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REVIEW ARTICLE

Intermittent theta burst stimulation in the treatment of neuropathic pain: systematic review and meta-analysis

Estimulação theta burst intermitente no tratamento da dor neuropática: revisão sistemática e meta-análise

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ABSTRACT

BACKGROUND AND OBJECTIVES: Intermittent theta burst stimulation (iTBS), a patterned form of repetitive transcranial magnetic stimulation (rTMS), is an established treatment for depression, but its role in neuropathic pain remains unclear. The objective of this study was to conduct a systematic review and meta-analysis to evaluate the effect of iTBS on neuropathic pain.

CONTENTS: The review followed the Cochrane Handbook and PRISMA guidelines (PROSPERO ID: CRD42024584969). Eligible randomized controlled trials in Portuguese, English, and Spanish were identified through searches in Pubmed, EMBASE, BVS, and Web of Science. The primary outcome was the change in pain intensity measured by the 11-point Numerical Rating Scale (NRS), considering a reduction of ≥2 points as clinically significant. Mean differences in NRS scores between baseline and post-intervention were analyzed. Subgroups were formed based on the type of control (sham or high-frequency rTMS), and a random-effects meta-analysis was performed. Of 1,062 records screened, four studies met the inclusion criteria. Two trials using sham controls demonstrated significant pain reduction with iTBS, while three comparing iTBS with rTMS favored rTMS. Substantial heterogeneity was observed (I^2 = 51% for sham and 53% for rTMS comparisons). No major adverse effects were reported.

CONCLUSION: Preliminary evidence suggests that iTBS may be an effective and time-efficient neuromodulatory approach for neuropathic pain, though results are inconsistent when compared to rTMS. Larger, multicenter randomized trials are required to confirm efficacy and clarify optimal stimulation protocols.

KEYWORDS: Neuralgia, Pain, Systematic review, Transcranial magnetic stimulation.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A estimulação *theta burst* intermitente (iTBS), uma forma padronizada de estimulação magnética transcraniana repetitiva (rTMS), é um tratamento estabelecido para depressão, mas seu papel na dor neuropática ainda não está bem definido. O objetivo deste estudo foi realizar uma revisão sistemática e meta-análise para avaliar o efeito da iTBS na dor neuropática.

CONTEÚDO: O estudo seguiu as recomendações do Cochrane Handbook e as diretrizes PRISMA (PROSPERO ID: CRD42024584969). Ensaios clínicos randomizados em português, inglês e espanhol foram identificados nas bases Pubmed, EMBASE, BVS e *Web of Science*. O desfecho primário foi a variação da intensidade da dor medida pela Escala Numérica de 11 pontos (NRS), considerando-se clinicamente significativa uma redução = 2 pontos. As diferenças médias entre o pré e o pós-intervenção foram analisadas, e as comparações foram divididas conforme o tipo de controle (sham ou rTMS de alta frequência). Foi realizada uma meta-análise com modelo de efeitos aleatórios. De 1.062 registros identificados, quatro estudos preencheram os critérios de inclusão. Dois ensaios com controle sham mostraram redução significativa da dor com iTBS, enquanto três comparando iTBS e rTMS favoreceram o rTMS. Observou-se heterogeneidade substancial (I^2 = 51% para o grupo sham e 53% para o grupo rTMS). Nenhum efeito adverso relevante foi relatado.

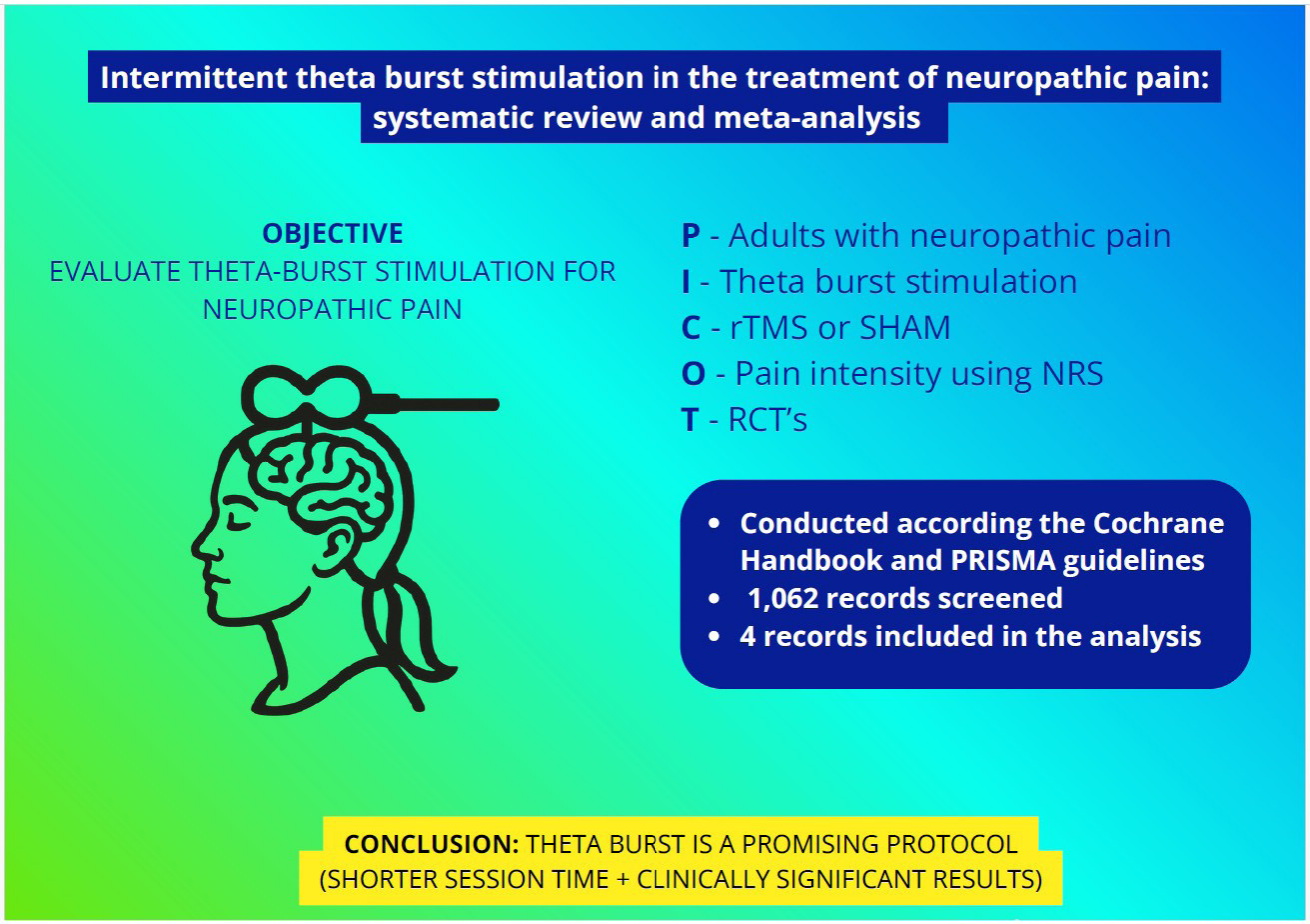
CONCLUSÃO: As evidências preliminares sugerem que a iTBS pode ser uma abordagem neuromodulatória eficaz e de curta duração para o tratamento da dor neuropática. No entanto, são necessários ensaios multicêntricos e de maior escala para confirmar sua eficácia e definir protocolos ideais de estimulação.

DESCRITORES: Dor, Estimulação magnética transcraniana, Neuralgia, Revisão sistemática.

HIGHLIGHTS

- Intermittent theta burst stimulation (iTBS) applied over the primary motor cortex produced statistically and clinically significant reductions in neuropathic pain intensity compared with sham stimulation
- In head-to-head comparisons, conventional high frequency rTMS achieved slightly greater analgesic effects than iTBS, but at the cost of substantially longer treatment sessions
- The current evidence base is still limited and heterogeneous, underscoring the need for larger, well-controlled multicenter trials to better define the role of iTBS in the treatment of neuropathic pain

GRAPHICAL ABSTRACT



INTRODUCTION

Neuropathic pain is delineated by the International Association for the Study of Pain (IASP) as "pain caused by a lesion or disease of the somatosensory nervous system"[1]. This condition includes a diverse range of diseases, including both central (e.g., stroke, spinal cord injury) and peripheral (e.g., herpetic neuralgia, diabetic neuropathy) origins, affecting approximately 7%-10% of the global population[2]. Beyond its high prevalence, neuropathic pain is associated with substantial disability, impaired quality of life, and increased healthcare utilization, underscoring the need for more effective and durable treatment strategies[3,4].

Pharmacological treatment with antidepressants and anticonvulsants is recommended for most patients, although fewer than 50% respond satisfactorily to this treatment, and the side effects of such therapy can become prohibitive for some individuals[5]. The diversity of pathophysiological pathways explains the challenge in achieving effective pain control. As a result, new approaches have been proposed, including non-invasive neurostimulation[2,6].

Among non-invasive neuromodulation techniques, repetitive transcranial magnetic stimulation (rTMS) over the primary motor cortex (M1) has emerged as one of the most promising strategies. High-frequency rTMS (≥5 Hz), typically delivered over M1 at 5-20 Hz, generates electric currents in cortical tissue via a rapidly changing magnetic field produced by specialized coils[2,6,7]. Clinical studies suggest that while single sessions yield transient analgesia, repeated daily sessions over one to two weeks can produce more sustained pain relief, with a favorable safety profile and predominantly mild adverse effects[2,6-8].

Mechanistically, high-frequency M1 stimulation is thought to modulate cortico-subcortical circuits involved in pain perception and regulation, inducing long-term potentiation (LTP)-like plasticity through NMDA-dependent glutamatergic mechanisms[9] Additional evidence implicates engagement of the endogenous opioid system, as well as GABAergic and monoaminergic pathways, in the maintenance of analgesic effects. Functional neuroimaging studies further suggest that M1 stimulation can influence key regions associated with the affective and cognitive dimensions of pain, such as the anterior cingulate cortex and insula, highlighting a broader neuromodulatory impact beyond purely sensory processing[6,10].

Although rTMS has historically been conceptualized in terms of "excitatory" versus "inhibitory" frequency-dependent effects, emerging data emphasize that outcomes also depend on stimulation parameters and the underlying cortical state, reinforcing the complexity of its mechanisms of action[11-13].

Intermittent theta burst stimulation (iTBS) is a patterned form of rTMS in which bursts of three pulses at 50 Hz are delivered repeatedly at a theta frequency of 5 Hz, typically organized in short trains up to a total of 600 pulses[14]. This theta-modulated burst structure produces robust, LTP-like increases in cortical excitability despite the very short stimulation time[14,15], and standard iTBS sessions usually last only a few minutes compared with conventional 5–20 Hz rTMS protocols[14-16]. When applied over the primary motor cortex, iTBS is thought to engage motor and pain-modulatory networks similarly to high-frequency rTMS, while offering a more practical and time-efficient alternative in therapeutic neuromodulation[7,17].

Both high frequency rTMS and iTBS are well-established with specific indications for treating depression[16,18,19] however, the use of iTBS for neuropathic pain remains a relatively unexplored area.

Given the high prevalence and refractory nature of neuropathic pain, the logistical advantages of iTBS over conventional high-frequency rTMS, and the lack of a consolidated synthesis focusing specifically on iTBS for neuropathic pain, a critical evidence gap persists. This systematic review and meta-analysis therefore aimed to evaluate the effects of iTBS on pain intensity in patients with neuropathic pain, providing a quantitative estimate of its analgesic efficacy and informing the design of future neuromodulation protocols in this population.

CONTENTS

A systematic literature review was conducted in accordance with the recommendations outlined in the Cochrane Handbook, incorporating the PRISMA guidelines[20]. This review is registered in PROSPERO ID CRD42024584969.

A comprehensive search strategy was devised to identify clinical trials evaluating the effects of intermittent theta burst stimulation (iTBS) in adult populations with neuropathic pain, including studies published in Portuguese, English, and Spanish. The search was conducted across four principal databases: Pubmed, EMBASE, BVS, and Web of Science. No date limits were applied, and all databases were searched from their inception up to August 2024. Controlled vocabularies (such as MeSH terms) and free-text keywords related to "transcranial magnetic stimulation" and "neuropathic pain" were utilized. Boolean operators (AND/OR) and truncation symbols were employed to combine concepts efficiently. The complete search strategies for each database are delineated in Supplementary Material 1. Duplicate records were removed. Two independent reviewers managed references and screened articles using EndNote Clarivate® software. Each reviewer initially evaluated titles and abstracts independently; their findings were subsequently compared. Full texts of potentially eligible studies were reviewed collaboratively by reviewers, with any disagreements resolved through consultation with a senior expert researcher.

Study selection

Studies were included based on predefined PICOT criteria: (P) Population — individuals aged 18 years or older with neuropathic pain; (I) Intervention — -Burst stimulation (TBS) applied in studies with at least 10 participants; (C) Comparison — rTMS or sham stimulation; (O) Outcome — pain intensity measured using the Numerical Rating Scale (NRS); and (T) Type of Study — randomized controlled trials (RCTs).

As the primary outcome, the change from baseline in average pain intensity scores using an 11-point Numerical Rating Scale (NRS) (0-10, where 0 = 'no pain' and 10 = 'worst imaginable pain') was evaluated. A decrease of at least 2 points in pain intensity was considered a clinically meaningful difference[21].

Data extraction

Data extraction was independently performed by three reviewers (L.T., F.F., and R.F.), who manually collected and recorded information using a pre-formatted Microsoft Excel spreadsheet. Extracted variables included the first author, year of publication, sample size, stimulation target, coil type, control intervention, stimulation frequency and intensity, number of pulses per session, total number of sessions, pain intensity scores, and study design. When outcomes were reported only in graphical form, data were extracted using WebPlotDigitizer® software.

When essential data were missing, the corresponding authors were contacted via email. If standard deviations were not available, they were estimated by deriving the standard error from the inverse z-score formula based on the reported p-values and mean differences, followed by conversion to standard deviation according to sample size.

For each study, the mean difference in pain intensity — measured using the NRS — between pre- and post-intervention was defined as the primary outcome. Additionally, comparisons between the intervention and control groups were analyzed. To further assess methodological quality, each study was classified according to Lefaucheur's criteria for levels of evidence in non-invasive brain stimulation trials[7].

Data synthesis

Meta-analyses were conducted using Review Manager (RevMan 5.0, Cochrane Collaboration). Given the heterogeneity observed among studies ($I^2 > 50\%$), a random-effects model was applied. To strengthen the robustness of the pooled estimates, a 99% confidence interval (CI) was adopted. The analysis was stratified into two subgroups according to the type of control intervention: one comparing iTBS with sham stimulation, and the other comparing iTBS with conventional rTMS.

Risk of bias assessment

Risk of bias was independently evaluated by the same three reviewers using the Cochrane Risk of Bias 2.0 (RoB 2.0) tool, in accordance with official Cochrane guidelines and including the additional domains recommended for crossover trials.

Discrepancies between reviewers were resolved through discussion or, when necessary, consultation with a senior expert researcher.

RESULTS

Study selection

The selection process commenced with the identification of 1062 records through the search strategy. Following the removal of duplicate entries, 967 studies were subjected to screening, out of which 249 were selected based on their titles. Subsequent abstract screening resulted in sixteen studies proceeding to full-text review, and ultimately, four studies were included in the analysis based on expert consensus, as illustrated in the PRISMA flowchart (Figure 1).

Study characteristics

Among the four included studies, three were randomized clinical trials-one of which was double-blind-and one employed a crossover design. The study[22] and studies[23,24] presented a gender imbalance between the intervention and control groups.

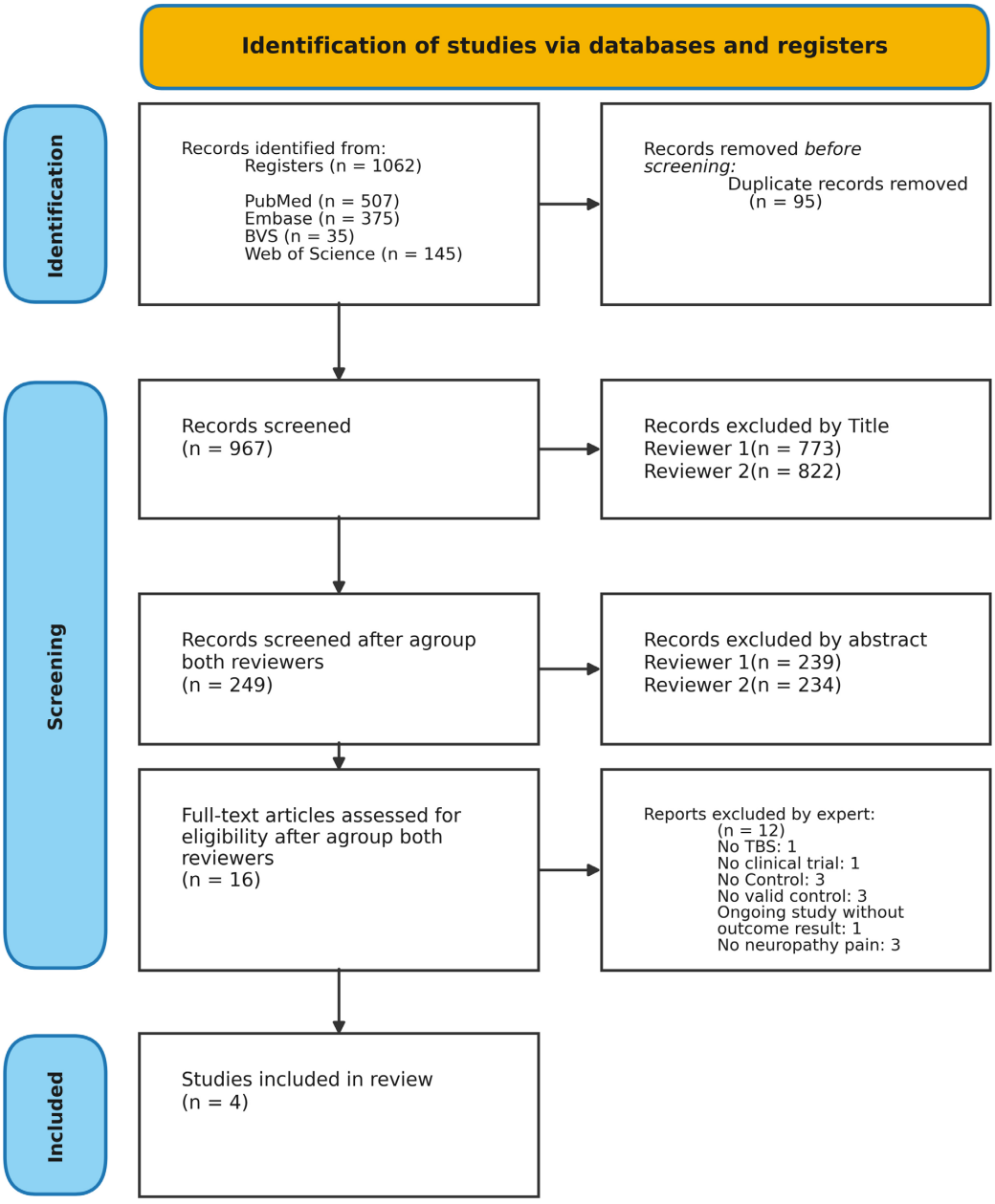


Figure 1. Flowchart of studies identification, screening, and inclusion process.

The control conditions varied across the trials. Sham stimulation was used as a control in three of the studies[22-24]. For active comparison, one trial employed a crossover design to directly compare iTBS with rTMS[25], while another study included rTMS as a separate active control group[22].

Blinding represented a methodological challenge for these protocols, as the operator needed to be aware of which treatment—rTMS or iTBS—was being administered due to their differing durations and parameters. To minimize bias, the authors[22-24] employed two independent researchers: one administered the stimulation and the other assessed pain intensity using the Numerical Rating Scale (NRS). In the study[25] participants reported their NRS scores directly on a notebook computer, without interaction with the operator administering the stimulation. Study details are summarized in Table 1.

Risk of bias assessment

Risk of bias was assessed using the Cochrane Risk of Bias 2.0 (RoB 2.0). Overall, one study was rated as low risk[24], two showed some concerns[22,23], and one was high risk[25], mainly due to issues in D1/D2 and selective reporting in D5. Figures 2 and 3 summarize RoB 2 judgments.

Stimulation targets and protocols

The stimulation parameters were largely consistent among the studies, differing only slightly. A reference author[25] applied 90% of the resting motor threshold, whereas the others used 80%. Another study[22] administered twenty sessions, while the remaining studies conducted five.

Regarding stimulation devices, two studies used figure-eight coils, one employed a double-coil design, and another utilized a circular coil. Three of the included studies targeted the primary motor cortex (M1) for stimulation[22-24], while the fourth targeted the central sulcus[25].

Pain outcomes and quantitative synthesis

In two sham-controlled trials comparing iTBS with tilted-coil sham stimulation[23,24], iTBS consistently outperformed sham stimulation. The pooled mean difference in NRS change favored iTBS by −2.36 points (99% CI −3.39 to −1.34), exceeding the commonly accepted 2-point threshold for clinically meaningful pain relief, despite moderate heterogeneity (I^2 = 51%; Figure 4).

In contrast, when iTBS was directly compared with conventional high frequency rTMS across three trials (22,23,25), the meta-analysis favored rTMS. The pooled mean difference in NRS change was 0.51 points in favor of rTMS (99% CI 0.18 to 0.83), with moderate heterogeneity (I^2 = 53%; Figure 5).

Only the baseline NRS means, and mean change scores were reported in the crossover study[25], with no corresponding standard deviations. Post-intervention NRS means were therefore derived by subtracting the mean change from the baseline value, and the missing dispersion measures could not be obtained despite email contact with the corresponding author.

Table 1. Characteristics of the included studies.

Authors	Study design (Lefaucheur class)	Neuropathy	Participants (mean age, male, female)	Target, coil type	Control intervention	Stimulation intensity iTBS	Number of pulses per session and number of sessions
André-Obadia et al.[25]	Randomized cross-over design (class I)	Mixed central and peripheral neuropathic pain (stroke, myelopathy, trauma, trigeminal, etc.)	Total: 46 (52.41yr,29M,17F) iTBS: 43 (3 only iTBS) rTMS: 42 (4 Only rTMS)	Central Sulcus, 8-Shaped Coil	rTMS	Intensity equals 90% of the resting motor threshold	600 pulses per session, one session per day, 5 sessions in total
Kim et al.[24]	Randomized sham-controlled trial (class I)	Mixed central neuropathic pain (stroke, TBI, myelopathy, etc.)	iTBS group: 15 (62.40yr, 12M,3F) Sham group: 15 (63.20yr, 7M, 8F)	Motor Cortex (M1), Double 70 mm air film	Sham (tilted coil)	Intensity equal to 80% of the resting motor threshold	600 pulses per session , one session per day, 5 sessions in total
Kim et al.[23]	Randomized, double-blind, sham-controlled trial (class I)	Spinal cord injury	iTBS group: 11 (61.27yr, 9M, 2F) rTMS group: 10 (60.70yr, 9M,1F) Sham group: 11 (58.27yr,9M,2F)	Motor Cortex (M1), Double 70 mm air film	rTMS and Sham (tilted coil)	Intensity equal to 80% of the resting motor threshold	600 pulses per session , one session per day, 5 sessions in total
Yang et al.[22]	Randomized clinical trial (class I)	Spinal cord injury	iTBS group: 12 (49.75yr, 9M,3F) rTMS group: 13 (51.00yr, 7M,6F) iTBS+rTMS group: 12 (46.94yr, 7M, 5F)	Motor cortex (M1), Circular 125 mm	rTMS and iTBS + rTMS	Intensity equal to 80% of the resting motor threshold	600 pulses per session , 5 sessions per week, 20 sessions in total

iTBS = intermittent theta-burst stimulation; rTMS = repetitive transcranial magnetic stimulation; M1 = primary motor cortex.

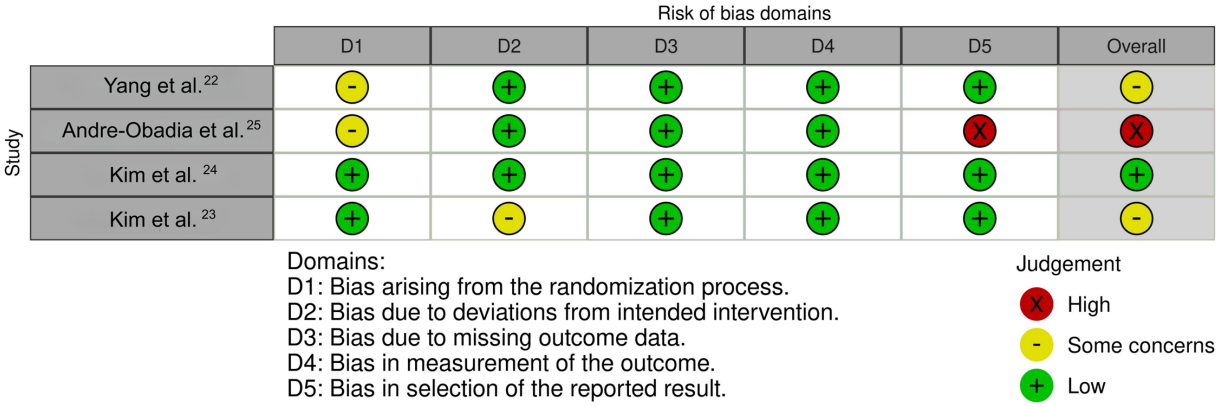


Figure 2. Assessment of each included study across the domains of the Cochrane Risk of Bias 2.0 tool.

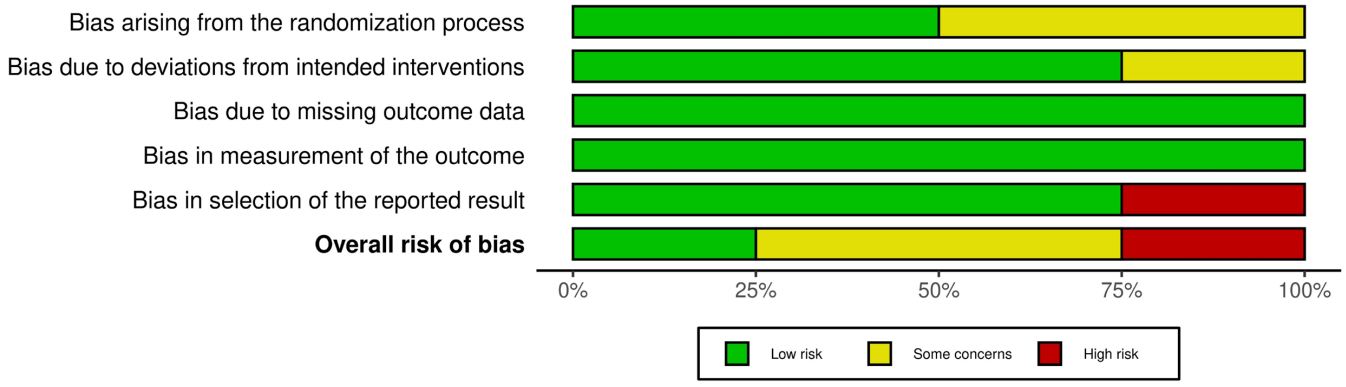


Figure 3. Proportional summary of risk of bias judgments across all included studies for each domain.

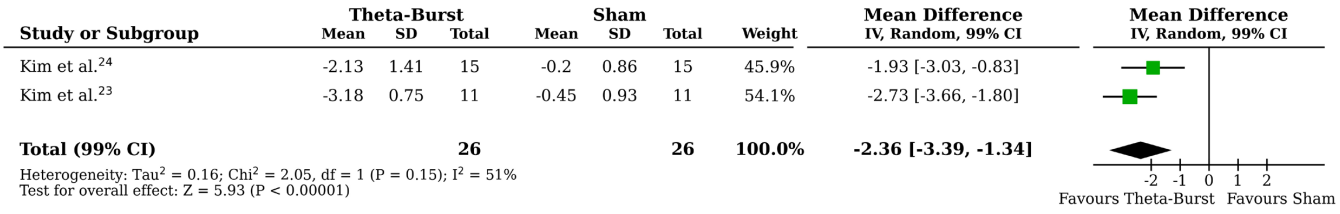


Figure 4. Mean difference in pain intensity scores (NRS). The diamond represents the pooled effect estimate (99% CI). Values to the left of the null effect line favor iTBS.

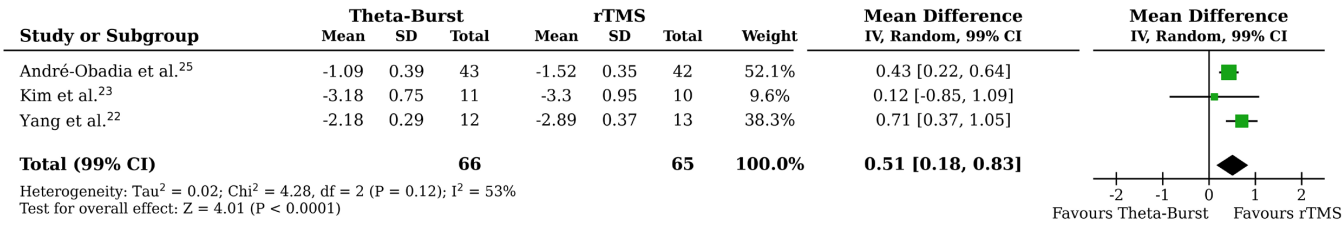


Figure 5. Mean difference in pain intensity scores (NRS). The diamond represents the pooled effect estimate (99% CI). Values to the right of the null effect line favor rTMS.

DISCUSSION

The present systematic review and meta-analysis indicate that intermittent iTBS is a promising therapeutic option for neuropathic pain, showing statistically significant efficacy compared with sham stimulation. In pooled analyses, iTBS not only produced a statistically significant effect but also yielded a clinically meaningful reduction in pain, with an average decrease of 2.36 points on the NRS (99% CI, −3.39 to −1.34) relative to sham. This magnitude of change exceeds the commonly accepted 2-point threshold for substantial clinical improvement[21], reinforcing the therapeutic potential of iTBS in this population.

At the same time, the available head-to-head comparisons suggest that conventional high frequency rTMS may provide somewhat greater analgesic effects than iTBS. Although the difference was statistically significant (mean difference = 0.51; 99% CI, 0.18 to 0.83), it is essential to contextualize the magnitude of this effect. A between-protocol difference of approximately half a point on the NRS is modest. It may not represent a clinically decisive advantage for many patients, particularly when weighed against the substantially shorter session duration and greater logistical efficiency of iTBS.

In the two decades following the initial publication on theta burst stimulation in humans in 2005[14], once daily iTBS protocols have become well established for the treatment of depression[16]. More recently, accelerated schedules with multiple sessions per day have gained prominence, showing not only meaningful antidepressant effects but also logistical advantages[26,27], particularly given that induction phases in depression may require up to 20 treatment sessions[28-30]. Although such high-dose or accelerated use of iTBS appears promising in mood disorders, this pattern may not translate directly to pain treatment, as multiple daily sessions can increase local discomfort and scalp pain during stimulation[31,32], potentially limiting tolerability and adherence in patients with chronic pain.

Conceptually, the present study speculates that neuromodulatory protocols that are experienced as markedly painful or uncomfortable during application could be suboptimal for engaging descending inhibitory pathways in individuals with already impaired endogenous pain modulation. In such a scenario, excessive nociceptive input during stimulation might risk reinforcing hyperalgesic circuits rather than facilitating adaptive inhibitory control. This possibility is consistent with contemporary models of impaired endogenous pain modulation and central sensitization[33-36], but has not yet been directly tested in iTBS/rTMS trials.

From a mechanistic standpoint, the discrepancy between the robust antidepressant effects of iTBS and its less consistent analgesic impact may reflect differences in how burst-pattern stimulation engages motor and pain-modulatory circuits. iTBS was originally developed to induce LTP-like increases in cortical excitability, particularly when applied over M1, thereby modulating corticospinal output and descending inhibitory pathways[14]. Neuropathic pain is characterized by altered thalamocortical rhythms, central sensitization, and impaired descending inhibition[37], which might require a higher total dose, different temporal structure, or distinct cortical targets than those optimized for mood regulation.

Several methodological and clinical factors may help explain why the study[25] failed to replicate the benefits observed in the other trials. Unlike the parallel-group designs of the remaining studies, the authors used a crossover design, which may increase vulnerability to carry-over effects and complicate the interpretation of treatment-specific responses. In addition, the sample comprised a highly heterogeneous group of neuropathic pain conditions (fifteen distinct diagnoses). In contrast, other trials focused on more homogeneous populations such as patients with spinal cord injury[22,23]. This diagnostic variability likely amplified clinical and neurobiological heterogeneity, reducing the power to detect consistent effects of iTBS.

Stimulation parameters and targeting strategies also differed in potentially relevant ways. The study[25] applied iTBS at a slightly higher intensity (90% of resting motor threshold) than the 80% used in the other studies, which could have influenced tolerability and cortical responsiveness. Moreover, the protocol targeted the central sulcus with a figure-of-eight coil, rather than M1 or an adjacent motor representation. Given the deeper location of this target, a double-cone coil might have been more effective in engaging the relevant circuitry[38]. This difference in targeting is important, as stimulation of M1 is typically linked to modulation of the affective–emotional dimensions of pain, whereas stimulation of the central sulcus is more directly related to sensory–discriminative processing[39,40]. Together, these design and targeting differences may have contributed to the discrepant findings in that study.

An apparent inconsistency emerges when examining the number of treatment sessions. Although the analgesic effect of rTMS is generally regarded as cumulative, the data presented in this review did not show a consistent trend of greater improvement with a higher number of sessions. Notably, the study[22], which involved 20 sessions, reported a mean pain reduction of -2.18 points. In contrast, the study[23], with only 5 sessions, achieved a more substantial reduction of -3.18 points. This discrepancy indicates that comparing studies with varying treatment durations constitutes a significant limitation, and that other factors — such as coil type and specific patient populations — may exert a more considerable influence on outcomes than the total number of sessions alone.

The study[22] also examined an innovative methodology by employing iTBS as a "priming" protocol prior to the application of conventional rTMS. In this experimental design, one of the intervention groups initially received iTBS, immediately followed by a session of rTMS. The results derived from this combined approach were noteworthy, as the group that received iTBS priming before rTMS exhibited a significantly greater reduction in pain relative to the groups that received either iTBS or rTMS independently. This finding indicates that iTBS may serve as a potentiating function, preparing neural circuits to be more receptive to the therapeutic effects of the subsequent rTMS[41].

Limitations

The conclusions of this review must be considered in light of several important limitations. The most significant is the small number of eligible studies; with only four articles included, the findings are preliminary, and the meta-analysis is susceptible

to the disproportionate influence of a single study, as was the case with study[25]. Furthermore, the analysis was marked by high heterogeneity, both clinically (in patient populations, stimulation targets, and parameters) and statistically, with I^2 values of 51% for the sham comparison and 53% for the rTMS comparison. This variability weakens the certainty of the pooled estimates. Finally, the risk of bias in the included studies is a concern, particularly the trial[25], which was rated as having a "high" overall risk of bias and carried significant weight in the iTBS versus rTMS comparison, potentially distorting the overall result.

From a methodological perspective, the search strategy covered four major electronic databases (Pubmed, EMBASE, Web of Science, and BVS), which likely captured most of the published trials in this highly specialized field. However, this study did not systematically search grey literature sources (e.g., trial registries, theses, conference proceedings), so the possibility that some unpublished or non-indexed studies has been missed cannot be excluded.

CONCLUSION

Although iTBS is a promising protocol, offering both shorter session times and clinically significant results, this review highlights the significant demand for larger, multicenter clinical trials to generate more robust evidence and draw stronger conclusions.

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SUPPLEMENTARY MATERIAL

Supplementary material accompanies this paper.
Supplementary Material 1. Search Strategy
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