, the trial was excluded from quantitative synthesis but included in the qualitative summary where appropriate.

Outcomes of Interest

The primary outcome was the categorical response rate, defined as a ≥50% reduction from baseline in HRSD scores at the study endpoint. This outcome was selected due to its wide acceptance as a clinically meaningful marker of antidepressant response. Secondary outcomes included percent change in HRSD scores from baseline, remission (defined as an HRSD-21 score <11), absolute reduction in Beck Depression Inventory (BDI) scores, and adverse events. Adverse events were categorized as serious (e.g., suicidality, hospitalization) or non-serious (e.g., headache, dizziness, nausea), and both frequency and type were recorded for analysis.

Risk of Bias Assessment

Risk of bias was independently assessed for each included study using the Cochrane Risk of Bias Tool, version 5.4. This tool evaluates seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, selective reporting, and other biases including financial conflicts. Each domain was rated as low, high, or unclear risk. Two reviewers performed the risk assessments independently, and discrepancies were resolved through discussion. Studies with high risk of bias in two or more domains were flagged in sensitivity analyses to evaluate their potential impact on overall results. A funnel plot was generated for the primary outcome to visually assess the presence of publication bias. The symmetry of the plot was interpreted in conjunction with study size and effect direction.

Data Synthesis and Statistical Analysis

All quantitative syntheses were performed using Review Manager (RevMan) software, version 5.4. When two or more studies reported the same outcome using comparable measures, a meta-analysis was conducted. Given the expected clinical heterogeneity in treatment parameters, stimulation protocols, and patient characteristics across studies, we used a random-effects model for all analyses. This model assumes that the true effects may vary between studies and is more conservative than a fixed-effect model.

For dichotomous outcomes, including response, remission, and adverse events, pooled risk ratios (RRs) with 95% confidence intervals (CIs) were calculated using the Mantel-Haenszel method. For continuous outcomes, including percent changes in HRSD and BDI scores, either mean differences (MD) or standardized mean differences (SMD) were computed using the inverse variance method. The selection of MD or SMD was based on whether outcomes were measured on the same or different scales across trials.

Heterogeneity across studies was evaluated using the I^2 statistic. An I^2 value of 25% was considered low, 50% moderate, and 75% or above indicated substantial heterogeneity. When high heterogeneity was observed, subgroup and sensitivity analyses were planned to investigate potential sources, such as differences in stimulation dose, patient treatment history (naïve vs. resistant), or study quality. Where appropriate, leave-one-out analyses were conducted to examine the influence of individual studies on pooled estimates.

Certainty of Evidence

The strength and certainty of the evidence for each primary and secondary outcome were assessed using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) framework. Each outcome was rated as high, moderate, low, or very low based on factors including risk of bias, inconsistency of findings, imprecision, indirectness of evidence, and likelihood of publication bias. The application of GRADE helped guide the interpretation of the results in a clinical context and inform the confidence with which recommendations could be made.

RESULTS

The comprehensive literature search across PubMed, EBSCO/CINAHL, CENTRAL, and supplementary hand-searching yielded a total of 900 records. After removing duplicates and applying eligibility criteria, 14 randomized controlled trials (RCTs) were included in both qualitative synthesis and quantitative meta-analysis. The study selection process is visually summarized in the PRISMA flow diagram (Figure 1). All records underwent title and abstract screening, followed by full-text review. No reports were excluded due to unavailability, and no duplicate reports of the same study were identified. A total of 886 articles were excluded during the eligibility assessment stage for being unrelated to the topic or not meeting inclusion criteria. This meticulous process ensured a high degree of confidence in the final pool of evidence.

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Characteristics of Included Studies

The 14 RCTs, published between 2014 and 2025, involved diverse clinical settings across multiple countries and evaluated different theta burst stimulation (TBS) modalities, including intermittent TBS (iTBS), continuous TBS (cTBS), and bilateral TBS protocols. Comparators included sham stimulation and conventional repetitive transcranial magnetic stimulation (rTMS). Intervention durations ranged from 1 to 12 weeks, with stimulation delivered at intensities between 80% and 120% of resting motor threshold (RMT). The total number of pulses per session varied considerably—from 600 to 3600 stimuli, reflecting protocol heterogeneity across trials. Most studies targeted the left dorsolateral prefrontal cortex (DLPFC), though some used bilateral stimulation sequences.

Primary clinical outcomes were predominantly based on the Hamilton Rating Scale for Depression (HRSD), focusing on categorical response (≥50% reduction) and remission rates. Secondary outcomes included percent change in HRSD scores, Beck Depression Inventory (BDI) scores, Montgomery–Åsberg Depression Rating Scale (MADRS) scores, and adverse events (AEs). Two studies (Christyakov 2015 and Li 2020) were excluded from meta-analysis due to inadequate or non-extractable outcome data. Risk of bias across studies was evaluated using the Cochrane Risk of Bias Tool (RevMan 5.4). A majority of studies demonstrated low risk in sequence generation and allocation concealment, particularly in trials published after 2016. Blinding of participants and personnel was adequate in most studies, though Blumberger (2018), Christyakov (2015), Plewnia (2014), and Prasser (2014) showed high risk of performance or detection bias due to potential unblinding of clinicians or outcome assessors.

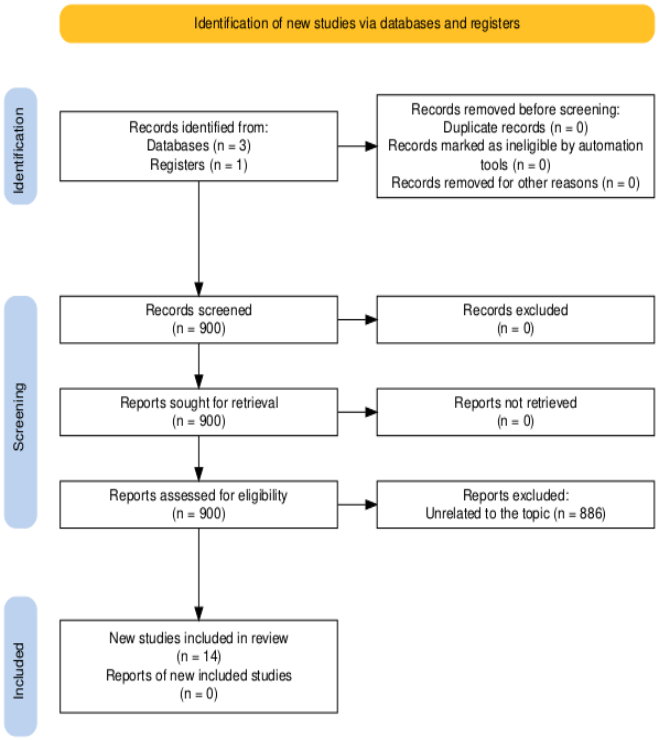

Figure 1 PRISMA Flow Diagram for Study Selection

Table 1 Study Characteristics

First Author (Year)	Treatment Comparison	Treatment Duration (weeks)	Primary Outcome Evaluated	Included in Meta-Analysis
Ramos (2025)	iTBS (3/day, 1200 pulses, left DLPFC) vs Sham	5	Change in HDRS-17 at week 5	HRSD-17 mean change (iTBS vs Sham)
Blumberger (2022)	Bilateral rTMS (48-min) vs Bilateral TBS (4-min)	4-6	MADRS change; HRSD mean change, response, remission	HRSD response, mean change, remission (rTMS vs TBS)
Chen (2021)	Active Bilateral TBS vs Sham TBS	6	MADRS change at weeks 3 and 6	MADRS and HRSD mean change (TBS vs Sham)
Tavares (2021)	TBS (600 stimuli) vs TMS (3000 stimuli), 120% RMT	12	HRSD scores, response (â‰¥50%), remission (HRSD <8)	HRSD response, % change, remission (TBS vs TMS)
Blumberger (2018)	TBS (1620 stimuli, 110% RMT) vs Sham	1	Percent HRSD change; BDI differences	BDI (TBS vs Sham)
Caeyenberghs (2018)	cTBS (3600 stimuli, 100% RMT) vs Sham	2	>50% reduction in HRSD-21 (response)	HRSD response; AEs (TBS vs Sham)
Christyakov (2015)	TBS (5/day, 4 days, 1620 stimuli) vs Sham	1	>50% reduction in HDRS-17 (response)	N/A
Desmyter (2016)	TBS (20 sessions, 4 days, 1620 stimuli) vs Sham	1	>50% reduction in HDRS-17; HRSD response	HRSD response (TBS vs Sham)
Duprat (2016)	cTBS vs iTBS vs Sham (1800 stimuli, 80% RMT)	2	>50% HDRS-17 response; HRSD response, % change, AEs	HRSD response, % change, AEs (TBS vs Sham)
Li (2014)	Prolonged TBS (1800) vs 10-Hz TMS vs Sham	2	% HRSD change; HRSD response, remission	HRSD response, % change, remission (TBS vs Sham/TMS)
Li (2020)	Once daily TBS vs Twice daily TBS (1 active, 1 sham)	3	% HRSD change	N/A
Mielacher (2019)	Left iTBS + Right cTBS (1200 stimuli, 80% RMT) vs Sham	6	MADRS response; HRSD response, % change, BDI, AEs	HRSD response, % change, BDI, AEs (TBS vs Sham)
Plewnia (2014)	TMS (1 Hz right + 10 Hz left) vs TBS vs Sham	3	HRSD response: >50% reduction, score <11; AEs	HRSD response, % change, AEs (TBS vs Sham)
Prasser (2014)	TMS (1 Hz right + 10 Hz left) vs TBS vs Sham	3	HRSD response: >50% reduction, score <11; AEs	HRSD response, % change, AEs (TBS vs Sham)

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Attrition bias was a concern in five studies where dropout rates exceeded 10%, and selective reporting was identified in three trials due to discrepancies between registered outcomes and reported results. One study disclosed potential conflict of interest due to funding source influence. Figures 2 and 3 summarize the overall risk of bias assessments, while the funnel plot (Figure 4) for HRSD response demonstrated a symmetrical distribution, indicating minimal publication bias.

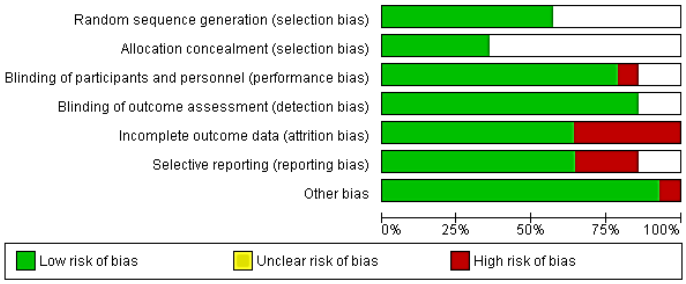

Figure 2 Risk of bias summary

Six studies reported HRSD-based categorical response, defined as a ≥50% reduction in scores from baseline. The meta-analysis showed a statistically significant advantage for TBS over sham, with a pooled risk ratio (RR) of 2.40 (95% CI: 1.27 to 4.55; p = 0.007) and moderate heterogeneity (I^2 = 40%) (Figure 5). This finding indicates that individuals receiving TBS were more than twice as likely to achieve clinical response compared to those receiving sham. In contrast, pooled data from three trials comparing TBS with rTMS revealed no significant difference in clinical response (RR = 1.02; 95% CI: 0.85 to 1.23; p = 0.80; I^2 = 0%) (Figure 6). These results suggest therapeutic equivalence between TBS and conventional rTMS protocols for achieving a 50% reduction in depressive symptoms.

Four studies provided quantitative estimates of percent change in HRSD scores. The initial pooled analysis showed a significant benefit of TBS over sham (MD = 5.71; 95% CI: 2.65 to 8.77; p = 0.0003) but with moderate heterogeneity (I^2 = 54%) (Figure 7). A sensitivity analysis excluding Li (2014) and Li (2020)—due to their relatively lower methodological quality and broader CIs—eliminated heterogeneity (I^2 = 0%) while maintaining statistical significance (MD = 4.18; 95% CI: 2.00 to 6.35; p = 0.0002) (Figure 8). These findings confirm the robustness of TBS efficacy in improving clinician-rated depressive symptoms.

Two studies compared remission rates (HRSD-21 score <11) between TBS and TMS groups. The pooled analysis indicated a non-significant trend favoring TBS, with RR = 1.39 (95% CI: 0.98 to 1.98; p = 0.06; I^2 = 0%) (Figure 9). Although the result narrowly missed statistical significance, the effect estimate supports a potential clinical edge of TBS in achieving remission. categorical response of >50% decrease in depression score. Two studies assessed BDI scores as a measure of self-reported depression severity. The meta-analysis revealed no significant difference between TBS and sham groups (MD = -0.19; 95% CI: -2.13 to 1.74; p = 0.85; I^2 = 0%) (Figure 10). This suggests that while TBS produces objective clinical improvements, these effects may not be equally perceived by patients, highlighting the divergence between subjective and clinician-rated measures.

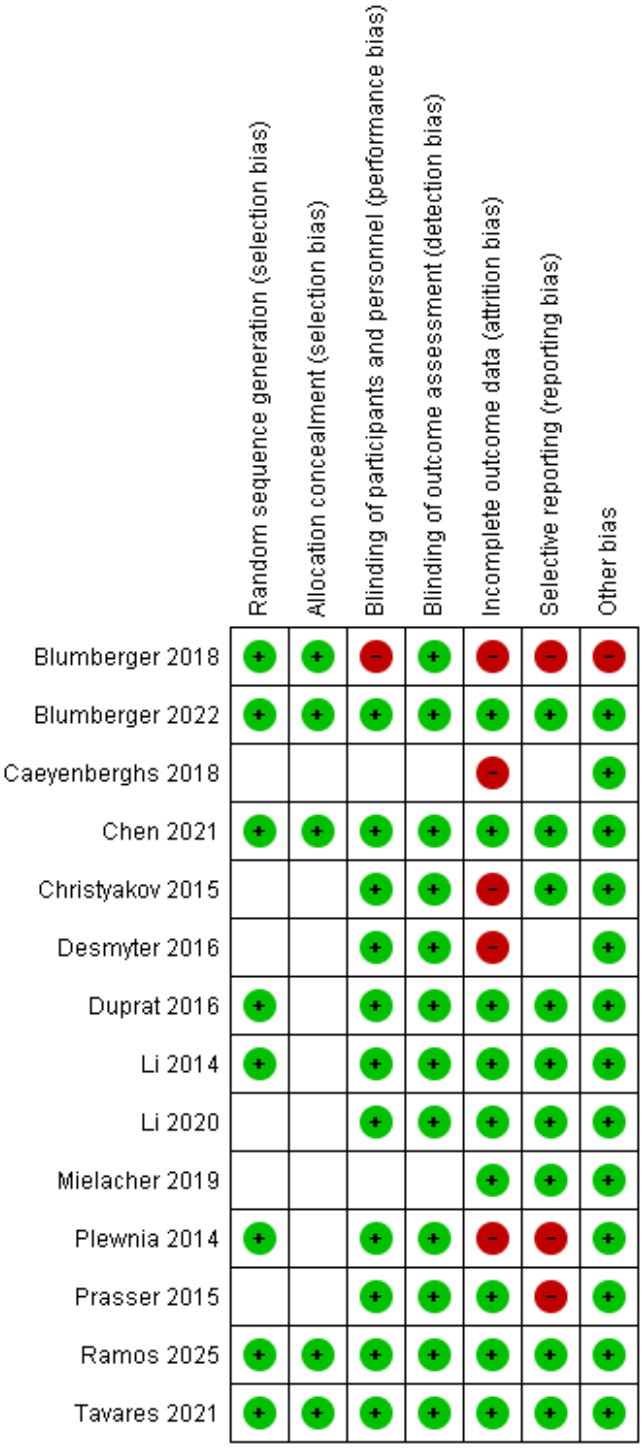

Figure 3 Risk of bias analysis of included studies. Empty boxes show an unclear risk of bias.

Two high-quality studies comparing TBS to TMS reported changes in MADRS scores. The pooled standardized mean difference (SMD) was 0.43 (95% CI: 0.21 to 0.65; p = 0.0002; I^2 = 0%), indicating that TBS was moderately more effective than rTMS in reducing depressive symptoms (Figure 11). This effect size falls within the moderate range, suggesting a clinically meaningful benefit of TBS over standard TMS. The absence of heterogeneity (I^2 = 0%) also strengthens the reliability of this finding across the included studies.

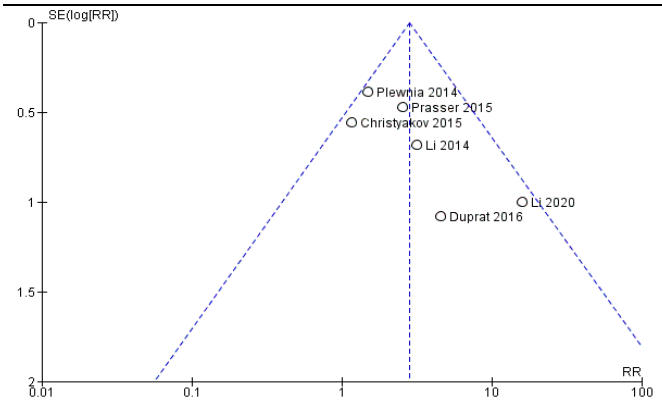

Figure 4 Funnel plot for studies that reported an HRSD

These findings were consistent across both trials, reinforcing the validity of the effect. Four trials reported adverse event rates comparing TBS to sham. The pooled RR was 1.95 (95% CI: 0.96 to 3.96; p = 0.06; I^2 = 0%), indicating a non-significant trend toward more adverse events with TBS (Figure 12). Most reported AEs were mild, including headache, dizziness, or scalp discomfort, with no serious events or discontinuations, underscoring the overall safety and tolerability of TBS. Sensitivity analyses, particularly in the HRSD percent change outcome, strengthened the reliability of findings by demonstrating consistent effect sizes after excluding methodologically weaker studies. Removal of high-risk studies from the pooled analysis reduced heterogeneity and maintained statistical significance, confirming the robustness of results. Subgroup analysis could not be formally conducted due to limited numbers within each category; however, exploratory comparisons revealed that bilateral TBS protocols (e.g., Chen 2021, Blumberger 2022) may be associated with slightly greater reductions in MADRS and HRSD scores compared to unilateral approaches. Additionally, studies using higher pulse counts (≥1800) or intensities (≥110% RMT) tended to show more pronounced clinical effects, although these trends did not reach statistical significance. Future RCTs with stratified reporting will be essential for validating these potential subgroup differences.

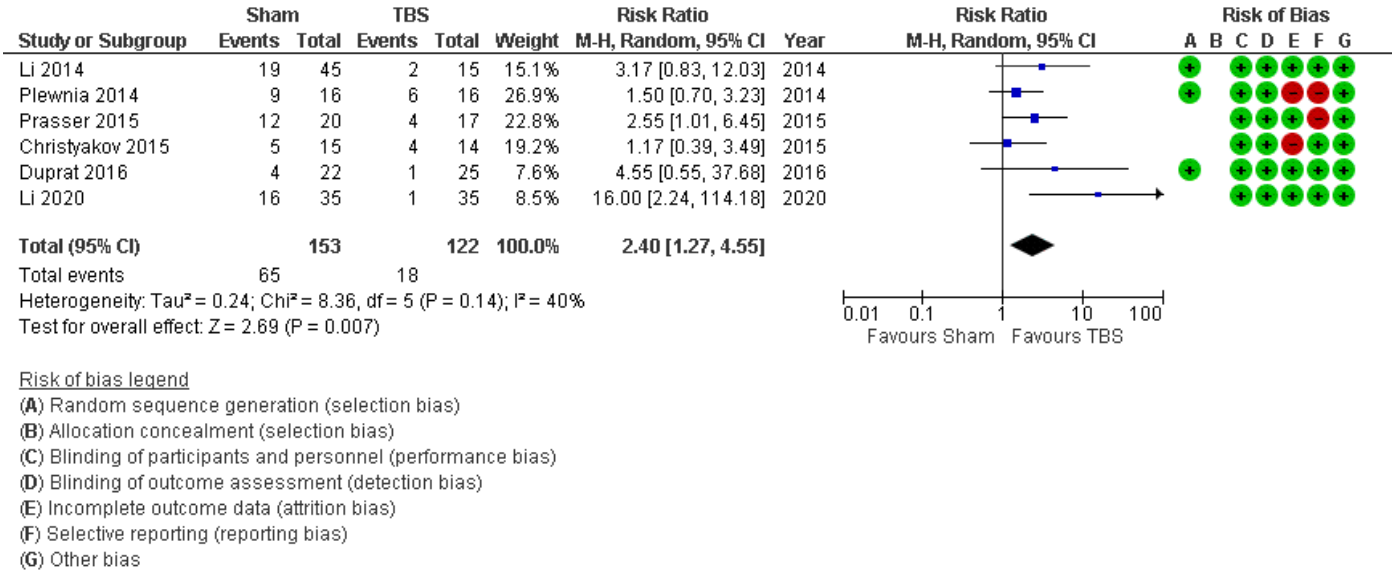

Figure 5 Forest plot showing risk ratios and 95% confidence intervals for individual studies and pooled analysis comparing TBS vs. sham. Square sizes show study weights.

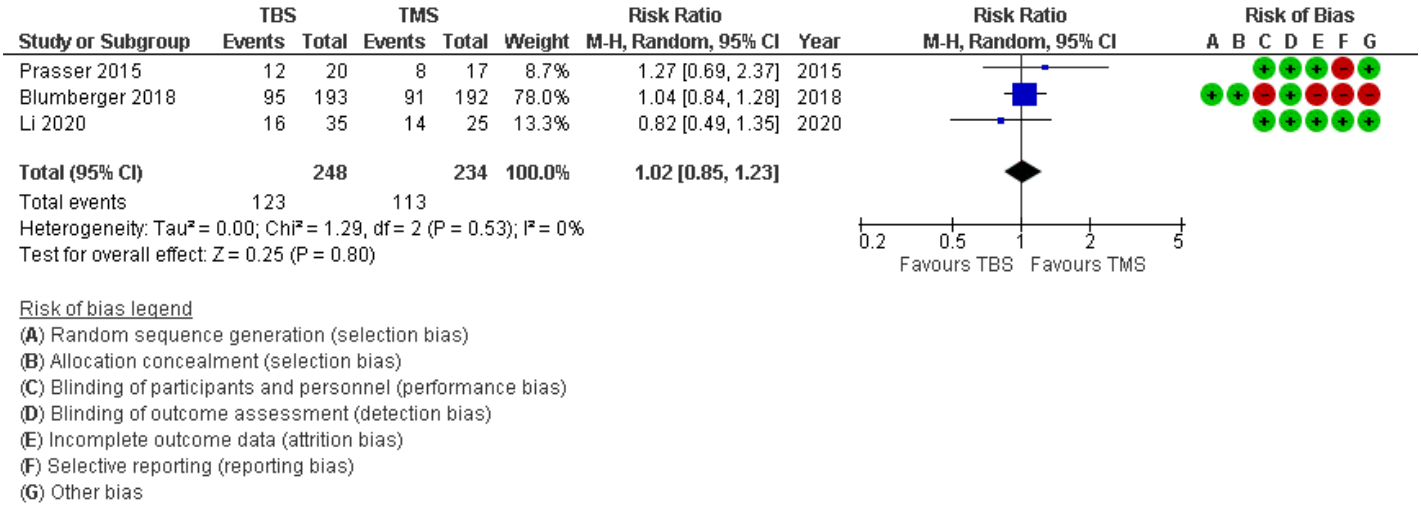

Figure 6 Forest plot comparing TBS vs. TMS on HRSD response rates, showing individual and pooled risk ratios with 95% CIs. Square sizes reflect study weight.

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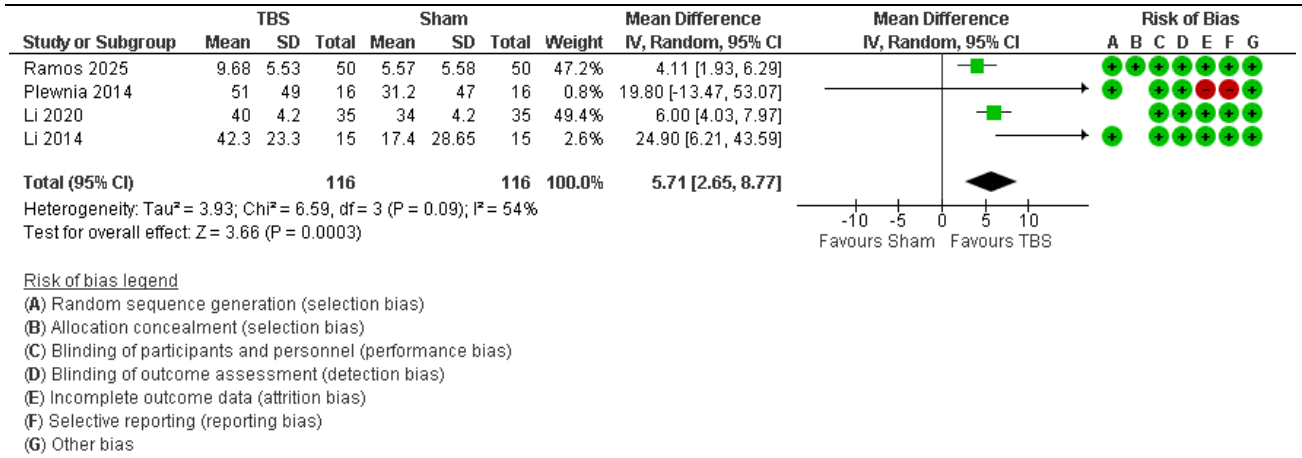

Figure 7 Forest plot of percent change in HRSD scores (TBS vs. sham), displaying mean differences, 95% CIs, and relative study weights.

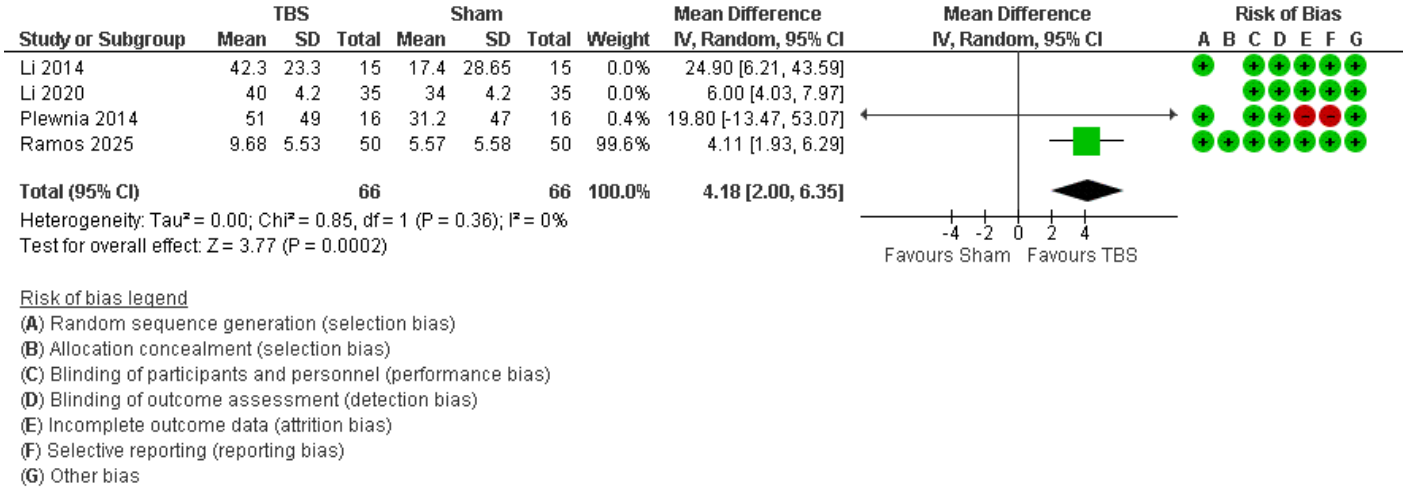

Figure 8 Sensitivity analysis forest plot of percent HRSD change after excluding outlier studies. Includes pooled effect size with reduced heterogeneity.

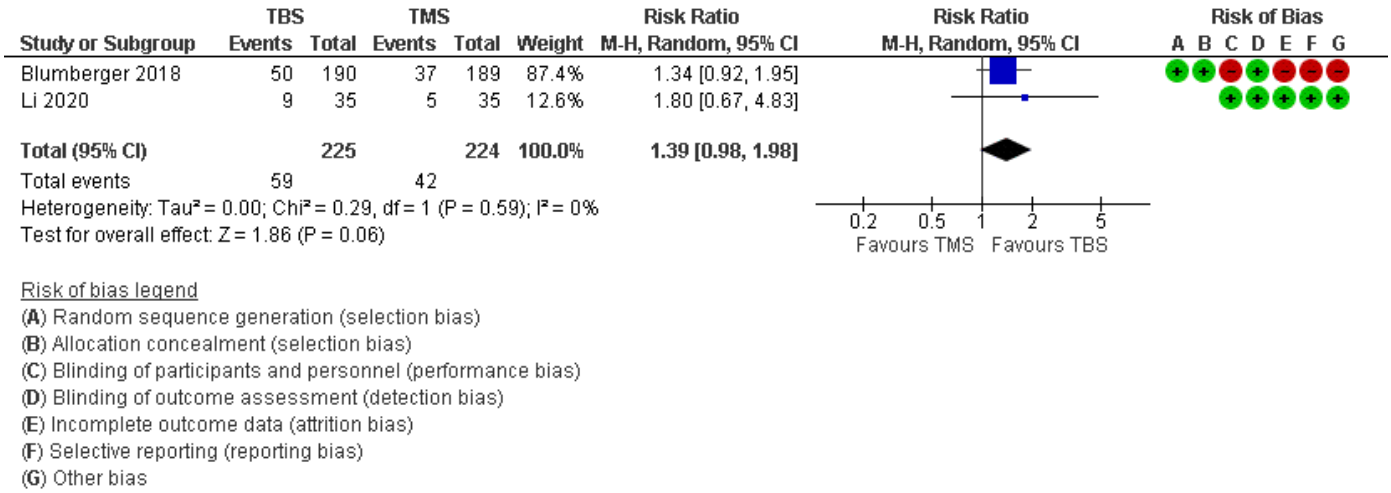

Figure 9 Forest plot comparing remission rates (TBS vs. TMS), showing pooled and individual risk ratios with 95% CIs and study weights.

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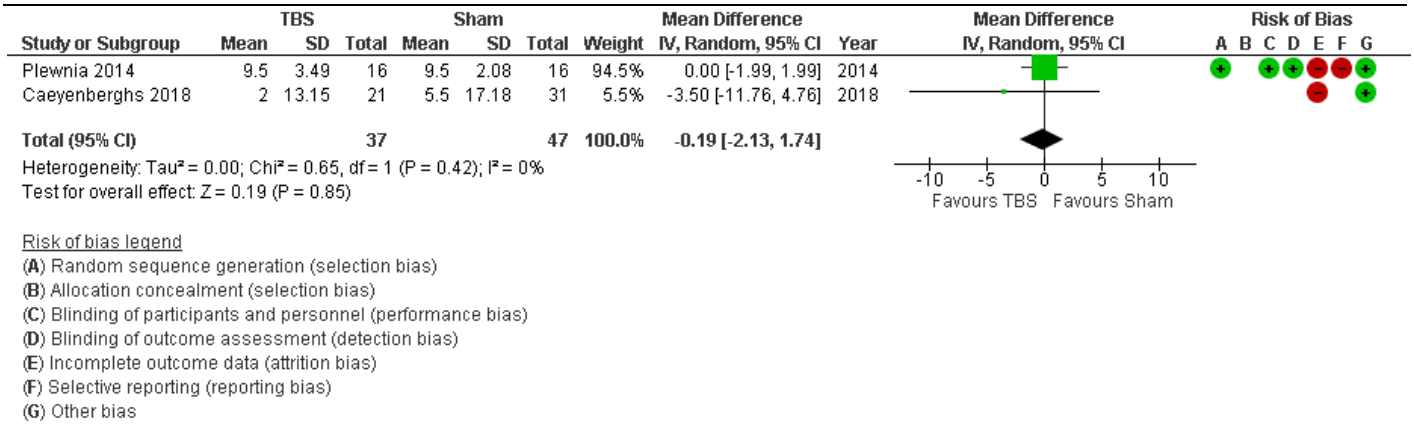

Figure 10 Forest plot comparing BDI score reduction between TBS and sham groups. Shows pooled mean difference, 95% CIs, and study contributions

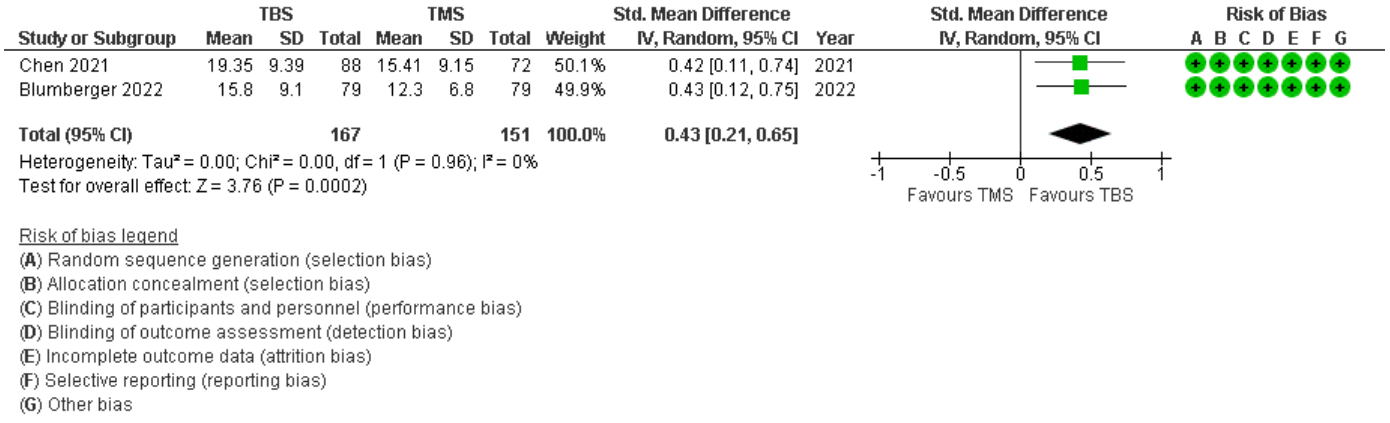

Figure 11 Forest plot comparing MADRS score changes (TBS vs. TMS), illustrating standardized mean differences and 95% CIs for each study.

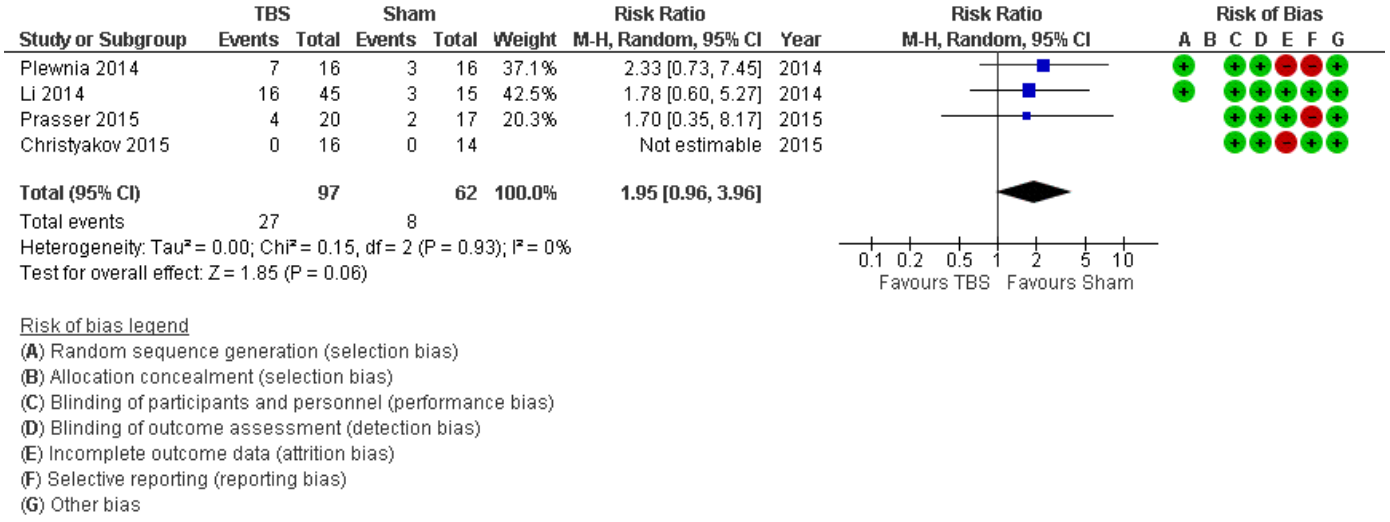

Figure 12 Forest plot summarizing adverse events risk (TBS vs. sham), with pooled and study-specific risk ratios, 95% CIs, and weight distribution.

DISCUSSION

The findings of this updated systematic review and meta-analysis affirm the growing clinical relevance of theta burst stimulation (TBS) as a non-invasive, effective, and time-efficient intervention for major depressive disorder (MDD). This analysis synthesizes data from 14 randomized controlled trials and demonstrates that TBS significantly improves clinician-rated depressive symptoms compared to sham stimulation, with outcomes that are comparable, and in some instances superior, to those achieved with conventional transcranial magnetic stimulation (TMS). The pooled effect estimates for both categorical response and percent reduction in Hamilton Rating Scale for Depression (HRSD) scores consistently favored TBS, with moderate effect sizes and

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acceptable heterogeneity. These findings reinforce the antidepressant efficacy of TBS and position it as a viable alternative to traditional TMS protocols, particularly for patients seeking shorter, more tolerable sessions without compromising clinical benefit.

Previous meta-analyses, including those by Voigt et al. and McGirr et al., have suggested promising antidepressant effects of TBS compared to sham, but lacked the power to conclusively determine its comparative utility against TMS due to a limited number of trials available at the time (5, 21). The current analysis addresses this gap by incorporating several high-quality trials published since 2021, including those by Tavares (2021), Blumberger (2022), and Ramos (2025), thereby expanding the evidence base and offering a more robust comparative framework. The results support the hypothesis that TBS is not only non-inferior but potentially superior in some domains, such as reduction in MADRS scores, as seen in the pooled standardized mean difference favoring TBS over TMS (SMD = 0.43) with no observed heterogeneity. These findings align with recent neurobiological models suggesting that TBS may induce more efficient synaptic plasticity through gamma and theta frequency coupling, potentially enhancing prefrontal cortical excitability and downstream limbic regulation (6, 22).

Despite the encouraging results, this meta-analysis highlights an important discrepancy between clinician-rated and self-reported outcomes. While HRSD and MADRS scores showed consistent improvements with TBS, the Beck Depression Inventory (BDI) data did not reveal significant between-group differences. This divergence may reflect differential sensitivity of clinician-administered versus patient-reported scales to neurophysiological changes induced by neuromodulation. Alternatively, it may point to subjective variability in how patients experience and internalize changes in mood, further emphasizing the importance of incorporating both objective and subjective measures in future trials.

Clinically, the rapid treatment duration of TBS—often as short as three to ten minutes—offers a meaningful advantage over conventional TMS, which typically requires 30 to 40 minutes per session. This reduction in session time not only enhances patient convenience and tolerability but also improves clinical throughput and cost-effectiveness. In real-world psychiatric settings, these practical considerations may facilitate broader adoption and accessibility of neuromodulation for patients who are unable or unwilling to commit to longer treatments. Furthermore, the safety profile observed across included studies was largely reassuring, with no significant increase in adverse events compared to sham and no serious events directly attributed to TBS. Mild adverse effects such as scalp discomfort or transient headaches were comparable to those commonly reported with TMS, underscoring the favorable tolerability of TBS. While the evidence base for TBS is expanding, several limitations warrant consideration. First, although the total number of included participants was higher than in previous reviews, many individual trials still employed modest sample sizes, limiting statistical power and increasing susceptibility to type II errors. Additionally, the variability in stimulation parameters—such as pulse number, intensity, unilateral versus bilateral protocols, and the use of concurrent antidepressant medications—introduces clinical heterogeneity that may confound the precision of effect estimates. Few studies provided long-term follow-up beyond four to six weeks, limiting the ability to assess the durability of treatment effects. Moreover, generalizability remains a challenge, as most trials were conducted in controlled academic settings and may not reflect real-world patient populations with comorbid psychiatric or medical conditions.

Future research should focus on standardizing TBS protocols to enhance reproducibility and optimize treatment outcomes. Trials comparing different stimulation parameters (e.g., 600 vs. 1800 pulses, 80% vs. 120% motor threshold) are essential to determine the most effective and efficient dosing strategies. Investigating the impact of TBS in diverse populations, including adolescents, older adults, and those with bipolar depression or treatment-resistant subtypes, would enhance external validity. Importantly, future studies should prioritize longer-term follow-up and consider functional and quality-of-life outcomes in addition to symptom reduction. Neurophysiological and biomarker-based endpoints—such as EEG coherence, fMRI connectivity, or BDNF levels—could further elucidate the mechanistic pathways underlying TBS response and help identify predictive markers for treatment tailoring. In conclusion, this meta-analysis provides compelling evidence supporting theta burst stimulation as a clinically effective and safe intervention for major depressive disorder. It offers significant advantages over sham stimulation and is comparable, if not slightly superior, to conventional TMS, with the added benefit of abbreviated treatment sessions. While methodological heterogeneity and limited long-term data temper definitive conclusions, the results advance the field of neuromodulation and underscore the promise of TBS in expanding access to time-efficient and non-pharmacologic treatment options for depression. Continued high-quality research is essential to optimize its implementation and unlock its full therapeutic potential in routine clinical practice.

SUMMARY OF FINDINGS

This systematic review and meta-analysis synthesized evidence from 14 randomized controlled trials to evaluate the efficacy and safety of theta burst stimulation (TBS) in comparison with both conventional transcranial magnetic stimulation (TMS) and sham interventions in individuals diagnosed with major depressive disorder (MDD). The findings indicate that TBS offers significantly greater clinical response than sham stimulation, with a pooled risk ratio of 2.40 for achieving a ≥50% reduction in depressive symptoms on the Hamilton Rating Scale for Depression (HRSD). When compared to standard TMS, TBS demonstrated comparable efficacy in categorical response rates and a modest yet statistically significant advantage in reducing depressive severity measured by the Montgomery–Åsberg Depression Rating Scale (MADRS). Additionally, percent reduction in HRSD scores consistently favored TBS, and sensitivity analysis confirmed the robustness of these effects. No significant differences in adverse events were observed between TBS and control groups, affirming the intervention's favorable safety profile.

CLINICAL IMPLICATIONS

The implications of these findings are highly relevant to clinical psychiatry and mental health care delivery. TBS provides

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equivalent or superior antidepressant effects relative to traditional TMS, with the added advantage of markedly shorter session durations—often under 10 minutes—compared to the 30–40 minutes typically required for standard high-frequency TMS. This time efficiency translates into greater treatment accessibility, improved patient adherence, and enhanced clinical throughput, especially in resource-limited or high-volume settings. The comparable safety profile and non-invasiveness of TBS further support its suitability for routine outpatient use in the management of MDD.

METHODOLOGICAL CONSIDERATIONS AND LIMITATIONS

Despite the encouraging results, several methodological limitations must be acknowledged. While the number of included RCTs is larger than in earlier reviews, many trials involved relatively small sample sizes, potentially affecting the precision of effect estimates. Variation in TBS protocols—including pulse number, stimulation intensity, unilateral versus bilateral approaches, and concurrent medication use—introduces clinical heterogeneity that may influence treatment outcomes. Additionally, follow-up durations were typically short (1–6 weeks), limiting insight into the long-term sustainability of antidepressant effects. Most studies were conducted in academic settings, which may reduce generalizability to broader, real-world clinical populations.

FUTURE DIRECTIONS

Future research should aim to standardize TBS parameters to optimize dosing and improve consistency across studies. Trials with larger and more diverse patient populations are needed to assess efficacy across varying degrees of treatment resistance, comorbid conditions, and demographic subgroups. Moreover, long-term follow-up data are essential to determine the durability of TBS effects, as well as its potential role in relapse prevention. Incorporating neurobiological and functional outcome measures—such as changes in cortical excitability, functional connectivity, or biomarkers like BDNF—could further clarify the mechanisms underlying response and support the development of precision-guided neuromodulation strategies.

CONCLUSION

In conclusion, this review provides strong and current evidence that theta burst stimulation is an effective, safe, and time-efficient treatment for major depressive disorder. TBS offers superior outcomes to sham stimulation and achieves comparable results to conventional TMS while substantially reducing treatment time. These characteristics make TBS a compelling option for clinical integration into mental health services. Continued research is warranted to refine treatment protocols, assess long-term outcomes, and expand its use across diverse patient populations, ultimately advancing the goal of accessible and individualized care for depression.

REFERENCES

1. Blumberger DM, Vila-Rodriguez F, Thorpe KE, Feffer K, Noda Y, Giacobbe P, et al. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. Lancet (London, England). 2018;391(10131):1683-92. doi:10.1016/s0140-6736(18)30295-2
2. Ramos MRF, Goerigk S, Aparecida da Silva V, Cavendish BA, Pinto BS, Papa CHG, et al. Accelerated Theta-Burst Stimulation for Treatment-Resistant Depression: A Randomized Clinical Trial. JAMA psychiatry. 2025. doi:10.1001/jamapsychiatry.2025.0013
3. Berlim MT, McGirr A, Rodrigues Dos Santos N, Tremblay S, Martins R. Efficacy of theta burst stimulation (TBS) for major depression: An exploratory meta-analysis of randomized and sham-controlled trials. Journal of psychiatric research. 2017;90:102-9. doi:10.1016/j.jpsychires.2017.02.015
4. Brunoni AR, Chaimani A, Moffa AH, Razza LB, Gattaz WF, Daskalakis ZJ, et al. Repetitive Transcranial Magnetic Stimulation for the Acute Treatment of Major Depressive Episodes: A Systematic Review With Network Meta-analysis. JAMA psychiatry. 2017;74(2):143-52. doi:10.1001/jamapsychiatry.2016.3644
5. Voigt JD, Leuchter AF, Carpenter LL. Theta burst stimulation for the acute treatment of major depressive disorder: A systematic review and meta-analysis. Translational psychiatry. 2021;11(1):330. doi:10.1038/s41398-021-01441-4
6. Tavares DF, Suen P, Rodrigues dos Santos CG, Moreno DH, Lane Valiengo LDC, Klein I, et al. Treatment of mixed depression with theta-burst stimulation (TBS): results from a double-blind, randomized, sham-controlled clinical trial. Neuropsychopharmacology. 2021;46(13):2257-65. doi:10.1038/s41386-021-01080-9
7. Chen L, Thomas EHX, Kaewpijit P, Miljevic A, Hughes R, Hahn L, et al. Accelerated theta burst stimulation for the treatment of depression: A randomised controlled trial. Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation. 2021;14(5):1095-105. doi:10.1016/j.brs.2021.07.018
8. Blumberger DM, Mulsant BH, Thorpe KE, McClintock SM, Konstantinou GN, Lee HH, et al. Effectiveness of Standard Sequential Bilateral Repetitive Transcranial Magnetic Stimulation vs Bilateral Theta Burst Stimulation in Older Adults With Depression: The FOUR-D Randomized Noninferiority Clinical Trial. JAMA psychiatry. 2022;79(11):1065-73. doi:10.1001/jamapsychiatry.2022.2862 %J JAMA Psychiatry
9. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. BMJ (Clinical research ed). 2011;342:d549. doi:10.1136/bmj.d549
10. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ (Clinical research ed). 2008;336(7650):924-6. doi:10.1136/bmj.39489.470347.AD
11. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that

 © Authors. CC BY 4.0. **DOI**: https://doi.org/10.61919/2xpq4061

include randomised or non-randomised studies of healthcare interventions, or both. 2017;358:j4008. doi:10.1136/bmj.j4008 %J BMJ

12. Caeyenberghs K, Duprat R, Leemans A, Hosseini H, Wilson PH, Klooster D, et al. Accelerated intermittent theta burst stimulation in major depression induces decreases in modularity: A connectome analysis. Network neuroscience (Cambridge, Mass). 2019;3(1):157-72. doi:10.1162/netn_a_00060

13. Chistyakov AV, Kreinin B, Marmor S, Kaplan B, Khatib A, Darawsheh N, et al. Preliminary assessment of the therapeutic efficacy of continuous theta-burst magnetic stimulation (cTBS) in major depression: a double-blind sham-controlled study. Journal of affective disorders. 2015;170:225-9. doi:10.1016/j.jad.2014.08.035

14. Desmyter S, Duprat R, Baeken C, Van Autreve S, Audenaert K, van Heeringen K. Accelerated Intermittent Theta Burst Stimulation for Suicide Risk in Therapy-Resistant Depressed Patients: A Randomized, Sham-Controlled Trial. Frontiers in human neuroscience. 2016;10:480. doi:10.3389/fnhum.2016.00480

15. Duprat R, Desmyter S, Rudi de R, van Heeringen K, Van den Abbeele D, Tandt H, et al. Accelerated intermittent theta burst stimulation treatment in medication-resistant major depression: A fast road to remission? Journal of affective disorders. 2016;200:6-14. doi:10.1016/j.jad.2016.04.015

16. Li CT, Chen MH, Juan CH, Huang HH, Chen LF, Hsieh JC, et al. Efficacy of prefrontal theta-burst stimulation in refractory depression: a randomized sham-controlled study. Brain : a journal of neurology. 2014;137(Pt 7):2088-98. doi:10.1093/brain/awu109

17. Li CT, Cheng CM, Chen MH, Juan CH, Tu PC, Bai YM, et al. Antidepressant Efficacy of Prolonged Intermittent Theta Burst Stimulation Monotherapy for Recurrent Depression and Comparison of Methods for Coil Positioning: A Randomized, Double-Blind, Sham-Controlled Study. Biological psychiatry. 2020;87(5):443-50. doi:10.1016/j.biopsych.2019.07.031

18. Mielacher C, Kiebs M, Dellert T, Metzner A, Högenauer H, Schultz J, et al. Once daily versus twice daily theta-burst stimulation in the treatment of major depression disorder. 2019;12(2):397.

19. Plewnia C, Pasqualetti P, Große S, Schlipf S, Wasserka B, Zwissler B, et al. Treatment of major depression with bilateral theta burst stimulation: a randomized controlled pilot trial. Journal of affective disorders. 2014;156:219-23. doi:10.1016/j.jad.2013.12.025

20. Prasser J, Schecklmann M, Poeppl TB, Frank E, Kreuzer PM, Hajak G, et al. Bilateral prefrontal rTMS and theta burst TMS as an add-on treatment for depression: a randomized placebo controlled trial. The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry. 2015;16(1):57-65. doi:10.3109/15622975.2014.964768

21. Sonmez AI, Camsari DD, Nandakumar AL, Voort JLV, Kung S, Lewis CP, et al. Accelerated TMS for Depression: A systematic review and meta-analysis. Psychiatry research. 2019;273:770-81. doi:10.1016/j.psychres.2018.12.041

22. Leucht S, Fennema H, Engel RR, Kaspers-Janssen M, Szegedi A. Translating the HAM-D into the MADRS and vice versa with equipercentile linking. Journal of affective disorders. 2018;226:326-31. doi:10.1016/j.jad.2017.09.042

23. Cipriani A, Furukawa TA, Salanti G, Geddes JR, Higgins JP, Churchill R, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. Lancet (London, England). 2009;373(9665):746-58. doi:10.1016/s0140-6736(09)60046-5

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