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Maria Inês Cunha Salgado

The impact of TMS on depressive symptomatology in patients with chronic pain disorders: A Systematic Review

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The impact of TMS on depressive symptomatology in patients with chronic pain disorders: A Systematic Review

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Doutor Patrick Alves

E sob a Coorientação de:

Professora Doutora Ana Rita Ferreira

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UC Dissertação - DECLARAÇÃO DE INTEGRIDADE

Eu, Maria Inês Cunha Salgado, abaixo assinado, nº mecanográfico 201703700, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro ter actuado com absoluta integridade na elaboração do meu trabalho de Dissertação ou Monografia.

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Medicina Clínica

TÍTULO DISSERTAÇÃO/MONOGRAFIA (riscar o que não interessa)

The impact of TMS on depressive symptomatology in patients with chronic pain disorders: A Systematic Review

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É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
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Faculdade de Medicina da Universidade do Porto, 18/03/2024

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UC Dissertação - DECLARAÇÃO DE TRANSPARÊNCIA RELATIVAMENTE À UTILIZAÇÃO DE FERRAMENTAS DE CHATBOT GENERATIVO BASEADAS EM LARGE LANGUAGE MODELS

Eu, Maria Inês Cunha Salgado abaixo assinado, nº mecanográfico 201703700, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro que:

X Não procedi à utilização de ferramentas de *chatbox* generativo baseadas em *large language models* para nenhuma das tarefas no contexto do meu trabalho de Dissertação ou Monografia

☐ Procedi à utilização de ferramentas de *chatbox* generativo baseadas em *large language models* no contexto do meu trabalho de Dissertação ou Monografia, encontrando-se todas as interacções (*prompts* e respostas) transcritas em anexo bem como a indicação das aplicações utilizadas.

Neste sentido, confirmo que a eventual utilização de ferramentas de *chatbox* generativo baseadas em *large language models* no contexto do meu trabalho de Dissertação ou Monografia foi exclusivamente descrita na sequência de *prompts* e respostas transcritos em anexo e nas aplicações indicadas.

Faculdade de Medicina da Universidade do Porto, 18/03/2024

Assinatura conforme cartão de identificação:

Maria Inês Cunha Salgado

Dedico este trabalho aos meus pais que são a minha inspiração e fonte de apoio incondicional,

à minha família por todo o carinho,

aos meus amigos que me acompanharam ao longo desta viagem que foram os 6 anos na Faculdade de Medicina da Universidade do Porto,

E ao João por todo o amor.

The impact of Transcranial Magnetic Stimulation (TMS) on depressive symptomatology in patients with chronic pain disorders: A Systematic Review

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ABSTRACT:

Objective: Transcranial Magnetic Stimulation (TMS) is a recognized therapy for treatment-resistant depression and has been studied for its potential in managing chronic pain. Knowing the intrinsic relationship between pain and depressive symptomatology, this systematic review aims to assess the impact of TMS on depressive symptoms in patients with chronic pain.

Methods: Electronic databases were systematically searched until November 2023 for studies applying TMS in chronic pain patients, with an assessment of both pain and depressive symptomatology.

Results: From the records screened, 29 studies met the inclusion criteria for qualitative synthesis. The results showed heterogeneous protocols with widely different results in depressive symptomatology across the studies, precluding meta-analysis. TMS was considered a safe treatment option with minor side effects.

Conclusions: The impact of TMS on depressive symptomatology among chronic pain patients is a complex subject. Considering the diversity of the protocols and results encountered, future research should prioritize the establishment of standardized TMS protocols to clarify their efficacy in managing depressive symptoms among chronic pain patients.

Significance: This systematic review highlights the need for further investigation of TMS as a dual therapeutic approach for chronic pain and depressive symptomatology, emphasizing the necessity of improving the protocols to enhance clinical outcomes.

Keywords: Transcranial Magnetic Stimulation; TMS; Chronic pain; Depression; Depressive symptomatology.

Highlights:

- TMS is an FDA - approved and safe therapy for treatment-resistant depression.
- Studies have explored TMS as a potential therapy for managing chronic pain.
- Pain and depressive symptomatology have a very intrinsic relationship.
- It remains unclear whether TMS protocols aimed at pain management also relieve depressive symptomatology.
- It's very important to establish standardized protocols and target site consistency to clarify the efficacy of TMS in managing depressive symptoms among chronic pain patients.

INTRODUCTION:

Depression, recognized as a leading cause of global mental and physical disability by the World Health Organization, has seen a significant increase in incident cases over the past three decades, affecting over 264 million individuals worldwide. (1)

Depression and pain symptoms are highly prevalent conditions encountered by primary care physicians and specialists. A growing body of literature has focused on the interaction between depression and pain, implying that the conditions often coexist, respond to similar treatments, exacerbate one another, and share biological pathways and neurotransmitters. (2)

Chronic pain, persisting for more than three months, whether as a primary complaint or secondary to an underlying condition, imposes substantial personal and economic burdens, impacting more than 30% of the global population. (3, 4)

A World Health Organization study in primary care showed a strong association between persistent pain and depressive disorders, with those experiencing chronic pain being substantially more likely to have depressive symptoms. (5) Clinical studies have revealed that chronic pain, a stress state, often induces depression and up to 85% of patients with chronic pain are affected by severe depression. (2, 6, 7) Therefore, addressing mood alongside chronic pain management becomes imperative. (8)

Neuromodulation techniques such as Transcranial Magnetic Stimulation (TMS) have received increasing attention as a treatment option for several disorders like treatment-resistant depression, pain disorders, schizophrenia, bipolar disorder, Parkinson's disease, tinnitus, and stroke. TMS involves the generation of magnetic fields capable of inducing electric currents within the brain and it has demonstrated the ability to modulate cortical excitability, both locally at the targeted area and in distal brain regions involved in cognition and emotion regulation. With adherence to safety recommendations, TMS exhibits a highly favorable side-effect profile and is well tolerated by patients. (9)

FDA (US Food and Drugs Administration) approval of TMS for treatment-resistant major depressive disorder (MDD) marked a significant milestone, leading to its widespread adoption in clinical practice globally. The dorsolateral prefrontal cortex (DLPFC) has been a primary target for neurostimulation in depression, with high-frequency repetitive TMS (HF-rTMS) applied to the left DLPFC being the gold standard approach for treating depression. (10, 11)

Within the field of chronic pain management, there aren´t any official recommendations concerning the efficacy of TMS in patients with chronic pain and depressive symptomatology co-

morbid. Transcranial magnetic stimulation has emerged as a promising intervention, primarily focused on targeting the primary motor cortex (M1). While M1 remains the primary site of stimulation, researchers have ventured into exploring alternative targets, such as the dorsolateral prefrontal cortex (DLPFC), particularly in patients with chronic depression. However, the effectiveness of DLPFC stimulation in alleviating pain has exhibited variability across various studies. (12)

Acknowledging the intrinsic relationship between depression and chronic pain and the lack of evidence regarding the effect of TMS on depressive symptomatology in patients with chronic pain disorders, the main purpose of this systematic review is to comprehensively assess the existing literature in managing both chronic pain and depressive symptoms. By synthesizing findings from several studies, we aim to clarify the potential benefits and limitations of TMS as a therapeutic approach. Furthermore, this review intends to identify the gaps in current research and provide insight for future investigations.

METHODS:

To study the impact of transcranial magnetic stimulation on depression or depressive symptomatology in patients with chronic pain, this Systematic Review was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) guidelines 2020. (13) This systematic review protocol was submitted in the PROSPERO database.

1. Eligilibity criteria:

A priori set of eligibility criteria was pre-specified based on the PICOS (Population; Intervention; Comparator; Outcomes; Study design) framework and is depicted in Table 1.

Table 1: Based on the PICOS framework

Domain	Inclusion Criteria	Exclusion Criteria
Participants	Patients older than 18 years old; Patients with a diagnosis of chronic pain of any etiology (e.g. fibromyalgia, cancer) and depressive symptomatology; No limitation on the setting (e.g. the community, hospitals, nursing homes); Studies were not excluded by sample size.	Studies conducted on populations other than those of interest; Studies not ascertaining chronic nor depression by formal and validated criteria reporting how chronic pain was assessed; Studies with the same sample as in other publications included in this systematic review.
Intervention	Different types of Transcranial Magnetic Stimulation protocols; No restriction on the intervention setting, duration, and frequency.	Interventions in which it's not possible to assess the real effect of the TMS protocol.
Comparator	Any control condition that could include other active alternatives of treatment, except TMS, wait list or usual care (regular medication for example); Studies with no control group, but in which the patients were evaluated for outcome measures before and after de TMS intervention.	None applied.
Outcomes	Studies including quantitative outcomes of depression or depressive symptoms as a primary, secondary or, tertiary study outcome; The outcome has to be evaluated at baseline and after the intervention period with validated measures of depression or depressive symptoms.	Studies not including depression or depressive symptoms as an outcome; Studies not ascertaining depression or depressive symptoms by formal and validated scores or scales, or not reporting how these were evaluated; Studies that had insufficient information on the outcome of interest or in which the outcomes were described with vague or generic terms; Studies not providing quantitative data.

Study design	Human studies, particularly, interventional studies such as randomized and non-randomized controlled clinical trials evaluating TMS interventions; Any language; Any geographical location; Any publication year.	Observational studies, case studies, literature reviews, and conference abstracts; Reports not providing original data, including those publishing methodologies, technology reviews/ appraisals and, protocols;

2. Information sources:

A comprehensive search was conducted on PubMed, Scopus (the selected field consisted of article title, abstract and keywords), Web of Science Core Collection (field consisted of topic), Clinical Trials.gov, and PsycINFO electronic databases and completed on the 27th of November 2023. For each electronic database, studies were searched from inception, and no language or date restrictions were applied, and if necessary, studies were translated to ascertain the eligibility of the records retrieved.

For additional records, grey literature was also searched through Google Scholar and completed on the 27th of November 2023. Moreover, to identify possible additional relevant records, the included studies underwent backward and forward citation tracking. This involved manually searching reference lists and conducting additional searches on Google Scholar, respectively. These steps aimed to minimize selection and publication biases.

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3. Search strategy:

The search strategy was informed by previously published reviews, consideration of MeSH terms and the wider literature in the field, with input and support from a university librarian. The search was first defined for PubMed and further adapted for the individual databases as needed. The following search queries were used for each of the electronic databases:

PubMed / Web of Science Core Collection / PshycolNFO / Google Scholar

(depression OR depressive disorder OR dysthymic disorder OR mood disturbance OR affective disorder OR affective disturbance OR psychological distress OR suicide OR sadness) AND (transcranial magnetic stimulation OR TMS OR rTMS) AND (chronic pain)

Scopus

(depression OR (depressive AND disorder) OR (dysthymic AND disorder) OR (mood AND disturbance) OR (affective AND disorder) OR (affective AND disturbance) OR (psychological AND distress) OR suicide OR sadness) AND ((transcranial AND magnetic AND stimulation) OR tms OR rtms) AND (chronic AND pain)

Clinicaltrials.gov

(depression OR depressive disorder OR dysthymic disorder OR mood disturbance OR affective disorder OR affective disturbance OR psychological distress OR suicide OR sadness) AND (transcranial magnetic stimulation OR TMS OR rTMS) AND (chronic pain)

4. Selection process:

After duplicates removal, the records retrieved from the databases and other information sources were reviewed for eligibility using a two-phase approach: title and abstract screening and full-text review, using the predefined inclusion and exclusion criteria. In the first phase, all titles and abstracts were independently screened by two authors (I. S., P. A.) using EndNote reference management software 21. All disagreements were discussed and solved by consensus or in consultation with the wider review team. Ambiguous abstracts due to insufficient information to make a define decision remained included until the next phase and full-texts were retrieved. In the second phase, the full-text of the selected records was retrieved and evaluated by the same authors, independently. The number of studies that were included and excluded at each stage and the reasons for exclusion were recorded and reported in the PRISMA flow diagram (Figure 1). For unavailable studies or if additional data were required, original study authors were contacted at least once by email or available channels. In the event that information was not provided unavailable, the study was finally excluded.

5. Data collection process and evidence synthesis:

For studies deemed eligible for inclusion, a pre-defined data-extraction form developed for this systematic review was completed to allow standardized reporting of results across studies. The extraction of data was done by one author (I.S.) and summarized in a tabular form (Table 2) including the following parameters: author, year, sample, TMS target, TMS protocol, outcome assessment, main results, and adverse effects. Whenever possible, intention-to-treat data (i.e., analyzing all participants according to the group randomization) were collected. The data extracted was further independently cross-checked and revised for errors and potential divergent results by two other authors (P.A., I.B.). Discrepancies were solved by consensus with the wither review team. The heterogeneity in the studies included, TMS protocols, and outcomes measures, precluded a meta-analysis, and a narrative synthesis approach to summarize and interpret the qualitative and quantitative data was undertaken. The studies were evaluated through tabular and thematic analysis by grouping them according to the cortex area used as a stimulation target. This approach has been defined has suitable to synthetize heterogeneous literature. (14)

6. Risk of bias assessment:

For each study included, the risk of bias was assessed using the revised Cochrane risk of bias tool for randomized trials (RoB 2) and the risk of bias in non-randomized studies of interventions (ROBINS – I) tools. RoB 2 addresses: 1- bias arising from the randomization process; 2- bias due

to deviations from intended interventions; 3- bias due to missing outcome data; 4- bias in the measurement of the outcome; 5- bias in the selection of the reported result. Each domain is required, and no additional domains should be added. (15) ROBINS-I addresses three bias domains evaluated in each study. Pre- intervention domain: 1- bias due to confounding; 2- bias in selection of participants into the study. At intervention: 3 - bias in classification of intervention. Post- intervention: 4- bias due to deviations from intended interventions; 5 - bias due to missing data; 6 - bias in measurement of outcomes; 7 - bias in selection of the reported result. Two authors independently graded the risk of bias for each study. Any disagreements were solved through consensus or referral to the review team. (16) To maximize the base of evidence, no study was excluded based on the quality alone.

RESULTS

1. Study Selection

The database search allowed us to identify 869 records, 131 from PubMed, 316 from Scopus, 237 from Web of Science Core Collection, 83 from PsycINFO, 2 from Clinicaltrials.gov, and 100 from Google Scholar. After removing all the duplicates (N=397), 472 titles and abstracts were screened, of which 32 full-text articles were assessed, 12 of them excluded. Reasons in the PRISMA Diagram Fig. 1. Reference list screening identified 14 studies, 5 of which were excluded. Therefore, 29 articles met the criteria to be included in this systematic review.

2. Study Characteristics

The studies included in this systematic review were published between 2007 and 2023 and are presented and summarized in Table 2. In terms of countries where the studies were conducted, 5 were in the USA, 2 in the Republic of Korea, 1 in Brazil, 2 in Egypt, 1 in Spain, 1 in Australia, 2 in India, 1 in Austria, 1 in Austria and Italy, 1 in Turkey, 1 in Russia, 1 in Japan, 4 in France, 2 in Finland, 4 in China. 28 are Randomized Controlled Trials (RCT) and 1 is a Non- Randomized Clinical Trial. The sample number varies between 4 (Borckardt et al. (2009)) and 149 patients (Attal et al. (2021)), with the overall number being 1059 participants. According to the inclusion criteria defined, all participants were older than 18 years old and had been diagnosed with a chronic pain condition, such as chronic migraine, fibromyalgia, poststroke central pain, failed back surgery syndrome, chronic widespread pain, mild traumatic brain injury-related headache, neuropathic pain, chronic facial pain, postherpetic neuralgia.

In all studies included, the primary focus was to assess the impact of repetitive TMS on pain scores in patients with a chronic pain condition. Therefore, the evaluation of depressive symptomatology was a secondary or tertiary outcome in all studies. The protocols were very heterogenic, the number of treatment sessions ranging from 3 to 23, each employing different frequencies, 0.5 Hz, 1 Hz (low-frequency), 5 Hz, 10 Hz, or 20 Hz (high frequency). Moreover, the stimulation intensity was varied as well, ranging from 70% (Bursali et al. (2021)) to 120% (Short et al. (2011); Avery et al. (2015); Nardone et al. (2016); Fitzgibbon et al. (2018); Petelin et al. (2022)) of the Resting Motor Threshold (RMT). Additionally, there are different targeting locations, such as the Left Dorsolateral Pre-Frontal Cortex (N=10), Right Dorsolateral Pre-Frontal Cortex (N=5), Primary Motor Cortex M1 (N=12), Left Primary Motor Cortex M1(N=5), S1/M1 and S2 (N=1).

The primary outcome of this systematic review is to evaluate the effect of different TMS protocols

on depressive symptomatology in patients with a diagnosed chronic pain condition. Multiple scales were used across studies, such as the Hamilton Depression Rating Scale (HAM-D), Beck Depression Inventory (BDI), Hospital Anxiety and Depression Scale (HADS) - depression sub-score, Depression, Anxiety, and Stress Scale (DASS) - depression sub-score, Montgomery - Asberg Scale (MADRS) and The Center for Epidemiological Studies 10-Item Depression Scale (CESD).

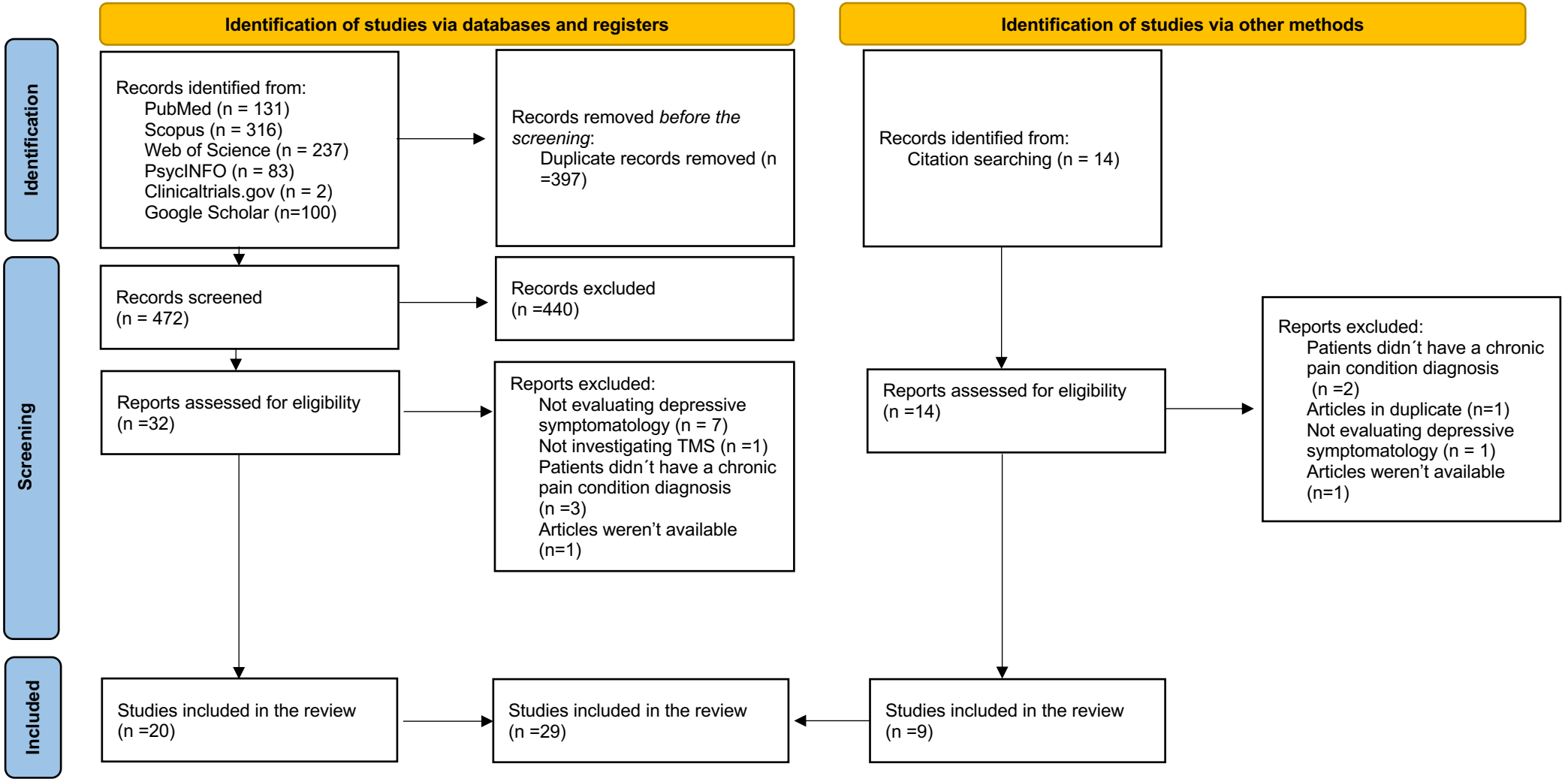

Fig. 1 PRISMA Flow Diagram

Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372: n71. doi: 10.1136/bmj.n71.
For more information, visit: http://www.prisma-statement.org/

Table 2: Summary of Studies Characteristics

ARTICLE	TYPE OF STUDY	SAMPLE	PAIN CONDITION	TARGET	PROTOCOL	OUTCOME ASSESSMENT	MAIN RESULTS	EFFECT ON PAIN	ADVERSE EFFECTS
Passard et al. (2007) (France) (17)	RCT with sham control	N=30	Fibromyalgia	Left M1	10 sessions (2 weeks) at 10 Hz, 80% RMT, 2000 pulses/session.	HDRS BDI HADS-depression sub-score	No statistically significant results in the depression scores.	Pain scores significantly lower in the active rTMS group (vs sham).	Mild and transient headaches Nausea Transient tinnitus Mild dizziness
Borckardt et al. (2009) (USA) (18)	RCT, cross over design	N=4	Chronic Neuropathic Pain	Left DLPFC	Randomized series of 3 real and 3 sham rTMS treatments. rTMS: 3 sessions (1 week) at 10 Hz, 100% RMT, 4000 pulses/session.	BDI CESD	No statistically significant results, although greater reductions associated with the real rTMS protocol.	Significant improvements in 3 of the 4 patients, associated with the real rTMS.	None reported
Carretero et al. (2009) (Spain) (19)	RCT with sham control	N=26	Fibromyalgia and Major Depression	Right DLPFC	20 sessions (4 weeks) at 1 Hz, 110% RMT, 1200 pulses/session.	HDRS	No statistically significant improvements on the HDRS scores.	There were no significant improvements on pain scores.	Neck pain and headache Worsening of the depressive symptoms Nausea and increased tiredness
Short et al. (2011) (USA) (20)	RCT with sham control	N=20	Fibromyalgia	Left DLPFC	10 sessions (5 per week for 2 weeks) at 10 Hz, 120% RMT, 4000 pulses/session.	HDRS	At 2 weeks follow-up, real rTMS group evidenced a significant improvement in HAM-D (vs sham group).	Pain scores improved significantly over time, but not between groups.	Headache

Mhalla et al. (2011) (France) (21)	RCT with sham control	N=40	Fibromyalgia	Left M1	14 sessions (21 weeks) at 10 Hz, 80% RMT, 1500 pulses/session.	BDI HADS-depression sub-score	No statistically significant results in the depression scores.	Pain scores improved significantly from day 5 of treatment in the active rTMS group compared to the sham group. The effect maintained until week 25.	Headache Transient mild headache Transient dizziness
Ohn et al. (2012) (Republic of Korea) (22)	Non-Randomized CT	N= 22	Poststroke Central Pain	M1	5 sessions (1 week) at 10 Hz, 90%RMT,1000 pulses/session.	HDRS	The HDRS score decreased significantly in all patients after rTMS. The responder group showed a significantly lower HAM-D score than the non-responder.	Responder group (N=14) Non-responder group (N=8). Antalgic effect persisted for 2 weeks.	None reported
Lee et al. (2012) (Republic of Korea) (23)	RCT with sham control	N=15	Fibromyalgia	Right DLPFC M1	The right DLPFC group (N=5): 10 sessions (2 weeks) at 1Hz, 110% RMT, 1600 pulses/session. The M1 group (N=5): 10 sessions (2 weeks) at 10 Hz, 80% RMT, 2000 pulses/session.	BDI	Right DLPFC group: BDI scores were significantly lower after ten sessions and 1 month later. M1 group: BDI scores were significantly lower after ten sessions but not 1 month later. Sham group: BDI scores were significantly lower after ten sessions but not 1 month later.	Right DLPFC group: pain scores were decreased immediately after ten sessions and increased slightly after 1 month, but was still lower compared to baseline. M1 group and Sham group: Pain scores were significantly lower immediately after ten sessions than at baseline but not 1 month later.	None reported

Hosomi et al. (2013) (Japan) (24)	RCT with sham control, cross-over design	N=70	Neuropathic pain	M1	Group A (N=34): real rTMS followed by sham. Group B (N=36): sham followed by real rTMS (in both groups - interval of 17 days). Real rTMS: 10 sessions (2 weeks) at 5 Hz, 90% RMT, 500 pulses/session.	BDI	BDI changes did not show significant differences between real and sham rTMS at any time points.	Pain scores reduction was significantly higher after real rTMS stimulation (vs sham).	Headache Deterioration of squeezing Deterioration of numbness Hypoglycemia Anxiety Appetite loss Dizziness
Conforto et al. (2014) (Brazil) (25)	RCT with sham control	N= 18	Chronic Migraine	Left DLPFC	23 sessions (within eight weeks) at 10 Hz, 110% RMT, 1600 pulses/session.	BDI	Active group with no significant improvements in the BDI score.	Number of headache days decreased significantly in sham group. No significant improvement in active group. Pain intensity improved in both groups at week 8.	Headache or local pain under the coil Sleepiness
Avery et al. (2015) (USA) (26)	RCT with sham control	N= 18	CWP	Left DLPFC	15 sessions (4 weeks) at 10 Hz, 120% RMT, 3000 pulses/session.	HDRS BDI	Significant improvements in both scores, with no statistically significant differences between TMS group and sham group.	Significant decreases in pain measures, but no significant differences between groups.	Pain at the site of stimulation Headache Dizziness
Khedr et al. (2015) (Egypt) (27)	RCT with sham control	N=34	Neuropathic Pain Secondary to Malignancy	M1	10 sessions (5 per week for 2 weeks) at 20 Hz, 80% RMT, 2000 pulses/session.	HDRS	Significant improvement in real rTMS group after the 10^{th} session. Effects persisted at 1 month.	Significantly higher improvement in active rTMS group when compared to sham group.	None reported
Leung et al. (2015) (USA) (28)	RCT with sham control	N=29	MTBI-HA	Left M1	3 sessions (1 week) at 10Hz, 80%RMT, 2000 pulses/session.	HDRS	No effect reported on depression assessment.	Active rTMS group revealed a significant reduction pain scores (vs sham).	Transient local tenderness Transient dizziness

Shu-Min Ma et al. (2015) (China) (29)	RCT with sham control	N=40	PHN	M1	10 sessions (2 weeks) at 10 Hz, 80% RMT, 1500 pulses/session.	SDS	SDS score was not significantly different between groups at any time points.	Real rTMS group showed greater reduction of pain scores (vs sham). Analgesic effects lasted for 1-3 months.	Neck pain and Headache Dizziness Dry mouth
Lindholm et al. (2015) (Finland) (30)	RCT, cross-over design	N=20	Neuropathic orofacial pain	S1/M1 Right S2	In a randomized order, all participants received 2 active rTMS treatments (S1/M1 and S2) and 1 sham treatment (between the 2 active). 2 sessions (4 weeks) at 10Hz, 90% RMT, 1000 pulses/session.	BDI	No significant changes in depression scores.	Pain scores were lowest after the S2 stimulation being significantly lower than after the S1/M1 stimulation or sham. At 1 month after S2 stimulation, pain scores remained lower than at baseline. The S1/M1 stimulation was inefficient or even hyperalgesic in some patients.	Unpleasant contraction of the temporal muscle
Nardone et al. (2016) (Austria; Italy) (31)	RCT with sham control	N=12	Neuropathic Pain with Spinal Cord Injury	Left DLPFC	10 sessions (2 weeks) at 10Hz, 120% RMT, 1250 pulses/session.	HDRS	Decrease in depression score at the end of the 2 weeks in active rTMS group (vs the sham group) but not statistically significant.	During treatment, pain scores decreased significantly in treatment group.	Slightly uncomfortable twitching of facial muscles
Fitzgibbon et al. (2018) (Australia) (32)	RCT with sham control	N=26	Fibromyalgia	Left DLPFC	20 sessions (4 weeks) at 10 Hz, 120% RMT, 3000 pulses/session	BDI	Improvement in depression score, over time with no statistically significant differences between groups.	Improvement of pain scores over time with no statistically significant differences between groups.	Site discomfort Headache Neck pain Nausea Dizziness

Leung et al. (2017) (USA) (33)	RCT with sham control	N=29	MTBI-HA	Left DLPFC	4 sessions (1-2 weeks) at 10 Hz, 80% RMT, 2000 pulses/session.	HDRS	Significant improvement in depressive symptomatology in real rTMS group.	Real rTMS group revealed a significant reduction in pain scores (vs sham group).	None reported
Bhatia et al. (2019) (India) (34)	RCT with sham control	N= 30	CTTH	Right DLPFC	20 sessions (4 weeks) at 1 Hz, 110% RMT, 1200 pulses/session.	HDRS	No statistically significant differences (sham vs active).	Significant analgesic effect in the rTMS group (vs sham).	None reported
Yang et al. (2019) (China) (35)	RCT with sham control	N=56	Parkinson disease associated with pain	M1	10 sessions (2 weeks), at 0.50Hz, 90% RMT, 3200 pulses/session.	HDRS	No statistically significant differences between groups.	Significant decrease in pain scores in active rTMS group (vs sham).	Transient headache Transient increase in blood pressure
Qian Pei et al. (2019) (China) (36)	RCT with sham control	N=75	PHN	M1	5-Hz rTMS group: 10 sessions at 5 Hz, 80% RMT, 1500 pulses/session. 10-Hz rTMS group: 10 sessions at 10 Hz, 80% RMT, 1500 pulses/session.	SDS	No significant differences in depression scores among the 3 groups.	5-Hz rTMS group and 10-Hz rTMS group with significant reduction in pain scores. Pain scores of the 10-Hz rTMS group significantly lower compared with 5-Hz rTMS group after the 7^{th} session.	Headache Neck pain Dizziness Dry mouth
Tanwar et al. (2020) (India) (37)	RCT with sham control	N=90	Fibromyalgia	Right DLPFC	20 sessions (4 weeks) at 1 Hz, 90% RMT, 1200 pulses/session.	HDRS	HDRS scores in rTMS group decreased significantly (vs sham) and were maintained through 6 months.	Significant decrease in pain scores in real rTMS group, sustained through 6 months.	Headache Neck pain Mild dizziness
Bursali et al. (2021) (Turkey) (38)	RCT with sham control	N= 23	FBSS	M1	10 sessions (5 per week for 2 weeks) at 5 Hz, 70% RMT, 1000 pulses/session.	BDI	BDI scores significantly lower in real rTMS group (vs sham group), at 10th day of treatment, 1 month and 3 months after treatment.	Significant decrease in pain scores with activity days 5, 10 and 1 month after treatment.	Mild headache

El-Badawy et al. (2021) (Egypt) (39)	RCT	N=30	Fibromyalgia	Left M1	rTMS group (N=15) - 8 sessions (4 weeks), at 10 Hz, 90% RMT, 1000 pulses/session. Anodal tDCS group (N=15): 8 daily sessions, an intensity of 2mA for 20 minutes.	HADS - depression sub-score	Both groups showed significant changes in the depression sub-score, but rTMS group showed more improvement.	Both groups showed highly significant improvements in the pain scores.	rTMS group: Transient headache Tingling tDCS group: tingling sensation headache dizziness
Freigang et al. (2021) (Austria) (40)	RCT partially sham-controlled	N=34	Chronic Low Back Pain or Neck pain	Left M1 Left DLPFC	M1 group (N=11) - 13 sessions (9 months), at 5 Hz, 90% RMT, 1800 pulses/session. DLPFC group (N=12) - 13 sessions (9 months), at 20 Hz, 95% RMT, 2000 pulses/session. Sham group (N=11)- followed the same schedule, however the experiment was stopped for ethical reasons.	DASS - depression sub-score	No significant results.	The overall pain intensity decreases after the rTMS stimulation. At the end of the treatment, pain intensity in the DLPFC-group was lower than the M1 group but the differences did not reach significance.	None reported
Guinot et al. (2021) (France) (41)	RCT with sham control	N=39	Fibromyalgia	M1	16 sessions (13 weeks) at 10 Hz, 80% RMT, 2000 pulses/session + 12 weeks of multicomponent therapy - 3 sessions per week. Sham control, only had the MT program.	BDI	BDI score decreased significantly in both groups, with no significant differences between them.	In both groups pain scores improved, with no differences between them.	None reported
Attal et al. (2021) (France) (42)	RCT with sham control	N=149	Chronic peripheral neuropathic pain	Left DLPFC M1	15 sessions (22 weeks) at 10 Hz, 80% RMT, 3000 pulses/session.	BDI HADS-depression sub-score	All groups improved depression scores similarly after rTMS sessions.	Active M1- rTMS, but not the DLPFC-rTMS group, induced significant effects on pain	Headache Pain at stimulation site

								scores compared to sham.	
Petelin et al. (2022) (Russia) (43)	RCT	N=25	Chronic pain disorder and refractory depression	Right DLPFC Left DLPFC	Right-side low-frequency stimulation group (N=12): 10 sessions (2 weeks) at 1Hz, 90% RMT, 1200 pulses/session. Left-side high-frequency stimulation (N=13): 10 sessions (2 weeks) at 10Hz, 100--120% RMT, 3000pulses/session.	MADRS	Left DLPFC group: Statistically significant decrease in depressive symptomatology. Right DLPFC group: Decrease in depressive symptomatology was not statistically significant. At one month follow-up, both protocols produced statistically significant differences from baseline MADRS scores.	Right DLPFC group: Pain intensity decrease was statistically significant. Left DLPFC group: Statistically significant effect, but clinically minor. At one month follow-up, the severity of pain was found to be statistically indistinguishable between the different protocols.	Unbearable pain in the stimulation
Säisänen et al. (2022) (Finland) (44)	RCT, cross over design	N=20	Chronic facial pain	M1	Two consecutive high-frequency rTMS protocol separated by six weeks, study period of two months. Protocol A - 5 sessions (1 week), at 10 Hz, 90% RMT, 2400 pulses/session. Protocol B - 5 sessions (1 week), at 20Hz, 90% RMT, 3600 pulses/session.	BDI	Depression scores improved slightly but non-significantly after rTMS.	Sustained decrease in pain intensity with the two-high frequency rTMS protocols in chronic facial pain. The second treatment causing a more pronounced decrease.	Tiredness Headache Dizziness Pain in the head Nausea Poor sleep ophthalmic branch tickling twitching of the hand tingling in the hand tightness in the chest/crushing chest pain

Yang et al. (2023) (China) (45)	RCT	N=39	Neuropathic pain with spinal cord injury	M1	rTMS group (N=13) - 20 sessions (4 weeks) at 10 Hz, 80% RMT, 1500 pulses/session. iTBS group (N=13) - 20 sessions (4 weeks), triplet 50 Hz bursts, repeated at 5 Hz, at 80% RMT, 600 pulses/session. iTBS + rTMS group (N=13) - iTBS at 80% RMT followed 2 minutes later by a 10 Hz rTMS delivered at 80% RMT for a total of 2100 pulses.	HDRS	Comparing the HDRS scores with the baseline, differences were significant in all groups. Among the three groups there were no statistically significant differences.	iTBS + rTMS produced greater analgesia than the other protocols.	None reported

RCT- Randomized Controlled Trial; M1 – Primary Motor Cortex; DLPFC – Dorsolateral Pre-Frontal Cortex; RMT – Resting Motor Threshold; HDRS – Hamilton Depression Rating Scale; BDI – Beck Depression Inventory; HADS- Hospital Anxiety and Depression scale; CESD – Center For Epidemiological Studies 10-Item Depression Scale; CT- Clinical Trial; CWP - Chronic Widespread Pain; MTBI-HA – Mild Traumatic Brain Injury- Related Headaches; PHN - Postherpetic Neuralgia; SDS – Self-rating Depression Scale; S1/M1-sensorimotor cortex ; S2 – Secondary Somatosensory Cortex; CTTH - Chronic Tension-type Headache; FBSS - Failed Back Surgery Syndrome; DASS- Depression, Anxiety and Stress Scale; tDCS – transcranial Direct Current Stimulation; iTBS - intermittent Theta Burst Stimulation

3. Risk of Bias

Table 3: Risk of Bias assessment using RoB 2.0

Randomized Controlled Trials assessed with RoB 2.0 for each risk of bias domain						
Articles	**Randomization process**	**Deviations from Intended Interventions**	**Missing Outcome Data**	**Measurement of the outcome**	**Selection of the reported result**	**Overall Risk of Bias**
Passard et al. (2007)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Borckardt et al. (2009)	Low Risk	Low Risk	Low Risk	High Risk	Low Risk	High Risk
Carretero et al. (2009)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Short et al. (2011)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Mhalla et al. (2011)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Lee et al. (2012)	Some Concerns	Low Risk	Low Risk	High Risk	Low Risk	High Risk
Hosomi et al. (2013)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Conforto et al. (2014)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Avery et al. (2015)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Khedr et al. (2015)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Leung et al. (2015)	Low Risk	Low Risk	Low Risk	High Risk	Some Concerns	High Risk
Shu-Min Ma et al. (2015)	Low Risk	Low Risk	Low Risk	High Risk	Some Concerns	High Risk
Lindholm et al. (2015)	Low Risk	Low Risk	High Risk	Low Risk	Some Concerns	High Risk
Nardone et al. (2016)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk

Leung et al. (2017)	Low Risk	Low Risk	Low Risk	High Risk	Low Risk	High Risk
Fitzgibbon et al. (2018)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Bhatia et al. (2019)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Yang et al. (2019)	Some Concerns	Low Risk	Low Risk	High Risk	Low Risk	High Risk
Qian Pei et al. (2019)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Tanwar et al. (2020)	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns	Some Concerns
Bursali et al. (2021)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
El-Badawy et al. (2021)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Freigang et al. (2021)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Guinot et al. (2021)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Attal et al. (2021)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Petelin et al. (2022)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Säisänen et al. (2022)	Low Risk	Low Risk	Low Risk	Low Risk	Some Concerns	Some Concerns
Yang et al. (2023)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk

The risks of bias were evaluated according to the Cochrane guidance, as outlined in the Tables 3 and 4. The assessment revealed varying levels of risk across different domains for each included randomized controlled trial within this systematic review, with 16 trials categorized as low risk, 5 trials as having some concerns, and 7 trials as high risk.

Regarding the randomization process, only two of the RCTs included were judged to have some concerns (Lee et al. (2012); Yang et al. (2019)). The remaining studies were rated as having low risk in this domain. The concerns regarding the randomization were due to the lack of information regarding information on how randomization was conducted in both studies.

Deviation from the intended intervention emerged as the most robust domain with all RCTs rated

low risk.

Concerning missing outcome data, most studies were rated as low risk, except for 1 study, which was rated high risk (Lindholm et al. (2015)) due to a high participant dropout rate (20%) and the absence of a statistical method for handling missing outcome data.

Additionally, 6 studies (Borckardt et al. (2009); Lee et al. (2012); Leung et al. (2015); Shu-Min Ma et al. (2015); Leung et al. (2017); Yang et al. (2019)) were rated as high-risk and 1 study (Tanwar et al. (2020)) was rated as some concerns regarding the outcome measurement. This was primarily attributed to insufficient information concerning the blindness of the outcome assessors and the potential influence of knowledge of intervention on the assessed outcomes.

Concerning the selection of the reported result, 8 studies (Carretero et al. (2009); Avery et al. (2015); Leung et al. (2015); Shu-Min Ma et al. (2015); Lindholm et al. (2015); Tanwar et al. (2020); El-Badawy et al. (2021); Säisänen et al. (2022)) were rated as having some concerns. These trials did not report whether the outcomes were analyzed following a pre-specified analysis plan finalized before unblinded outcome data were available.

Table 4: Risk of Bias assessment using ROBINS-I

Pre/post uncontrolled trials assessed with ROBINS-I for each risk of bias domain								
Articles	**Confounding**	**Selection of participants into the study**	**Classification of interventions**	**Deviations from the intended interventions**	**Missing data**	**Measurement of the outcome**	**Selection of the reported result**	**Overall risk of Bias**
Ohn et al. (2012)	Critical	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Critical

In case of pre/post studies, only one of the studies included, conducted by Ohn et al. (2012), was a non-randomized clinical trial. This study assessed low risk in all ROBINS-I domains except for the confounding domain which was categorized as having critical risk. Despite the study's efforts to consider various potential confounders the uncontrolled nature of these studies presents a challenge in achieving sufficient adjustment for confounding variables. Therefore, the risk of bias related to confounding factors remains a significant concern in interpreting the results of this study.

4. The impact of TMS in depressive symptomatology

4.1 Protocols targeting the DLPFC:

4.1.1 Left DLPFC:

Seven studies included (Borckardt et al. (2009); Short et al. (2011); Conforto et al. (2014); Avery et al. (2015); Nardone et al. (2016); Fitzgibbon et al. (2018); Leung et al. (2017)) investigated the use of high-frequency protocols (10 Hz) targeting the left DLPFC. At the end of treatment, four of the studies (Short et al. (2011); Avery et al. (2015); Nardone et al. (2016); Fitzgibbon et al. (2018)), reported significant differences of depressive symptomatology scores over time with no statistically significant differences between the sham and the active TMS group. However, Short et al. (2011), at two weeks follow-up reported a significant improvement of the HDRS score of the active group (vs sham group). Leung et al. (2017) showed significant improvement of the HDRS score in the active group. In contrast, Conforto et al. (2014), reported statistically significant improvements in the BDI score of the sham group compared to the active group.

In a RCT with a cross-over design, Borckardt et al. (2009) investigated the effects of rTMS in four patients diagnosed with chronic neuropathic pain. The participants were randomly assigned to a series of three real rTMS treatments followed by three sham treatments, with a three-week interval. The rTMS protocol employed high-frequency stimulation at 10Hz. At the end of the treatment, there were no statistically significant results in terms of depressive symptomatology, although greater reductions in depression scores were associated with the real rTMS protocol.

4.1.2 Right DLPFC:

Three of the studies included (Carretero et al. (2009); Bhatia et al. (2019); Tanwar et al. (2020)) detailed protocols targeting the right DLPFC, using low-frequency rTMS (1Hz) for 20 sessions over four weeks. In Carretero et al. (2009), a RCT was conducted in patients diagnosed with fibromyalgia and comorbid major depression, with no statistically significant improvements in the HDRS score in both active rTMS group and sham group. Conversely, Tanwar et al. (2020) conducted a RCT with 90 patients diagnosed with fibromyalgia demonstrating significant improvement of the HDRS score in the real treatment group, compared to the sham group, with sustained improvements through six months of follow-up. Bhatia et al. (2019), another RCT was conducted involving 30 patients diagnosed with Chronic Tension-type Headache (CTTH) revealing improvement of HDRS score in both groups (sham and active group). However, there were no

statistically significant differences observed between the groups.

4.1.3 Left and Right DLPFC:

Petelin et al. (2022) reported a RCT with 25 patients diagnosed with chronic pain disorders of various etiologies and refractory depression. Patients were randomly assigned to two groups: one receiving a low-frequency (1Hz) TMS protocol applied to the right DLPFC (N=12) while the other group receiving a high-frequency (10 Hz) TMS protocol targeting the left DLPFC (N=13). The left DLPFC stimulation group showed a statistically significant reduction in depressive symptomatology compared to baseline. However, the right DLPFC stimulation group did not demonstrate a statistically significant decrease in depressive symptomatology. At one month follow up, both protocols resulted in statistically significant differences in MADRS scores compared to baseline.

4.2 Protocols targeting the M1:

We included 14 studies in our analysis that investigated targeting the Primary Motor Cortex M1 (Ohn et al. (2012); Hosomi et al. (2013); Khedr et al. (2015); Shu-Min Ma et al. (2015); Yang et al. (2019); Qian Pei et al. (2019); Bursali et al. (2021); Guinot et al. (2021) Säisänen et al. (2022); Yang et al. (2023)) with different rTMS protocols, 4 of them targeting the Left M1 (Passard et al. (2007); Mhalla et al. (2011). Leung et al. (2015); El-Badawy et al. (2021)).

Hosomi et al. (2013) conducted RCT employing a cross over design, involving 70 patients diagnosed with neuropathic pain. Participants were randomly assigned to two groups, with one undergoing real rTMS sessions followed by a sham period, while the other group experience the reverse sequence. The real rTMS consisted of 10 sessions of high-frequency stimulation over a two-week period, delivered at 5Hz, with a 17-day interval between real and sham treatments. During the study, the evaluation of depressive symptomatology using the BDI score revealed no significant differences between the real rTMS and the sham stimulation groups at any point.

Khedr et al. (2015) and Bursali et al. (2021) conducted RCTs employing rTMS high-frequency protocols (20Hz and 5 Hz, respectively), consisting of 10 sessions. Both studies reported significant reductions in depressive symptomatology when comparing active stimulation to the sham treatment, with these effects persisting for at least one-month after the treatment. Ohn et al. (2012) executed a clinical trial of five sessions of high-frequency rTMS (10Hz), that also demonstrated significant reductions in the depressive symptomatology. In both this study and the one conducted by Khedr et al. (2015), significant correlations were established between the antalgic effects induced by the rTMS intervention and the reduction observed in HDRS scores.

Shu-Min M et al. (2015) documented a RCT with 40 patients diagnosed with postherpetic

neuralgia. The study implemented a high-frequency (10 Hz) protocol of 10 sessions. However, the results revealed no statistically significant differences between the real rTMS group and the sham group.

Qian Pei et al. (2019) conducted a RCT employing high-frequency protocols of rTMS targeting the primary motor cortex in 75 patients with postherpetic neuralgia. The patients were randomized into three groups, one group receiving 10 sessions at 5Hz, the other, 10 sessions at 10 Hz and the sham group. After treatment, statistical analysis revealed no significant differences among the three groups in terms of depressive symptomatology evaluated by Self-Rating Depression Scale.

Guinot et al. (2021) investigated the effect of 16 sessions of a high-frequency (10Hz) protocol complementing 12 weeks of multicomponent therapy in patients diagnosed with fibromyalgia, comparing it to the effects of multicomponent therapy alone. The study revealed a reduction in depressive symptomatology in both groups, although no statistically significant differences were found between groups. Säisänen et al. (2022) reported a study with two consecutive high-frequency five-sessions protocols (protocol A- 10Hz, protocol B- 20 Hz) separated by an interval of six weeks. Although, there were improvements of the BDI scores, the findings did not reach statistical significance, similar to the study conducted by Guinot et al. (2021).

In contrast with the preceding studies, Yang et al. (2019) conducted a RCT targeting the M1, employing a low frequency protocol, in a cohort of 56 patients diagnosed Parkinson's disease associated with pain. The intervention protocol comprised 10 sessions over two-week period, employing a frequency of 0.50 Hz. Following the treatment, no statistically significant differences were found in the HDRS scores in the active rTMS group and the sham group.

Yang et al. (2023) conducted a RCT in 39 patients with neuropathic pain due to spinal cord injury. The patients were randomly allocated into three groups: one receiving treatment with rTMS, one receiveing treatment with intermittent theta burst stimulation (iTBS), and one receiving combined treatment with both rTMS and iTBS. All groups underwent 20 sessions of treatment over a 4-week period. The rTMS group (N=13) employed 20 sessions of rTMS at a frequency of 10Hz. The iTBS group (N=13) underwent 20 sessions of iTBS involving triplet 50Hz bursts repeated at 5Hz. The iTBS + rTMS group underwent 20 sessions of iTBS followed by 10Hz rTMS. At the end of the treatment period, the HDRS scores were compared among the three groups. The analysis revealed no statistically significant differences in depressive symptomatology among the 3 treatment groups.

Passard et al. (2007), Mhalla et al. (2011) and Leung et al. (2015) each conducted randomized controlled trials using high-frequency protocols (10Hz), targeting the Left Primary Motor Cortex (M1). The studies implemented varying number of treatment sessions, with Leung et al. (2015) employing three sessions, Passard et al. (2007) employing ten sessions

and Mhalla et al. (2011) employing fourteen sessions. Both Passard et al. (2007) and Mhalla et al. (2011) focused on patients diagnosed with Fibromyalgia, while Leung et al. (2015) focused on patients with Mild Traumatic Brain Injury Related Headache. Despite the differing conditions and treatment durations, none of the studies reported statistically significant effect on the depressive symptomatology in either active rTMS group or the sham group following treatment.

El-Badawy (2021) investigated the therapeutic effect of rTMS and Anodal tDCS (transcranial Direct Current Stimulation) targeting the M1 in patients diagnosed with Fibromyalgia. Through a randomized allocation process, patients were assigned to either the rTMS group or the anodal tDCS group. The rTMS group (N=15) received eight sessions at 10 Hz, and the anodal tDCS group (N=15) underwent eight sessions as well at an intensity of 2mA for 20 minutes. In both groups, at the end of the treatment course, there were significant improvements in Hospital Anxiety and Depression Scale (HADS) - depression sub-score, but the rTMS group showed a higher degree of improvement compared to the anodal tDCS group.

4.3 Protocols targeting the Left DLPFC and the Left M1:

Freigang et al. (2021) conducted a RCT with 34 patients with chronic low back pain or neck pain. The patients were randomized into three groups according to the target of stimulation. The Left M1 (N=11) underwent a protocol consisting of 13 sessions at 5Hz, the left DLPFC group (N=12) underwent the same number of sessions, but at 20 Hz of frequency, and the sham group (N=11). At the end of the treatment, no significant results in the Depression, Anxiety, and Stress Scale (DASS) - depression sub-score were observed in any of the groups.

4.4 Protocols targeting the Right DLPFC and the M1:

Lee et al. (2012) conducted a RCT with 15 patients diagnosed with Fibromyalgia. Patients were randomized into three groups. One group (N=5) received 10 sessions at 1 Hz (low frequency protocol) applied to the right DLPFC, other group (N=5) received 10 sessions at 10 Hz (high frequency protocol) to the M1, and the sham group (N=5). In the right DLPFC group, the BDI scores were significantly lower immediately after ten sessions compared to baseline. And one month after, those changes maintained. In the M1 group, the BDI scores were significantly lower after the 10th session, but not one month later.

4.5 Protocol targeting the Left DLPFC and the M1:

In a RCT conducted by Attal et al. (2021), 149 patients diagnosed with chronic peripheral neuropathic pain were enrolled. The study aimed to compare the effects of stimulation of the M1 area (N=49), the left DLPFC (N=52) and a sham group (N=48). The patients were

randomly allocated to one of the three groups. The M1 stimulation group employed 15 sessions at 10 Hz targeting the primary motor cortex, over a duration of 22 weeks. The left DLPFC-group employed 15 sessions at 10 Hz targeting the left dorsolateral prefrontal cortex, also over a duration of 22 weeks. At the end of the treatment, all groups exhibited improvement in the depressive symptomatology. However, there were no statistically significant differences observed between the groups in terms of the magnitude of improvement.

4.6 Protocols targeting the S1/M1 and S2:

Lindholm et al. (2015) conducted a RCT with cross-over design involving 20 patients with diagnosed neuropathic orofacial pain. In randomized order, all patients received two rTMS stimulations and one sham stimulation, between the two active ones. The rTMS stimulations were delivered at a frequency of 10 Hz targeting specific cortical regions. One session targeted the S1/M1 (Primary somatosensory cortex and precentral gyrus) and the other targeted the right S2 (Secondary somatosensory cortex). At the end of the treatment no statistically significant changes in depressive scores were observed among any of the participants.

DISCUSSION:

The main purpose of this systematic review was to evaluate the impact of TMS on depressive symptomatology among individuals diagnosed with chronic pain disorders. To our knowledge, this is one of the first reviews that assess TMS interventions in patients with chronic pain in which depressive symptomatology is treated as a primary outcome.

General interpretation:

The results obtained from the articles included in this systematic review are found to be very diverse. All the papers found studied TMS' efficacy in the treatment of chronic pain and had evaluation of the effect in depressive symptomatology as a secondary outcome.

A review by Galhardoni et al. (2015) reports that the M1 target has been the most assessed for cortical stimulation studies in chronic pain. However, there is a solid basis for targeting other areas like the left and right DLPFC. Studies in healthy volunteers have shown that high-frequency rTMS to the right DLPFC was able to trigger analgesic effects similar to M1 stimulation, despite their differences in mechanisms of action. The left DLPFC has also been used in rTMS studies in

patients with fibromyalgia, but it has shown a small analgesic effect. (46) Another meta-analysis, by Zhu et al. (2023) studied the effects of high-frequency stimulation on the M1 and DLPFC in patients with fibromyalgia. In the subgroup analysis, the results showed no statistical significance but the trend of analgesic effect in the M1 region was better than that in the DLPFC region. (47) In accordance with those studies, Passard et al. (2007), Mhalla et al. (2011) and El-Badawy et al. (2021) reported significant improvement of pain scores with high-frequency rTMS stimulation of the left M1. Lee et al. (2012) compared stimulation of the right DLPFC and the M1 describing that in both groups there was an improvement in BDI scores, although only the right DLPFC group maintained these improvements for one month. Short et al. reported no significant differences in the improvement of pain scores between the active rTMS and the sham group when stimulating the left DLPFC in patients with fibromyalgia. In terms of treating neuropathic pain, a systematic review and meta-analysis by Jiang et al. (2022) reported that active high-frequency rTMS had a significant clinical effect on pain symptoms in patients with NP compared with sham rTMS. Low-frequency stimulation had no therapeutic effect reported. With regards to the rTMS site, their analysis revealed that stimulation at M1 was superior to other sites. (48) Attal et al. (2021) compared stimulation of the left DLPFC and the M1 reporting significant improvement in pain scores in the group stimulated in the primary motor cortex, but not in the group stimulated in the left DLPFC, as described above. Qian Pei et al. (2019) reported significant improvement of pain scores when stimulating the M1 with more significant results in the group with higher frequency of stimulation. Knowing that all protocols were directed at relieving pain and that pain treatment with TMS remains highly experimental, it is easily justifiable that the protocols varied so much in terms of target location and parameters of stimulation.

A common finding in the studies included revealed that a significant reduction in pain scores wasn't always accompanied by a significant improvement on depressive symptomatology. We hypothesize that this happened for two main reasons. Firstly, some studies excluded patients with comorbid major depression (Passard et al. (2007), Mhalla et al. (2011), Conforto et al. (2014), Attal et al. (2021)). In these cases, the baseline Beck Depression Inventory scores were minimal (0-9) or mild (10-18) indicating that the patients had lesser depressive symptoms. This alone reduces the chance of TMS effectively treating these symptoms and creates lower compliance with psychological evaluations as described by Conforto et al. (2014). Secondly, among patients with comorbid pain and depression, those with depression tended to respond less effectively to treatments directed solely to pain levels, as reported by Ohn et al. (2012). A review by Zis et al. (2017) describes how perception of pain is sensitive to various mental processes such as the feelings and beliefs that someone has about pain. Therefore, it's not exclusively driven by the noxious input. (49) In patients with pain, depression is associated with more pain complaints, greater pain intensity, longer duration of pain and, greater likelihood of non-recovery. Depression

also predicts increased healthcare utilization, poorer adherence to treatment, worse patient satisfaction, and future episodes of pain. (2, 7)

Comparing the results through the stimulation target, we can't take many conclusions since the results were so diverse. The studies in which the stimulated area was the left DLPFC didn´t report statistical differences in the effect of TMS on depressive symptomatology between the active rTMS group and the sham group, except for the one conducted by Leung et al. (2017). This could be explained by the differences between the parameters used for the stimulation and the ones standardized for major depression by the FDA-approved protocol.

The FDA-cleared repetitive Transcranial Magnetic Stimulation protocol entails a high-frequency (10Hz) stimulation targeted at the left dorsolateral prefrontal cortex. Each session lasts approximately 38 minutes, with a stimulation intensity set at 120% of the RMT, 3000 pulses per session, encompassing 30 sessions administered over six weeks (five days per week). (50) Another established protocol, theta burst stimulation (TBS), delivers 600 pulses in a 3-minute session, with the same stimulation intensity and number of sessions. iTBS has shown effectiveness on par with rTMS. (51) However, the studies included in our analysis exhibit significant deviations from these standardized protocols. Notably, none of the studies adhere strictly to the 30-session rTMS regimen, and many diverge from the prescribed stimulation intensity of 120% RMT. Therefore, it can be expected that numerous protocols didn't have a significant impact on depressive symptomatology. Out of the 29 studies, only six (Carretero et al. (2009); Conforto et al. (2014); Fitzgibbon et al. (2018); Bhatia et al. (2019); Tanwar et al. (2020); Yang et al. (2023)) investigated the effects of a TMS protocol consisting of at least 20 sessions. Furthermore, only 5 studies (Short et al. (2011); Nardone et al. (2016)) report 120% RMT and of those only 3 (Avery et al. (2015); Fitzgibbon et al. (2018); Petelin et al. (2022)) report the application of 3000 pulses per session.

Comparing the studies with protocols applied to the primary motor cortex, most of them didn't report any statistically significant results in depressive symptomatology. This outcome was expected since M1 is not the target of choice for depression treatment. However, since we evaluated studies that treated pain as a primary outcome, it is to be expected that this is frequently targeted. From what we gathered, only Ohn et al. (2012), Khedr et al. (2015) and Bursali et al. (2021) reported significant reductions in depressive symptomatology compared to the sham treatment. In both, significant correlations were made between the antalgic effects of rTMS and the depressive symptomatology reduction, suggesting that depressive symptoms improve as a consequence of the improvement of the pain conditions. (2)

Moreover, there are certain studies where both active and sham control groups reported improvement in depressive symptomatology following rTMS intervention, with no discernible differences between them, as observed in the ones conducted by Lee et al. (2012) and Attal et al. (2021). These studies highlight a significant placebo effect, characterized by similar outcomes between the treated and untreated groups. This is also evident in the research conducted by Conforto et al. (2014), where the group receiving the rTMS intervention showed no significant change in depression scores, while the control group exhibited a significant improvement of depressive symptomatology despite not receiving stimulation. From a psychological viewpoint, numerous mechanisms contribute to placebo effects. Among them two key mechanisms are widely recognized: expectations and conditioning. The presence of a conditioning protocol to increase expectations results in larger placebo analgesic responses, demonstrating that expectation can both mediate and modulate placebo effects as well as interact with other factors such as emotion. (52)

In terms of safety, the most feared side-effect of TMS is the triggering of epileptic seizures. However, studies with large samples have concluded that, in a population with no risk of epileptic attack, there is no greater risk than normal of the development of a new attack. Other temporary effects may be seen such as headaches (20 to 25%), neck pain (10 to 15%), tinnitus, cognitive effects (temporary concentration and memory disorders), acute mood changes (irritability), and neurocardiogenic syncope. According to the international safety guidelines, with appropriate patient selection and defined treatment parameters, TMS can be a safe technique. (53) In accordance, this review also describes TMS as a safe intervention since many studies reported an absence of unintended consequences and others reported mild and transient headaches or tingling/discomfort on the site of stimulation as the most prevalent side effects. Dizziness, neck pain, and nausea were other side effects mentioned across studies, albeit with a lesser frequency. A Review by Rossi et al. (2021) recommends that TMS may be delivered by a physician or by an appropriately trained individual operating under the supervision of the physician. TMS should be delivered in a context where anticipated side effects may be appropriately managed, like a clinical setting. (54)

Included articles limitations:

The main limitation identified among the studies included in our review is the heterogeneity in the transcranial magnetic stimulation protocols, which encompasses variations in the number of sessions, applied frequency, resting motor threshold intensity, and number of pulses per session. Such discrepancies pose challenges in comparing and extrapolating findings across studies.

An additional limitation arises from the fact that the evaluation of depressive symptomatology was

not the primary outcome in any of the included studies. Consequently, the assessment of depressive symptoms may lack precision, potentially influencing the quality and reliability of the results.

Furthermore, the cohort intervals in the studies range from 4 to 149, with a median value of 29, demonstrating that most have small samples. This translates to modest statistical power derived from quantitative analyses, often failing to achieve statistical significance.

Moreover, a notable limitation concerns the timeline of the studies. Most of them (except for Tanwar et al. (2020) who reported a 6-month follow-up) did not provide long-term treatment outcomes. This limitation confines our review to short-term antidepressant effects, exacerbated by the fact that most studies employed 2-week protocols, which may not allow adequate time to evaluate changes in depressive symptomatology.

Limitations of the review itself:

In the course of conducting this systematic review, it's important to note that studies were not excluded based on their quality or risk of bias. It became apparent that excluding studies solely based on their quality would greatly restrict the pool of available evidence. Therefore, this decision was made to ensure an inclusive assessment of the available literature allowing for a comprehensive analysis of the evidence regarding this topic.

The presence of deadlines posed a significant limitation during the systematic review process. Due to time constraints, there was a limited window available for conducting the literature search, screening studies, and synthesizing the findings. Consequently, it may have restricted the depth of the review process and the number of studies that could be included.

Implications for practice, policy, and future research:

In essence, this paper showed that the impact of TMS on depression among chronic pain patients is a complex and vast subject that requires future research with more standardized protocols and consistency of sites stimulated. Studies including a significant number of patients with chronic pain and co-morbid depression, evaluating the effect of TMS on depressive symptoms as a primary outcome, will allow us to better understand the potential of TMS for this specific situation.

Finally, TMS as a treatment for chronic pain remains highly experimental, and further investigations and growing evidence in this field would also help determine what are the most effective TMS protocols for these patients.

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ANEXOS

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	**Página 1: The impact of Transcranial Magnetic Stimulation (TMS) on depressive symptomatology in patients with chronic pain disorders: A Systematic Review.**
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Página 2: **Objective:** Transcranial Magnetic Stimulation (TMS) is a recognized therapy for treatment-resistant depression and has been studied for its potential in managing chronic pain. Knowing the intrinsic relationship between pain and depressive symptomatology, this systematic review aims to assess the impact of TMS applied on depressive symptoms in patients with chronic pain. **Methods:** Electronic databases were systematically searched until November 2023 for studies applying TMS in chronic pain patients, with assessment of both pain and depressive symptomatology. **Results:** From the records screened, 29 studies met the inclusion criteria for qualitative synthesis. The results showed heterogenous protocols with widely different results in depressive symptomatology across the studies, precluding meta-analysis. TMS was considered a safe treatment option with minor side effects. **Conclusions:** The impact of TMS on depressive symptomatology among chronic pain patients is a complex subject. Considering the diversity of the protocols and results encountered, future research

Section and Topic	Item #	Checklist item	Location where item is reported
			should prioritize the establishment of standardized TMS protocols to clarify its efficacy in managing depressive symptoms among chronic pain patients. **Significance:** This systematic review highlights the need for further investigation of TMS as a dual therapeutic approach for chronic pain and depressive symptomatology, emphasizing the necessity of improving the protocols to enhance the clinical outcomes.
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Página 3: A World Health Organization study in primary care showed a strong association between persistent pain and depressive disorders, with those experiencing chronic pain being substantially more likely to have depressive symptoms. (5) Clinical studies have revealed that chronic pain, a stress state, often induced depression and up to 85% of patients with chronic pain are affected by severe depression. (2, 6, 7) Therefore, addressing mood alongside chronic pain management becomes imperative. (8) Página 4: Acknowledging the intrinsic relationship between depression and chronic pain and the lack of evidence regarding the effect of TMS on depressive symptomatology in patients with chronic pain disorders, the main purpose of this systematic review is to comprehensively assess the existing literature in

Section and Topic	Item #	Checklist item	Location where item is reported
			managing both chronic pain and depressive symptoms. By synthesizing finding from several studies, we aim to clarify the potential benefits and limitations of TMS as a therapeutic approach. Furthermore, this review intends to identify the gaps in current research and provide insight for future investigations.
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Página 4: Acknowledging the intrinsic relationship between depression and chronic pain and the lack of evidence regarding the effect of TMS on depressive symptomatology in patients with chronic pain disorders, the main purpose of this systematic review is to comprehensively assess the existing literature in managing both chronic pain and depressive symptoms. By synthesizing finding from several studies, we aim to clarify the potential benefits and limitations of TMS as a therapeutic approach. Furthermore, this review intends to identify the gaps in current research and provide insight for future investigations.
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	**Página 4: Eligilibity criteria:** A priori set of eligibility criteria was pre-specified based on the PICOS (Population; Intervention; Comparator; Outcomes; Study design) framework and is depicted in Table 1. **Table 1:** Based on the PICOS framework

Section and Topic	Item #	Checklist item	Location where item is reported
			Página 8: The studies were evaluated through tabular and thematic analysis by grouping them according to the cortex area used as a stimulation target.
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Página 7: A comprehensive search was conducted on PubMed, Scopus (the selected field consisted of article title, abstract and keywords), Web of Science Core Collection (field consisted of topic), Clinical Trials.gov, and PsycINFO electronic databases and completed on the 27th of November 2023. For each electronic database, studies were searched from inception, and no language or date restrictions were applied, and if necessary, studies were translated to ascertain the eligibility of the records retrieved. For additional records, grey literature was also searched through Google Scholar and completed on the 27th of November 2023. Moreover, to identify possible additional relevant records, the included studies underwent backward and forward citation tracking. This involved manually searching reference lists and conducting additional searches on Google Scholar, respectively. These steps aimed to minimize selection and publication biases. .

Section and Topic	Item #	Checklist item	Location where item is reported
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Página 7: The search strategy was informed by previously published reviews, consideration of MeSH terms and the wider literature in the field, with input and support from a university librarian. The search was first defined for PubMed and further adapted for the individual databases as needed. The following search queries were used for each of the electronic databases: ***PubMed / Web of Science Core Collection / PshycoINFO / Google Scholar*** (depression OR depressive disorder OR dysthymic disorder OR mood disturbance OR affective disorder OR affective disturbance OR psychological distress OR suicide OR sadness) AND (transcranial magnetic stimulation OR TMS OR rTMS) AND (chronic pain) ***Scopus*** (depression OR (depressive AND disorder) OR (dysthymic AND disorder) OR (mood AND disturbance) OR (affective AND disorder) OR (affective AND disturbance) OR (psychological AND distress) OR suicide OR sadness) AND ((transcranial AND magnetic AND stimulation) OR tms OR rtms) AND (chronic AND pain) ***Clinicaltrials.gov*** (depression OR depressive disorder OR dysthymic

Section and Topic	Item #	Checklist item	Location where item is reported
			disorder OR mood disturbance OR affective disorder OR affective disturbance OR psychological distress OR suicide OR sadness) AND (transcranial magnetic stimulation OR TMS OR rTMS) AND (chronic pain)
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Página 8: After duplicates removal, the records retrieved from the databases and other information sources were reviewed for eligibility using a two-phase approach: title and abstract screening and full-text review, using the predefined inclusion and exclusion criteria. In the first phase, all titles and abstracts were independently screened by two authors (I. S., P. A.) using EndNote reference management software 21. All disagreements were discussed and solved by consensus or in consultation with the wider review team. Ambiguous abstracts due to insufficient information to make a define decision remained included until the next phase and full-texts were retrieved. In the second phase, the full-text of the selected records was retrieved and evaluated by the same authors, independently. The number of studies that were included and excluded at each stage and the reasons for exclusion were recorded and reported in the PRISMA flow diagram (Figure 1).

Section and Topic	Item #	Checklist item	Location where item is reported
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Página 8: The extraction of data was done by one author (I.S.) and summarized in a tabular form (Table 2) including the following parameters: author, year, sample, TMS target, TMS protocol, outcome assessment, main results, and adverse effects. Whenever possible, intention-to-treat data (i.e., analyzing all participants according to the group randomization) were collected. The data extracted was further independently cross-checked and revised for errors and potential divergent results by two other authors (P.A., I.B.). Discrepancies were solved by consensus with the wither review team.
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Página 8: The data extracted was further independently cross-checked and revised for errors and potential divergent results by two other authors (P.A., I.B.). Discrepancies were solved by consensus with the wither review team. The heterogeneity in the studies included, TMS protocols, and outcomes measures, precluded a meta-analysis, and a narrative synthesis approach to summarize and interpret the qualitative and quantitative data was undertaken. The studies were evaluated through tabular and thematic analysis by grouping them according to the cortex area used as a stimulation target. This approach has been defined has suitable to synthetize heterogeneous literature. (14)

Section and Topic	Item #	Checklist item	Location where item is reported
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Não aplicável.
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Página 8-9: For each study included, the risk of bias was assessed using the revised Cochrane risk of bias tool for randomized trials (RoB 2) and the risk of bias in non-randomized studies of interventions (ROBINS – I) tools. RoB 2 addresses: 1- bias arising from the randomization process; 2- bias due to deviations from intended interventions; 3- bias due to missing outcome data; 4- bias in the measurement of the outcome; 5- bias in the selection of the reported result. Each domain is required, and no additional domains should be added. (15) ROBINS-I addresses three bias domains evaluated in each study. Pre-intervention domain: 1- bias due to confounding; 2- bias in selection of participants into the study. At intervention: 3 - bias in classification of intervention. Post- intervention: 4- bias due to deviations from intended interventions; 5 - bias due to missing data; 6 - bias in measurement of outcomes; 7 - bias in selection of the reported result. Two authors independently graded the risk of bias for each study. Any disagreements were solved through consensus or referral to the review team. (16) To maximize the base of evidence, no study was excluded based on the quality alone.

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Não aplicável
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Não aplicável.
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Não aplicável.
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Não aplicável.
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Não aplicável.
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Não aplicável.
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Não aplicável.
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Não aplicável.
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Não aplicável.
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	“Figure 1: PRISMA flow diagram summarizing the selection process”
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	“Figure 1: PRISMA flow diagram summarizing the selection process”
Study characteristics	17	Cite each included study and present its characteristics.	“Table 2: Summary of Studies Characteristics”
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	“Table 3: Risk of Bias assessment using RoB 2.0” “Table 4: Risk of Bias assessment using ROBINS-I”
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Não aplicável.
Results of	20a	For each synthesis, briefly summarise the characteristics and risk of bias among	Não aplicável.

Section and Topic	Item #	Checklist item	Location where item is reported
syntheses		contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Não aplicável.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Não aplicável.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Não aplicável.
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Não aplicável.
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Não aplicável.
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Página 29: A common finding in the studies included revealed that a significant reduction in pain scores wasn't always accompanied by a significant improvement on depressive symptomatology. We hypothesize that this happened for two main reasons. Firstly, some studies excluded patients with comorbid major depression (Passard et al. (2007), Mhalla et al. (2011), Conforto et al. (2014), Attal et al. (2021)). In these cases, the baseline Beck Depression Inventory scores were minimal (0-9) or mild (10-18) indicating that the patients had lesser depressive symptoms. This alone reduces the chance of TMS effectively treating these symptoms and creates lower compliance with psychological evaluations as described by Conforto et al. (2014). Secondly, among patients with comorbid pain and depression, those with depression tended to respond less effectively to

Section and Topic	Item #	Checklist item	Location where item is reported
			treatments directed solely to pain levels, as reported by Ohn et al. (2012). A review by Zis et al. (2017) describes how perception of pain is sensitive to various mental processes such as the feelings and beliefs that someone has about pain. Therefore, it's not exclusively driven by the noxious input. (48) In patients with pain, depression is associated with more pain complaints, greater pain intensity, longer duration of pain and, greater likelihood of non-recovery. Depression also predicts increased healthcare utilization, poorer adherence to treatment, worse patient satisfaction, and future episodes of pain. (2, 7) Página 30: Comparing the results through the stimulation target, we can't take many conclusions since the results were so diverse. The studies in which the stimulated area was the left DLPFC didn´t report statistical differences in the effect of TMS on depressive symptomatology between the active rTMS group and the sham group, except for the one conducted by Leung et al. (2017). This could be explained by the differences between the parameters used for the stimulation and the ones standardized for major depression by the FDA-approved protocol. Página 30: Comparing the studies with protocols applied to the primary motor cortex, most of them

Section and Topic	Item #	Checklist item	Location where item is reported
			didn't report any statistically significant results in depressive symptomatology. This outcome was expected since M1 is not the target of choice for depression treatment. However, since we evaluated studies that treated pain as a primary outcome, it is to be expected that this is frequently targeted. From what we gathered, only Ohn et al. (2012), Khedr et al. (2015) and Bursali et al. (2021) reported significant reductions in depressive symptomatology compared to the sham treatment. In both, significant correlations were made between the antalgic effects of rTMS and the depressive symptomatology reduction, suggesting that depressive symptoms improve as a consequence of the improvement of the pain conditions. (2) Página 31: Moreover, there are certain studies where both active and sham control groups reported improvement in depressive symptomatology following rTMS intervention, with no discernible differences between them, as observed in the ones conducted by Lee et al. (2012) and Attal et al. (2021). These studies highlight a significant placebo effect, characterized by similar outcomes between the treated and untreated groups. This is also evident in the research conducted by Conforto et al. (2014), where the group receiving the rTMS intervention showed no significant change in depression scores, while the control group exhibited a significant improvement of depressive symptomatology despite not receiving stimulation.

Section and Topic	Item #	Checklist item	Location where item is reported
			From a psychological viewpoint, numerous mechanisms contribute to placebo effects. Among them two key mechanisms are widely recognized: expectations and conditioning. The presence of a conditioning protocol to increase expectations results in larger placebo analgesic responses, demonstrating that expectation can both mediate and modulate placebo effects as well as interact with other factors such as emotion. (51)
	23b	Discuss any limitations of the evidence included in the review.	Páginas 31-32: The main limitation identified among the studies included in our review is the heterogeneity in the transcranial magnetic stimulation protocols, which encompasses variations in the number of sessions, applied frequency, resting motor threshold intensity, and number of pulses per session. Such discrepancies pose challenges in comparing and extrapolating findings across studies. An additional limitation arises from the fact that the evaluation of depressive symptomatology was not the primary outcome in any of the included studies. Consequently, the assessment of depressive symptoms may lack precision, potentially influencing the quality and reliability of the results.

Section and Topic	Item #	Checklist item	Location where item is reported
			Furthermore, the cohort intervals in the studies range from 4 to 149, with a median value of 29, demonstrating that most have small samples. This translates to modest statistical power derived from quantitative analyses, often failing to achieve statistical significance. Moreover, a notable limitation concerns the timeline of the studies. Most of them (except for Tanwar et al. (2020) who reported a 6-month follow-up) did not provide long-term treatment outcomes. This limitation confines our review to short-term antidepressant effects, exacerbated by the fact that most studies employed 2-week protocols, which may not allow adequate time to evaluate changes in depressive symptomatology.
	23c	Discuss any limitations of the review processes used.	Página 32: In the course of conducting this systematic review, it's important to note that studies were not excluded based on their quality or risk of bias. It became apparent that excluding studies solely based on their quality would greatly restrict the pool of available evidence. Therefore, this decision was made to ensure an inclusive assessment of the available literature allowing for a comprehensive

Section and Topic	Item #	Checklist item	Location where item is reported
			analysis of the evidence regarding this topic. The presence of deadlines posed a significant limitation during the systematic review process. Due to time constraints, there was a limited window available for conducting the literature search, screening studies, and synthesizing the findings. Consequently, it may have restricted the depth of the review process and the number of studies that could be included.
	23d	Discuss implications of the results for practice, policy, and future research.	Página 32: In essence, this paper showed that the impact of TMS on depression among chronic pain patients is a complex and vast subject that requires future research with more standardized protocols and consistency of sites stimulated. Studies including a significant number of patients with chronic pain and co-morbid depression, evaluating the effect of TMS on depressive symptoms as a primary outcome, will allow us to better understand the potential of TMS for this specific situation. Finally, TMS as a treatment for chronic pain remains highly experimental, and further investigations and growing evidence in this field would also help determine what are the most effective TMS protocols for these patients.

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
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Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Não aplicável.
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Não aplicável.
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Não aplicável.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Página 1: This research did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors.
Competing interests	26	Declare any competing interests of review authors.	Não aplicável.
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Não aplicável.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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GUIDELINES REVISTA: CLINICAL NEUROPHYSIOLOGY

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