Evidence Brief: Transcranial Magnetic Stimulation (TMS) for Chronic Pain, PTSD, TBI, Opioid Addiction, and Sexual Trauma

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PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The program is composed of three ESP Centers across the US and a Coordinating Center located in Portland, Oregon. Center Directors are VA clinicians and recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Center Program and Cochrane Collaboration. The Coordinating Center was created to manage program operations, ensure methodological consistency and quality of products, and interface with stakeholders. To ensure responsiveness to the needs of decision-makers, the program is governed by a Steering Committee composed of health system leadership and researchers. The program solicits nominations for review topics several times a year via the program website.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, Deputy Director, ESP Coordinating Center at Nicole.Floyd@va.gov.

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EXECUTIVE SUMMARY

Key Findings

- Most studies of transcranial magnetic stimulation (TMS) therapy employed repetitive TMS (rTMS). rTMS may reduce symptoms in people with chronic pain, post-traumatic stress disorder (PTSD), traumatic brain injury (TBI), and opiate addiction, but findings are mixed among included studies.
- rTMS could be a treatment option for patients who have exhausted other available options for treatment of chronic pain, PTSD, TBI, opiate addiction, but practical aspects of more widely implementing TMS in a healthcare system need to be considered.
- Future research should focus on studies with larger samples, robust methodology, and standardized TMS parameters.

Transcranial magnetic stimulation (TMS) is a noninvasive therapy that uses coils to pass magnetic pulses through the skull to induce electrical currents. These currents stimulate the underlying brain cortex. TMS therapy can vary based on the types of coils used, the brain area stimulated, the frequency and intensity of the magnetic pulses, and the number and speed of pulses delivered. The most common therapeutic use of TMS is for treatment of major depressive disorder (MDD), and the FDA began approving various devices for this application in 2008.

Since approval for MDD, TMS has been investigated for treatment of other conditions, including traumatic brain injury (TBI), post-traumatic stress disorder (PTSD), pain, schizophrenia, dementia, and substance use disorder. Compared to MDD, fewer studies have examined the efficacy of TMS for these conditions, and there remain open questions about the generalizability of existing evidence, the reliability of treatment effects, and the optimal treatment protocol for each condition.

Based on evidence from 39 included controlled studies, our review suggests that repetitive TMS (rTMS), the most common form of TMS therapy, may be effective for treating chronic pain, PTSD, TBI, and opiate addiction (Table ES-1). However, there were inconsistent findings among studies, and about half of included studies found that reduction in chronic pain, PTSD, and TBI symptoms did not significantly differ between TMS therapy and sham therapy control groups. No studies specifically examined TMS as a therapy for sexual trauma, and no studies directly compared rTMS to novel forms of TMS such as theta-burst or electroencephalogram (EEG)-guided TMS.

Purpose

The ESP Coordinating Center is responding to a request from the Center for Compassionate Care Innovation for an evidence brief on the use of transcranial magnetic stimulation (TMS) for the treatment of mental and physical health diagnoses (not including major depressive disorder). Findings from this evidence brief will be used to inform a VHA pilot program to provide access to TMS for Veterans suffering from chronic pain, post-traumatic stress disorder (PTSD), traumatic brain injury (TBI), opioid addiction, or sexual trauma as required by HR 1162, "No Hero Left Untreated Act". The goal of this review is to synthesize important and recent evidence on TMS effectiveness and safety for treatment of chronic pain, PTSD, TBI, opioid addiction, and sexual trauma.

Methods

To identify studies, we searched MEDLINE®, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and other sources up to August 2020. We used prespecified criteria for study selection, data abstraction, and rating internal validity and strength of the evidence. See our PROSPERO protocol for our full methods.

Despite the mixed effectiveness findings, TMS was found to be a safe and generally well-tolerated therapy.

There was considerable variation in patient populations (demographics, disease or symptom characteristics, *etc*), TMS protocols (TMS coil type and position, stimulation parameters, *etc*), and study methodology (sample size, outcomes and number of timepoints assessed, *etc*), among the included studies. This variation may contribute to the inconsistency in the observed effects of TMS therapy. Moreover, the generally small sample sizes of studies could have limited statistical power to detect differences between TMS and control conditions.

Practical aspects of more widely implementing TMS in a health care system need further consideration, particularly as they relate to patient and provider burden, cost, and accessibility. TMS therapy generally consists of daily therapy, usually for a period of 4 to 6 weeks, and patients must travel daily to a designated clinic where TMS is offered. TMS therapy also requires assessment by a trained physician to determine if TMS therapy is appropriate and to prescribe the therapy. Limitations in transportation or clinic access for patients, staff availability, training requirements, and the need for a designated clinic site with TMS technology may be barriers in expanding use of TMS.

Pairing these considerations with the findings that suggest potential effectiveness and high patient safety and acceptability, it is reasonable to conclude that TMS therapy, in particular rTMS, could be considered a treatment option for patients who have exhausted other available options for treatment of chronic pain, PTSD, TBI, or opiate addiction. With this approach, a limited expansion of rTMS could be conducted, which would provide additional information about implementation feasibility and would allow for more rigorous trials to be conducted.

Table ES-1. Summary of Findings

Condition	Evidence	Summary
Chronic Pain	17 controlled studies 14 rTMS, 3 iTBS Low to Moderate SOE	rTMS and iTBS may reduce pain, but inconsistent findings among studies
PTSD	10 RCTs 8 rTMS, 1 iTBS, 1 sTMS Low SOE	rTMS and sTMS may reduce PTSD symptoms, but inconsistent findings among studies
TBI	10 controlled studies* Low SOE	rTMS may improve symptoms after TBI, but inconsistent findings among studies
Opiate Addiction	2 RCTs* Moderate SOE	rTMS likely improves opiate craving in adults with heroin addiction
Sexual Trauma	0 studies	–

*All included studies examined rTMS

Abbreviations: rTMS=repetitive transcranial magnetic stimulation; iTBS=intermittent theta-burst TMS; SOE=strength of evidence; PTSD=post-traumatic stress disorder; RCT=randomized controlled trial; sTMS=synchronized TMS; TBI=traumatic brain injury

EVIDENCE BRIEF

INTRODUCTION

PURPOSE

The ESP Coordinating Center (ESP CC) is responding to a request from the Center for Compassionate Care Innovation for an evidence brief on the use of transcranial magnetic stimulation (TMS) for the treatment of mental and physical health diagnoses (not including major depressive disorder). Findings from this evidence brief will be used to inform a VHA pilot program to provide access to TMS for Veterans suffering from chronic pain, post-traumatic stress disorder (PTSD), traumatic brain injury (TBI), opioid addiction, or sexual trauma as required by HR 1162, "No Hero Left Untreated Act".[1]

BACKGROUND

What is Transcranial Magnetic Stimulation?

TMS is a noninvasive therapy that uses magnetic pulses to induce electrical currents in various parts of the brain.[2] TMS was introduced in 1985,[3] and has been used in a variety of applications, including for intraoperative neurologic monitoring,[4] to investigate nerve conduction, to diagnose neurologic conditions,[5] and for the treatment of psychiatric and neurologic conditions. Therapeutic use of TMS involves placing an insulated coil over various areas of the scalp and passing magnetic pulses through the skull and into the brain.[6] The exact biological mechanism of TMS is unknown, but it is hypothesized that as magnetic pulses pass through the skull, electrical activity is induced in nerve cells, activating underlying areas of the brain cortex.[3,7] This induced activity may alter synaptic plasticity, or the ability of nerve cell connections to strengthen or weaken over time.[8] Biological studies have shown changes in neural activity with TMS treatment, including increased blood flow and dopamine transmission in areas of the brain targeted by TMS.[3]

TMS therapy can vary based on the types of coils used, the brain area stimulated, the frequency and intensity of the magnetic pulses, and the number and speed of pulses delivered. Depending on the type of coil used, magnetic pulses can be delivered over large regions or more focused areas of the brain. The most common coil types are circular coils, figure-8 coils, and H-coils.[9] The multiple layers of coils inside the H-coil helmet allow for deeper stimulation (~4 cm) into the brain compared to conventional circular or figure-8 coils, which can stimulate about 1 cm into the brain.[10] Additionally, different areas of the brain can be targeted by placing the coil over different locations of the scalp. Common locations for stimulation include the primary motor cortex and dorsolateral prefrontal cortex (DLPFC), with variation in placement over the right hemisphere, left hemisphere, or midline.[11,12]

The magnetic pulses during TMS therapy can be delivered at different frequencies (measured in Hertz [Hz]) and intensities. Low frequency (< 5 Hz) stimulation has inhibitory effects on neural activity in the brain, while high frequency (≥ 5 Hz) stimulation has excitatory effects.[9] The intensity of TMS therapy is often individualized, and is set at a proportion of an individual's motor threshold (described as the strength of stimulus required to produce movement of the thumb or fingers). Intensities set at more than 100% of this threshold may have greater risk of

adverse events, including seizure.[3] However, typically MDD TMS protocols treat at 100-120% of RMT without significant side effects in most patients.[13] TMS therapy can also vary based on the number and duration of magnetic pulses delivered. Repetitive TMS (rTMS) delivers magnetic pulses to the brain rapidly at regular intervals and is the most widely studied and commonly used type of TMS. Alternatively, TMS can be delivered as a single pulse, where 1 pulse occurs no faster than once every few seconds.[14]

Novel TMS therapies proposed to enhance the therapeutic effect of TMS include theta-burst TMS (iTBS), synchronized TMS (sTMS), and electroencephalogram (EEG)-guided TMS. Theta-burst TMS delivers either an intermittent or continuous triple-pulse magnetic stimulation, which is hypothesized to induce longer-lasting therapeutic effects. It is delivered at a higher frequency (~50 Hz) than rTMS (~5-10 Hz) and requires shorter TMS sessions (~3 minutes vs ~20-30 minutes). In synchronized TMS, magnetic fields are synchronized to a person's intrinsic alpha frequency using multiple magnets. EEG-guided TMS involves placing the TMS coil over an EEG cap so that brain activity can be measured during TMS therapy, allowing for real-time assessment of the optimal TMS parameters.[5] Another form of EEG-guided TMS, Magnetic eResonance Therapy (MeRT^{SM}),[15] involves recording and analyzing a patient's EEG at various time points during the course of treatment to develop a tailored TMS treatment plan. It is unclear whether these forms of TMS offer improved outcomes over rTMS.

Therapeutic Uses for Transcranial Magnetic Stimulation

The most common therapeutic use of TMS is for treatment of depression. In 2008, the first rTMS device for treatment of major depressive disorder (MDD) was approved by the FDA,[16] and several other devices have since been cleared for this use.[17] Numerous studies have shown benefits of rTMS therapy in patients with depression, including decreases in depression symptom severity, and greater response and remission rates among patients with the use of rTMS compared to sham TMS.[7,18] There are various treatment protocols for rTMS for depression, but a typical protocol may be daily (5 days/week) 20 to 40 minute rTMS sessions over a period of 4 to 8 weeks, with each session delivering 3,000 to 6,000 pulses at 10 Hz.[3] The American Psychiatric Association and National Network of Depression Centers rTMS Task Group issued guidance for clinicians to help navigate the variety of rTMS protocols available for the treatment of depression.[13] This guidance outlines recommendations for coil selection and placement, magnetic field intensity and frequency (Hz), and number and duration of pulses. Additionally, it is recommended to assess patients for risk factors, including history of stroke or seizure, alcohol and drug use, sleep deprivation, and any side effects of previous rTMS use, prior to implementing rTMS and again at each session.[13]

Since approval for MDD, rTMS has been investigated for treatment of other conditions, including TBI,[19-21] PTSD,[22-27] pain,[28,29] schizophrenia,[24,30] dementia,[22] and substance use disorder.[22,31,32] The FDA expanded the approved marketing of rTMS for treatment of certain headaches in 2013 and for obsessive-compulsive disorder (OCD) in 2018.[17] Compared with MDD, fewer studies have examined the efficacy of TMS for these conditions, and there remain open questions about the generalizability of existing evidence, the reliability of treatment effects, and the optimal treatment protocol for each condition.

Usage of TMS in the VHA

TMS therapy in the VHA is offered through the National Clinical rTMS program, which began in 2017 as an effort to expand access to rTMS therapy for Veterans.[33] There are currently 35 VA rTMS clinics across the US, with additional clinics under development. Currently, rTMS is most commonly used within the VHA for treatment of depression, and the VA/DoD guideline for major depressive disorder recommends offering rTMS during a major depressive episode in patients with treatment-resistant MDD.[34] There is interest in expanding the use of TMS to treat other conditions, including TBI, PTSD, chronic pain, opioid addiction, and sexual trauma, but the evidence on the use of TMS therapy for these conditions among Veterans is less established. VA/DoD guidelines for PTSD,[34] mild TBI (tinnitus after mild TBI, update in progress),[34] and headache[34] state that there is insufficient evidence to recommend for or against the use of rTMS for treatment of these conditions (supplemental materials Appendix A).

The goal of this evidence brief is to synthesize important and recent evidence on TMS effectiveness and safety for treatment of chronic pain, PTSD, TBI, opioid addiction, and sexual trauma. The review is intended to inform development of a TMS program for treatment of Veterans with these conditions.

KEY QUESTIONS

Key Question 1: What is the effectiveness of TMS for the treatment of post-traumatic stress disorder, traumatic brain injury, sexual trauma, chronic pain, or opioid addiction?

Key Question 2: What are the potential adverse effects of using TMS for the treatment of post-traumatic stress disorder, traumatic brain injury, sexual trauma, chronic pain, or opioid addiction?

Key Question 3: Do the effectiveness and potential adverse effects of TMS differ according to patient or intervention characteristics (*eg*, patient demographics, comorbidities, disease severity, TMS frequency)?

ELIGIBILITY CRITERIA

The ESP included studies that met the following criteria:

Population: Adults with post-traumatic stress disorder, traumatic brain injury, sexual trauma, chronic pain, or opioid addiction

- **I**ntervention: Transcranial magnetic stimulation (*eg,* repetitive, theta-burst, EEG-guided, EKG-guided, or combination EEG/EKG guided)
- **C**omparator: Any
- **O**utcomes: Symptom improvement (*eg*, response, remission), mortality, quality of life, adverse events (*eg*, headache, worsening symptoms, nausea, seizure)
- **T**iming: Any

- **S**etting: Any

- **S**tudy design: Using a best-evidence approach, we will prioritize evidence from systematic reviews and multisite comparative studies that adequately controlled for potential patient-, provider-, and system-level confounding factors. Inferior study designs (*eg*, single-site, inadequate control for confounding, noncomparative) will only be accepted to fill gaps in higher-level evidence

METHODS

DATA SOURCES AND SEARCHES

To identify articles relevant to the key questions, our research librarian searched MEDLINE (Ovid), CINAHL (EBSCO), PsycINFO (Ovid), and CENTRAL (Ovid) databases as well as AHRQ, CADTH, Cochrane, VA HSR&D, and Clinicaltrials.gov websites using terms for *transcranial magnetic stimulation, post-traumatic stress disorder, traumatic brain injury, opioid disorders, and sexual trauma* from January 2012 to August 2020. We located an existing systematic review on TMS and chronic pain[35] with an end search date in 2017, so we searched the same databases using terms for *transcranial magnetic stimulation* and *chronic pain* from January 2017 to August 2020 (see Appendix B in supplemental materials for full search strategies). Because of the large number of citations for chronic pain, we excluded pain areas that were of low interest to the report nominators (bladder pain, hemiplegic shoulder pain, and orofacial pain). Additional citations were identified from hand-searching reference lists and consultation with content experts. We limited the search to published and indexed articles involving human subjects available in the English language. Study selection was based on the eligibility criteria described above. Titles and abstracts and full-text articles were reviewed by 1 reviewer and checked by another. All disagreements were resolved by consensus or discussion with a third reviewer.

DATA ABSTRACTION AND QUALITY ASSESSMENT

We used predefined criteria to rate the internal validity of all controlled studies. We used Cochrane's Risk of Bias Tools to rate the internal validity of systematic reviews and concurrently controlled studies.[36-38] We abstracted data from all included studies and results for each included outcome. All data abstraction and internal validity ratings were first completed by 1 reviewer and then checked by another. All disagreements were resolved by consensus.

SYNTHESIS

Strength of evidence (SOE) grading was based on the AHRQ Methods Guide for Comparative Effectiveness Reviews,[39] by considering risk of bias (includes study design and aggregate quality), consistency, directness, and precision of the evidence. Ratings typically range from high to very low, indicating our confidence that the evidence reflects an unbiased and precise estimate of the true effect. For this review, we applied the following general algorithm: evidence composed of multiple, large studies with low risk of bias were rated as "high strength" evidence, evidence composed of multiple studies with low to unclear risk of bias and consistent findings were rated as "moderate strength", evidence composed of single studies, or multiple small studies with unclear to high risk of bias and/or inconsistent findings were rated as "low strength", and evidence composed of a single study with high risk of bias was rated as "very low strength". These criteria were applied to primary outcomes for all conditions. Because quality of life was inconsistently reported as a primary or secondary outcome in TBI-related studies, strength of evidence was evaluated for any quality of life outcome reported by these studies. Strength of evidence ratings were completed by 1 reviewer and checked by another. We synthesized the evidence qualitatively by condition, prioritizing controlled studies.

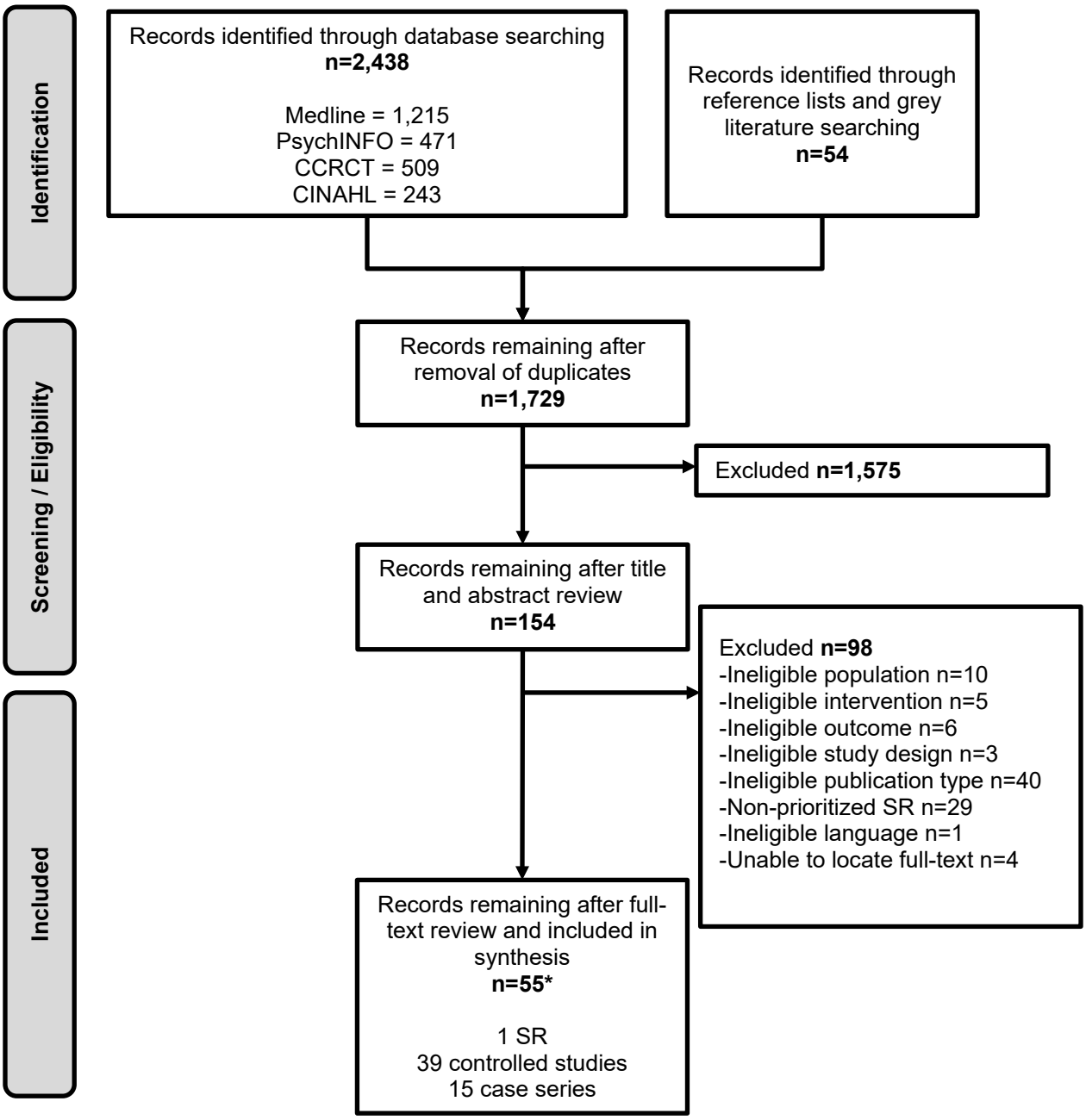
A draft version of this report was reviewed by peer reviewers as well as clinical leadership (see supplemental materials for disposition of peer review comments). The complete description of our full methods can be found on the PROSPERO international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO/; registration number CRD42020202648).

RESULTS

LITERATURE FLOW

The literature flow diagram (Figure 1) summarizes the results of the study selection process (full list of excluded studies available in supplemental materials, Appendix C).

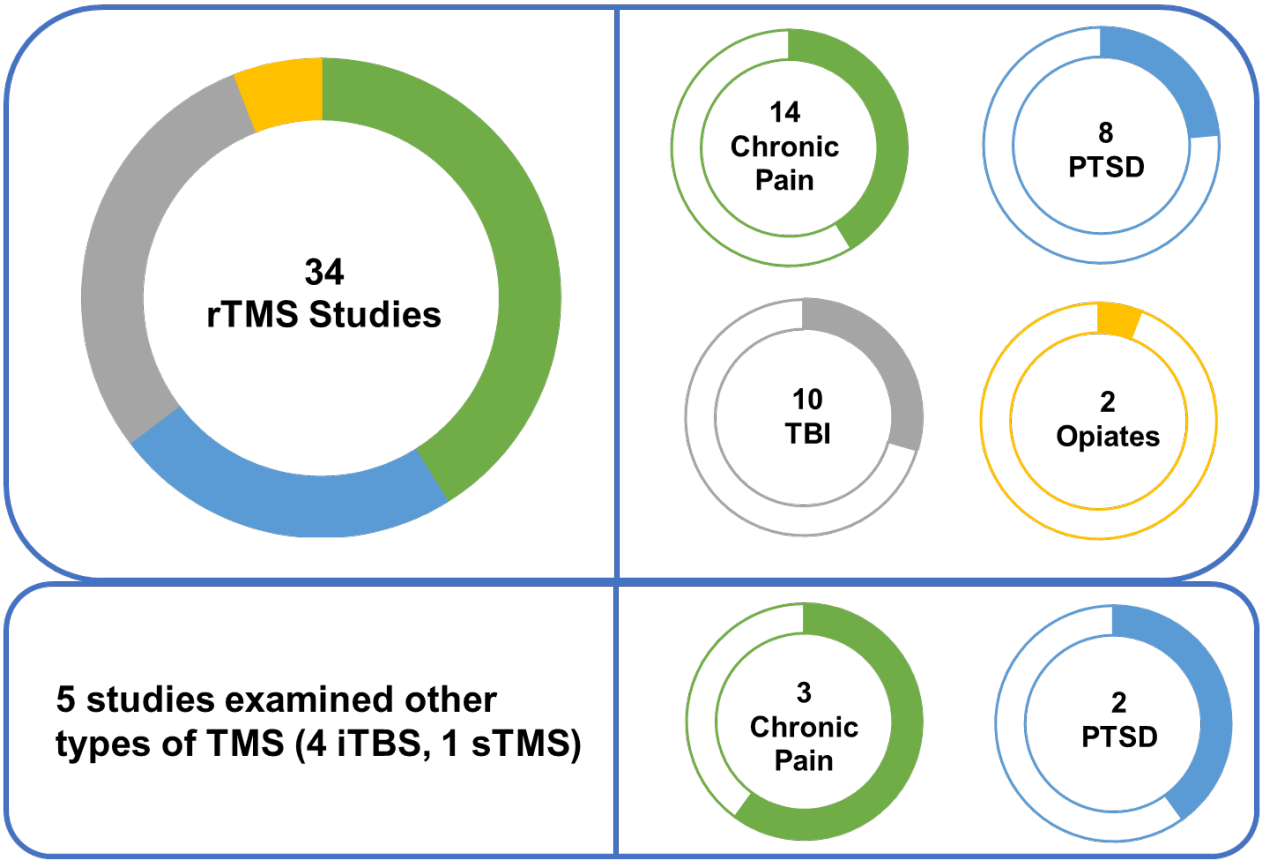
Figure 1: Literature Flowchart



*In 56 publications (1 study with 2 publications)
CCRCT=Cochrane Register of Controlled Trials, CINAHL=Cumulative Index to Nursing and Allied Health Literature, SR = systematic review

Our search identified 1,729 potentially relevant articles. We included 55 studies: 1 systematic review (see Appendix D in supplemental materials for primary studies included in this review),[35] 39 controlled studies (in 40 publications),[40-79] and 15 case series.[80-94] The majority of the controlled studies were in populations with chronic pain (n = 17), PTSD (n = 10), or TBI (n = 10). Two studies were identified in patients with opiate addiction,[71,95] and no studies were identified in patients with sexual trauma. We also identified 39 ongoing studies (see Appendix E in supplemental materials for details), 13 for chronic pain, 7 for PTSD, 5 for TBI, and 14 for opiate addiction. Most studies investigated rTMS (N=34), but several studies examined use of intermittent theta-burst stimulation (iTBS)[54,70,48,67] or synchronized TMS (sTMS)[65] (Figure 2).

Figure 2. Overview of Included Controlled Studies



Abbreviations: rTMS=repetitive TMS; PTSD=post-traumatic stress disorder; TBI=traumatic brain injury, iTBS=intermittent theta-burst TMS; sTMS=synchronized TMS

Most of the included controlled studies were RCTs (N=34), with follow-up ranging from 1 week to 7 months (Table 1). TMS protocols varied widely by TMS target location, frequency and intensity of stimulation, and number and duration of sessions (for full study details see Appendix F in supplemental materials). Sham TMS most often consisted of a "sham coil" which mimicked the vibrations and sounds of the TMS coil, or placement of the TMS coil at 90° away from the skull.

Most studies had unclear risk of bias (N=24) (supplemental materials, Appendix G) and common study limitations were unclear or inappropriate handling of missing outcome data, lack of reporting of study follow-up or withdrawal, unclear allocation concealment, and self-reported

outcomes (Figure 3). Self-reported outcomes were considered a potential risk of bias, given that self-reporting may be subject to bias and is unblinded by definition. However, because most outcomes assessed in the primary studies were, by necessity, self-reported (*eg*, change in severity of pain, opiate cravings, or PTSD symptoms), use of self-reported measures was not considered sufficient to increase the overall risk rating of studies (*eg*, from low to unclear overall risk).

Table 1. Characteristics of Included Controlled Studies

Author, Year N	Study Design Follow-up	Population	Intervention	Primary Outcome(s)	TMS Protocol		
					Location	Frequency Intensity	# Sessions
Chronic Pain: Neuropathic							
Ahmed, 2020[41] N=30	RCT 1 week	Patients with a diagnosis of diabetic neuropathy	rTMS and aerobic training exercises	Pain	Precentral motor cortex	20 Hz 80-90% RMT	5 sessions (daily)
Andre-Obadia, 2018[43] N=35	Randomized crossover trial NR	Patients with upper limb or facial neuropathic pain	rTMS	Pain	Hand or facial motor cortex	20 Hz 90% RMT	3 sessions (2 active, 1 sham)
Galhardoni, 2019[49] N=100	RCT 12 weeks	Patients with chronic central neuropathic pain	Deep rTMS	Pain	ACC or PSI	10 Hz 90% RMT	16 (daily for 5 days, then 1 session/wk for 11 wks)
Hosomi, 2020[51] N=144	RCT 5 weeks	Adult patients with neuropathic pain	rTMS	Pain	Primary motor cortex	5 Hz 90% RMT	5 sessions (daily), then 1 session/wk for 4 wks (responders only)
Kim, 2020[54] N=30	RCT 7 months	Patients with CNP	iTBS	Pain	Ipsilateral hemisphere	50 Hz 80% RMT	5 sessions (daily)
Quesada, 2020[68] N=42	Randomized crossover trial 7 months	Adult patients with medically refractory chronic central neuropathic pain	rTMS	Pain	Primary motor cortex	20 Hz 80% RMT	8 sessions over 9 wks
Shimizu, 2017[72] N=18	Randomized crossover trial 3 months	Patients with intractable neuropathic pain in lower limbs	Deep rTMS or rTMS	Pain	Primary motor cortex	5 Hz, 90% RMT	15 (5 consecutive sessions with each type of stimulation)
Sun, 2019[79] N=21	RCT 6 weeks	Right-handed inpatient rehab patients with neuropathic pain following SCI	rTMS	Pain	Left primary motor cortex	10 Hz 80% RMT	Daily sessions for 6 weeks, with 1-day interval per week
Chronic Pain: Fibromyalgia							
Abd Elghany, 2019[76] N=120	nRCT 1 month	Outpatients with FMS	rTMS	Pain	DLPFC	10 Hz NR	15 sessions (every other day for 1 month)

Atlas, 2019[42] N=30	RCT 3 weeks	Right-handed, female patients with FMS	rTMS	Pain	Left primary motor cortex or left DLPFC	10 Hz 90% RMT	15 (5 sessions/wk for 3 wks)
Bilir, 2020[44] N=20	RCT 6 weeks	Adult patients with diagnosis of FMS	rTMS	Pain	Left DLPFC	10 Hz 90% RMT	14 (5 days/wk for 2 wks, then 1 session/wk for 4 wks)
Cheng, 2019[45] N=20	RCT 2 weeks	Patients with FMS and MDD	rTMS	Pain	Left DLPFC	10 Hz 100% RMT	10 (5 sessions/wk for 2 wks)
Fitzgibbon, 2018[77] N=26	RCT 1 month	Patients with FMS	rTMS	Pain	Left DLPFC	10 Hz 120% RMT	20 (5 consecutive sessions/wk for 4 wks)
Guinot, 2019[50] N=39	RCT 6 months	Patients with FMS	rTMS + multicomponent therapy	Pain	Primary motor cortex	10 Hz 80% RMT	5 sessions/wk for 2 wks, then 12-wk decreasing maintenance phase
Chronic Pain: Headache							
Mattoo, 2019[63] N=30	RCT 8 weeks	Right-handed patients with history of headache >15 days a month for 3 months or more	rTMS	Pain	Right DLPFC	NR 110% RMT	20 (5 sessions/wk for 4 wks)
Sahu, 2019[70] N=41	RCT 2 weeks	Right-handed patients with a diagnosis of migraine with or without aura	iTBS	Headache symptoms	Left DLPFC	50 Hz 80% RMT	10 (2x/day for 5 days)
Chronic Pain: Complex Regional Pain Syndrome							
Gaertner, 2018[48] N=21	Cohort 2 weeks	Patients with CPRS	iTBS followed by TMS	Pain	Motor cortex to stimulate CPRS affected region	50 Hz (iTBS) then 10 Hz (TMS) 70% (iTBS) then 80% (TMS)	1 or 5 sessions over 5 days
PTSD							
Ahmadizadeh, 2018[40] N=65	RCT 4 weeks	Veterans with current combat-related PTSD symptoms	rTMS	PTSD symptoms	Bilateral or right DLPFC	20 Hz 100 % RMT	10 (3 sessions/wk for 2 wks then 2 sessions/wk for 2 wks)

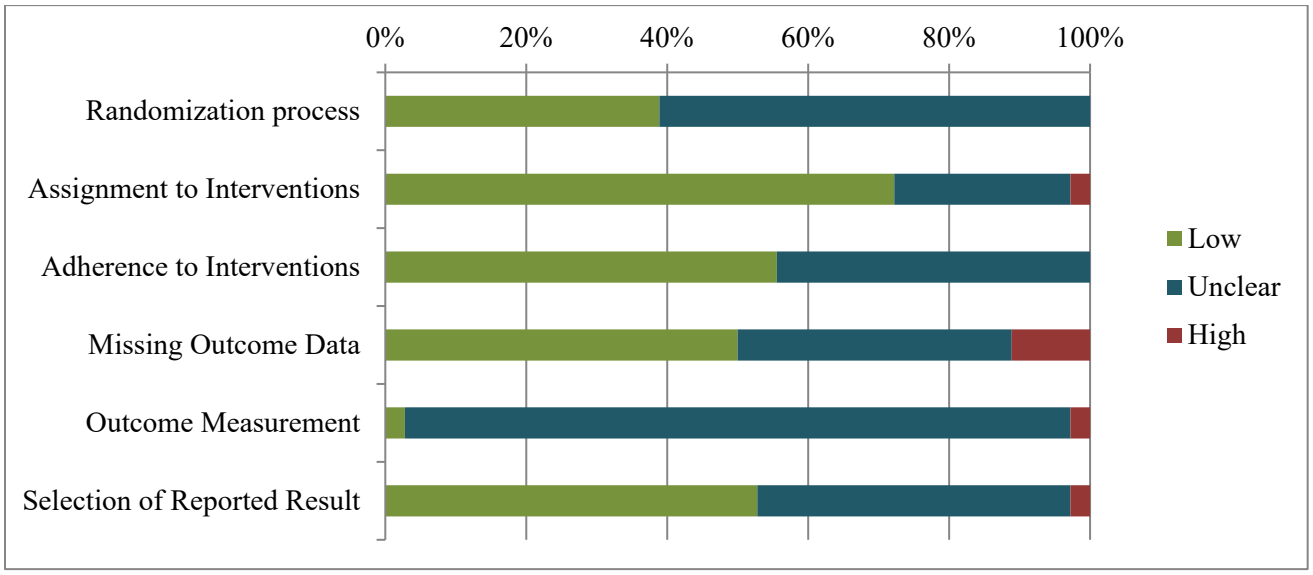
Fryml, 2019[47] N=8	RCT 8 weeks	Veterans (OIF/OEF) with combat-related PTSD	rTMS and Prolonged exposure therapy (PE)	PTSD symptoms	Right or left prefrontal cortex	10 Hz 120% RMT	8 (1 session/wk for 8 wks)
Isserles, 2013[53] N=30	RCT 4 weeks	Veterans with PTSD	Deep rTMS + traumatic imagery	PTSD symptoms	Prefrontal cortex	20 Hz 120% RMT	12 (3 sessions/wk for 4 wks)
Kozel, 2018[55] N=103	RCT 6 months	Veterans deployed to combat regions, 2001-present	rTMS + cognitive processing therapy	PTSD symptoms	Right DLPFC	1 Hz 110% RMT	12 (1 session/wk for 12 wks)
Kozel, 2019[56] N=35	RCT 3 months	Veterans with PTSD with and without depressive symptoms	rTMS	PTSD symptoms	Right DLPFC	1 Hz or 10 Hz 110% RMT	36 (timing NR)
Leong, 2020[58] N=31	RCT 3 months	Civilians with non-combat related PTSD	rTMS	PTSD symptoms	Right DLPFC	1 Hz or 10 Hz 120% RMT	10 (5 sessions/wk for 2 wks)
Nam, 2013[64] N=18	RCT 8 weeks	Patients with non-military related PTSD	rTMS	PTSD symptoms	Right prefrontal cortex	1 Hz 100% RMT	15 (5 consecutive sessions/wk for 3 wks)
Petrosino, 2020[65]* N=46	RCT 1 year	Veterans with PTSD	iTBS	Clinical relapse	Right DLPFC	50 Hz 80% RMT	10 sessions (5 consecutive sessions/wk for 2 weeks)
Philip, 2019[67]* N=50	RCT 1 month	Veterans with PTSD	iTBS	PTSD symptoms	Right DLPFC	50 Hz 80% RMT	10 sessions (5 consecutive sessions/wk for 2 weeks)
Philip, 2019[66] N=23	RCT 8 weeks	People with PTSD and MDD	Synchronized TMS (sTMS)	PTSD symptoms	NR	NR NR	20 (5 sessions/wk for 4 wks)
Watts, 2012[75] N=20	RCT 10 weeks	People with PTSD	rTMS	PTSD symptoms	Right DLPFC	1 Hz 90% RMT	10 sessions (5 consecutive days/wk for 2 wks)
TBI							
Choi, 2018[46] N=12	RCT 6 weeks	Adults with mild TBI and pain lasting ≥ 6 months	rTMS	Pain	Primary motor cortex	10 Hz 90% RMT	10 sessions (5 per wk for 2 wks)
Hoy, 2019[52] N=21	RCT 4 weeks	People with TBI with current depressive episode	rTMS	Depression symptoms	Left or right DLPFC	1 Hz (right), 10 Hz (left) 110% RMT	20 sessions (over 4 wks)

Lee, 2018[57] N=13	RCT 2 weeks	Patients with TBI without severe depression	rTMS + neurodevelopmental therapy	Depression symptoms	Right DLPFC	1 Hz 100% RMT	10 (5 consecutive sessions/wk for 2 wks)
Leung, 2016[59] N=24	RCT 4 weeks	Veterans with mild TBI and post-traumatic headache	rTMS (targeted by neuronavigated TMS)	Headache symptoms	Left motor cortex	10 Hz 80% RMT	3 sessions (within 1 wk)
Leung, 2018[60] N=29	RCT 4 weeks	Veterans with mild TBI related headache	rTMS (targeted by neuronavigated TMS)	Headache symptoms	Left prefrontal cortex	10 Hz 80% RMT	4 sessions (within 1 wk)
Manko, 2013[62] N=40	nRCT NR	People with severe TBI and prolonged coma	rTMS	Mental and physical comfort	NR	NR NR	NR
Neville, 2019[78] N=36	RCT 90 days	People with chronic TBI	rTMS	Change in executive function	Left DLPFC	10 Hz 110% RMT	10 sessions (daily)
Rao, 2019[69] N=34	RCT 16 weeks	People with TBI and MDD	rTMS	Depressive symptoms	Right DLPFC	1 Hz110% RMT	20 (5 consecutive sessions/wk for 4 wks)
Siddiqi, 2019[73] N=12	RCT NR	People with TBI and TRD	rTMS (targeted by resting-state network mapping)	Depressive symptoms	Left and right DLPFC	1 Hz (right), 10 Hz (left) 120% RMT	20 sessions (over 5 wks)
Stilling, 2020[74] N=20	RCT 6 months	People with post-TBI headache	rTMS	Headache symptoms	Left DLPFC	10 Hz 70 % RMT	10 (5 consecutive sessions/wk for 2 wks)
Opiate Addiction							
Liu, 2020[61] N=118	RCT 90 days	Male heroin use disorder patients	rTMS	Craving score: Subjective 0-100 scale	Left DLPFC	10 Hz or 1 Hz 100% RMT	20 sessions over 28 days
Shen, 2016[71] N=20	RCT 5 days	Heroin addicted adults	rTMS	Craving score: Subjective 0-100 scale	Left DLPFC	10 Hz 100% RMT	5 sessions (daily)

*Petrosino, 2020 and Philip, 2019 are two reports of the same study.

Abbreviations: TMS=Transcranial magnetic stimulation; RCT= Randomized controlled trial; rTMS=Repetitive transcranial magnetic stimulation; Hz=Hertz; RMT=Resting motor threshold; ACC=Anterior cingulate cortex; PSI=Posterior superior insula; nRCT=non-randomized controlled trial, DLPFC=Dorsolateral prefrontal cortex; CNP =Central neuropathic pain; iTBS=Intermittent theta-burst stimulation, SCI=Spinal cord injury; MDD=Major depressive disorder; TRD=Treatment resistant depression; wk/wks = week/weeks

Figure 3. Risk of Bias in Included Randomized Controlled Trials



CHRONIC PAIN

Overall Pain Reduction

A 2018 Cochrane systematic review[35] examined the use of non-invasive brain stimulation therapies for chronic pain. Forty-two studies on the effect of rTMS for pain were included. These studies measured pain severity using visual analog scales (VAS) or numerical rating scales (NRS). Overall, meta-analyses showed a significant reduction in pain associated with rTMS within 7 days post-intervention (SMD = -0.22, 95% CI [-0.29, -0.16]; 27 studies). Reductions in pain were also observed between 1 and 6 weeks post-intervention (SMD = -0.28, 95% CI [-0.61, 0.05]; 11 studies) and at greater than 6 weeks post-intervention (SMD = -0.14, 95% CI [-0.44, 0.17]; 4 studies), but these effects were nonsignificant. Significant improvement in reported quality of life (Fibromyalgia Impact Questionnaire) was observed within 7 days post-intervention (SMD = -10.8, 95% CI [-15.04, -6.55]; 4 studies). Minor and brief-duration adverse effects were commonly reported across studies and included headache, pain at stimulation site, and dizziness. Studies varied by type of pain conditions included and rTMS protocols used. Study quality was rated mostly as "unclear" and was limited by unclear blinding of participants (inadequate sham), small sample size, and short study duration.

Our search identified 17 controlled studies published since the end search date of this systematic review.[35] Findings from these studies are discussed by pain type, below.

Neuropathic Pain

8 controlled studies
Low SOE

18-144 participants
mean age 37-63

5 studies: reduced pain
3 studies: no reduction in pain (compared to control)

rTMS therapy may reduce pain (measured by VAS or NRS) in patients with neuropathic pain, but the evidence is limited by inconsistent findings, and unclear or lack of blinding of patients or outcome assessors, and unclear or inadequate handling of missing data in several studies. Among 8 controlled trials, 5 studies[43,54,68,72,79] reported reduction in pain with TMS compared to sham TMS, while 3 studies[41,49,51] reported no significant difference in pain between TMS and sham groups. In the 2 largest trials (N=100;[49] N=144[51]), no significant difference was found between rTMS and sham groups in pain reduction. Most studies reported shorter-term outcomes (1 to 6 weeks), but 3 studies reported outcomes at 3 to 7 months (1 study no pain reduction,[49] 2 studies pain reduction[68,72] compared to sham). A single study compared iTBS to sham iTBS,[54] and all other studies utilized rTMS. Studies varied with respect to pain areas (upper limb, lower limb, central neuropathic pain, *etc*), types of TMS (2 studies deep TMS,[49,72] 1 study intermittent theta-burst TMS[54]) and TMS protocols (target location, frequency, intensity, and number of sessions). Evidence from 3 case series[88,89,92] generally agreed with trial findings, indicating reductions in pain over time with TMS therapy.

Fibromyalgia


6 controlled studies
Low SOE


20-120 participants
mean age 45-50


All studies: no reduction in pain (compared to control)

In patients with fibromyalgia syndrome, rTMS therapy may be no better than sham rTMS therapy in reducing overall pain symptoms (measured by VAS or NRS).[42,44,45,76,50,77] This evidence is limited by small sample sizes (4 of 6 studies had 30 or fewer participants) and lack of or inadequate randomization in several studies. Six controlled studies reported reduction in pain outcomes in both rTMS and sham rTMS groups, with generally no significant differences in outcomes between groups. However, several studies reported greater reduction of pain with rTMS therapy for specific rTMS target locations (reduction in pain with primary motor cortex vs sham but not left DLPFC vs sham),[42] time points (reduction in pain with rTMS compared to sham at week 2 vs week 1, but no significant difference when comparing weekly pain scores),[45] or outcomes (more patients achieving 30% reduction in pain in TMS group compared to sham group, but no significant difference in average pain reduction between groups).[77] Most studies reported shorter-term outcomes (2 to 6 weeks), with the exception of 1 study reporting no significant reduction in pain at 6 months compared to control.[50] All studies used rTMS and targeted either the primary motor cortex[42,50] or the left DLPFC[42,44,45,77] with 10 Hz stimulation at 80-100% RMT, but the number and duration of TMS sessions varied among the studies.

Headache


2 controlled studies
Moderate SOE


30-41 participants
mean age 31-36

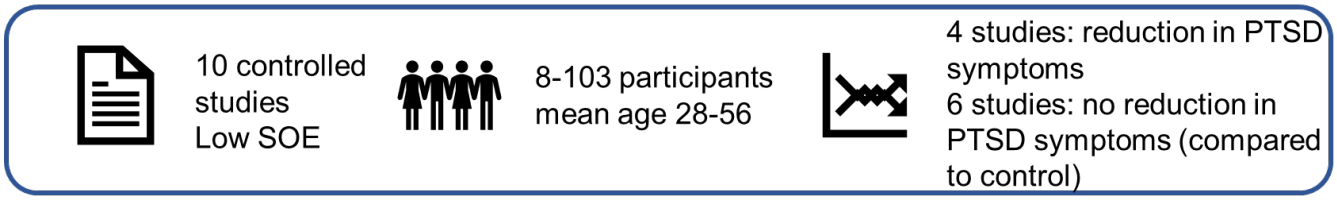

All studies: reduction in headache pain or symptoms (compared to control)

TMS therapy likely reduces headache pain and symptoms compared to sham TMS in patients with chronic headache or migraine,[63,70] but the evidence is limited by small sample sizes, and non-random allocation and unclear handling of missing data in 1 study.[70] Two studies reported decreases in pain (using NRS)[63] or migraine frequency, severity, and duration[70] at 8 to 12 weeks with rTMS therapy targeted to the right DLPFC[63] or iTBS therapy targeted to the left DLPFC[70] compared to sham.

Multiple or Other Pain Conditions

A single small cohort study and several case series examined multiple or other pain conditions. The cohort study[48] reported reductions in pain (measured by VAS and NRS) in patients with complex regional pain syndrome with both 1 or 5 sessions of iTBS stimulation immediately followed by rTMS, with no differences between groups. Since all patients in this study received some type of TMS stimulation, it is not possible to determine the effectiveness of TMS compared to sham. Three case series reported reductions in pelvic pain[91,93] and general pain (from multiple conditions)[90] over time with TMS therapy. These studies are limited by a study design without a control group.

POST TRAUMATIC STRESS DISORDER

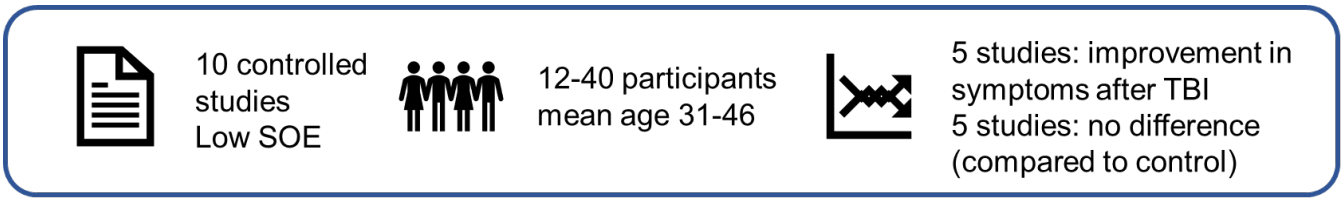


rTMS therapy may improve PTSD symptoms compared to sham, but evidence is limited by inconsistent findings and methodological limitations, including unclear or inappropriate handling of missing data, differential attrition between intervention groups, and unclear blinding in several studies. Among 10 controlled studies (in 11 publications),[40,47,53,55,56,64-67,75,58] most studies reported improvements in PTSD symptoms, as measured by the Clinician-Administered PTSD Scale (CAPS) or the PTSD Checklist (PCL). However, only 4 studies reported greater improvement in symptoms with TMS compared to sham. Among included studies, TMS protocols varied in target location, frequency, intensity, and number of sessions.

One study[40] reported a greater proportion of responders (defined as 2 or more standard deviations from the mean PCL score) with rTMS compared to sham, but no significant difference in mean PCL improvement between groups. Six studies were in Veterans with PTSD,[40,47,53,55,56,67] the largest of which (N=113)[55] reported improved PTSD symptoms at 6 months with rTMS therapy compared to control. Only 2 other studies reported outcomes beyond 8 weeks, and these studies found no significant difference in PTSD symptoms at 3 months compared to control.[56,58] Two studies compared different frequencies of rTMS stimulation: 1 study[55] found improved CAPS score with both 1 Hz and 10 Hz stimulation, but no significant difference between groups, while another study[58] found improved CAPS score with 1 Hz rTMS compared to sham, but not with 10 Hz rTMS compared to sham. Several case series[80,82,84-87,94] generally agreed with findings of randomized trials, reporting improvements in PTSD symptoms with rTMS therapy over time.

Two RCTs examined the effect of theta-burst TMS (iTBS)[65,67] or synchronized TMS (sTMS),[66] and found no significant differences between groups on PCL or CAPS scores at 2 to 4 weeks following treatment. In the study of sTMS, however, significantly fewer PCL items (symptoms) were rated as moderate or higher severity among participants receiving sTMS compared to sham 4 weeks post-treatment. The iTBS study also examined clinical relapse – defined as suicide attempt, suicide-related death, inpatient psychiatric hospitalization, or need for retreatment with rTMS – at 1 year and found that fewer patients had clinical relapse with iTBS compared to sham.[65] One case series[82] examined EEG-guided magnetic resonance therapy (MeRT^{SM}) and reported improvement in PTSD symptoms after treatment. We also identified 1 RCT (abstract only)[96] that reported improvement in PTSD symptoms in 8 subjects with use of MeRT^{SM}, but there was no significant difference in outcomes between MeRT^{SM} and sham therapy.

TRAUMATIC BRAIN INJURY



rTMS therapy may improve symptoms after TBI, but evidence is limited by inconsistent findings, small sample sizes, and unclear blinding of outcome assessors and unclear or inadequate handling of missing data in several studies. TBI can result in lasting cognitive sequelae, mood sequelae, and other symptoms, and we included any study that examined the effects of TMS on any symptom subsequent to any severity (mild, moderate, or severe) TBI. Included studies reported on a variety of symptoms following TBI, including pain, depressive symptoms, headache, and executive function. Most studies included patients with mild to moderate TBI,[46,57,59,60,69,73,74] but 3 studies[52,62,78] included patients with severe TBI exclusively or along with other TBI severity levels.

rTMS therapy improved headache symptoms,[60,74,83] and overall pain (using NRS)[46] compared to sham therapy in patients with TBI. Two studies in Veterans[60,83] reported improvement in headache symptoms after mild TBI at 4 weeks with rTMS compared to sham therapy, while another study reported no significant difference in headache symptoms with rTMS after mild TBI compared to sham therapy at 6 months in a sample of patients from Canada.[74] Four studies[52,57,69,73] reported improved depressive symptoms with rTMS therapy after mild to moderate TBI, but there were no significant differences between rTMS and sham therapy in 3 of the 4 studies. One study[69] reported no significant difference in rates of depression response or remission after mild to moderate TBI between rTMS and sham groups.

Seven studies examined the effect of rTMS therapy on executive function in patients after mild to severe TBI.[52,57,60,69,74,78,83] Most studies found some improvement in function, but only 2 studies reported differences between rTMS and sham groups.[57,83] Several studies[46,62,74] also examined the effect of rTMS on quality of life. Most studies reported improvements in quality of life overall, but only one study reported significant differences between rTMS and sham therapy.[62]

Most studies reported outcomes at 2 to 6 weeks, but 3 studies reported no significant difference in TBI symptoms at 3 to 6 months compared to control.[69,74,78] All studies examined rTMS, but varied in target location, frequency, intensity, and number of sessions. Two case series[81,83] generally agreed with these findings, reporting improvements in post-concussive symptoms and pain with rTMS therapy over time.

OPIATE ADDICTION

In adults with heroin addiction, rTMS therapy likely improves craving scores compared to sham therapy.[61,71] Only 2 studies examined the effectiveness of rTMS for opiate use, and these studies are limited by unclear blinding of outcome assessors and/or participants and unclear handling of missing data. Both studies reported decreases in craving scores (0 to 100 craving scale) with rTMS therapy targeting the left DLPFC at 10 Hz and 100% resting motor threshold compared to sham rTMS. These studies assessed rTMS effects at different timepoints, ranging from 5 days after treatment[71] to 90 days after treatment.[61]

ADVERSE EFFECTS OF TMS

TMS therapy appears to be well-tolerated among patients with chronic pain, PTSD, TBI, and opiate addiction. About half of the included studies reported mild side effects including headache, nausea, pain at the target location, and dizziness, and 8 studies[40,48,55,56,58,61,68,69] reported withdrawal of a small number of patients from the study due to side effects. No serious adverse events were reported in any included studies.

SUMMARY AND DISCUSSION

rTMS therapy is widely used for treatment of MDD, and there is interest in expanding its use for other conditions including chronic pain, PTSD, TBI, opiate addiction, and sexual trauma. Our review of recent studies and systematic reviews suggests that rTMS therapy may be effective for treating chronic pain, PTSD, TBI, and opiate addiction. Importantly, however, about half of controlled studies examining the efficacy of TMS for reducing symptoms of chronic pain, PTSD, and TBI found that reduction in symptoms did not significantly differ between TMS and control groups (sham TMS). The majority of studies utilized rTMS, with few studies examining novel forms of TMS (*eg*, iTBS, sTMS, or EEG-guided TMS) and no studies directly compared rTMS to other forms of TMS.

Most studies examined differences in mean changes in outcome scores, which may yield statistically significant findings, but the magnitude of the difference may not translate into a clinically meaningful outcome for the patient. The 3 studies[56,69,77] which examined symptom response or remission reported no significant difference between treatment and control groups in fibromyalgia pain,[77] PTSD,[56] or TBI[69] symptom response or remission. Further, only 2 studies evaluated the efficacy of rTMS for opiate addiction,[61,71] and no studies specifically examined TMS as a therapy for sexual trauma. Some patients with PTSD may have experienced sexual trauma, but less than half (4 of 10) of the included studies in patients with PTSD reported trauma history. Among these, only 2 studies listed patients with sexual trauma (range: 10 to 52% of patients). Further research on effectiveness of TMS among persons who have experienced sexual trauma, regardless of whether they have received a PTSD diagnosis, is needed.

In addition to these mixed or limited findings, there was considerable variation in patient populations, outcomes assessed, and TMS protocols implemented among the included studies. As a result, the effectiveness of TMS therapy may vary by patient factors (age, sex, sleep deprivation, *etc*) and technical factors (TMS coil type and position, stimulation parameters, *etc*).[97] Reviewed studies also varied methodologically (*eg*, sample size, outcomes and number of timepoints assessed, *etc*), which could contribute to the inconsistency in the observed effects of TMS therapy. Moreover, the generally small sample sizes of studies could have limited statistical power to detect differences between TMS and control conditions. Despite the mixed effectiveness findings, TMS was found to be a safe and well-tolerated therapy.

Practical aspects of more widely implementing TMS in a healthcare system need further consideration, particularly as they relate to patient and provider burden, cost, and accessibility. TMS therapy generally consists of daily therapy, usually for a period of 4 to 6 weeks, and patients must travel daily to a designated clinic where TMS is offered. This may present challenges for Veterans living in rural areas or for those with transportation limitations. Although TMS therapy can be provided by a trained technician, a physician must perform a formal assessment to determine if TMS therapy is appropriate, followed by a prescription for the therapy. Limitations in staff availability, training requirements, and the need for a designated clinic site with TMS technology may be barriers in expanding the use of TMS.

Pairing these considerations with the findings that suggest potential effectiveness and high patient safety and acceptability, it is reasonable to conclude that TMS therapy, in particular rTMS, could be considered a treatment option for patients who have exhausted other available options for treatment of chronic pain, PTSD, TBI, and opiate addiction. A limited expansion of

TMS for this purpose would provide further information about TMS implementation feasibility, while allowing additional efficacy and effectiveness trials to be conducted.

LIMITATIONS

The evidence included in this review has several important limitations. Studies were mostly small, and varied in patient populations, outcomes, and TMS protocols, making generalizations of findings across studies difficult. Studies were also inconsistent in their methodological quality and findings, resulting in mostly low strength of evidence for the effect of TMS on chronic pain, PTSD, TBI, and opiate addiction (Table 2, Appendix H in supplemental materials). Additionally, although several studies followed patients for up to 7 months, most studies assessed outcomes at only 1 to 4 weeks. Without longer follow-up periods, the durability of symptom improvement following TMS remains unclear. Finally, no studies were found that specifically examined the effect of TMS among individuals who experienced sexual trauma or that examined differential effects of TMS among those with PTSD and sexual trauma compared to those with PTSD and other trauma history.

Limitations of our review methods include restricting our literature search date for chronic pain to the end search date of the O'Connell 2018[35] review. Additionally, we used a second reviewer check during study selection, data abstraction, and quality assessment rather than dual independent review.

Table 2. Evidence Summary

Outcome	Studies (N)	Strength of Evidence (SOE) Summary
Chronic Pain: Neuropathic		
Pain	8 RCTs (N=420) 7 rTMS,[41,43,49,51,68,72,79] 1 iTBS[54]	Low SOE rTMS may decrease pain compared to sham, but confidence is limited by inconsistent findings and low to high RoB among studies.
*Chronic Pain: Fibromyalgia**		
Pain	5 RCTs (N=135)[42,44,45,50,77] and 1 nRCT (N=120)[76]	Low SOE rTMS may be no better than sham in decreasing pain compared to sham, but confidence is limited by small sample sizes and low to high RoB among studies.
Chronic Pain: Headache		
Headache pain and symptoms	2 RCTs (N=71) 1 rTMS,[63] 1 iTBS[70]	Moderate SOE TMS likely decreases headache pain and symptoms compared to sham but confidence is limited by small sample size and low to unclear RoB among studies.
PTSD		
PTSD symptoms	10 RCTs (N=383) 8 rTMS,[40,47,53,55,56,58,64,75] 1 iTBS,[67] 1 sTMS[66]	Low SOE rTMS may improve PTSD symptoms compared to sham, but confidence is limited by inconsistent findings and low to high RoB among studies.
Clinical relapse**	1 RCT (N=46), iTBS[65]	Low SOE iTBS may improve clinical relapse compared to sham, but confidence is limited by a single study.

Outcome	Studies (N)	Strength of Evidence (SOE) Summary
*TBI**		
Pain	1 RCTs (N=12)[46]	Low SOE rTMS may improve pain compared to sham, but confidence is limited confidence by a single, small study with unclear RoB.
Depression symptoms	4 RCTs (N=83)[52,57,69,73]	Low SOE rTMS may improve depressive symptoms compared to sham, but confidence is limited by inconsistent findings and unclear RoB among studies.
Headache symptoms	3 RCTs (N=73)[60,74,83]	Low SOE rTMS may improve headache symptoms compared to sham, but confidence is limited by inconsistent findings and low to unclear RoB among studies.
Quality of Life	2 RCTs[46,74] (N=32) and 1 nRCT (N=12)[62]	Low SOE It is unclear whether rTMS improves quality of life in patients with TBI, and confidence is limited by inconsistent findings and low to high RoB among studies
Function	7 RCTs (N=177)[52,57,60,69,74,78,83]	Low SOE It is unclear whether rTMS improves function in patients with TBI, and confidence is limited by inconsistent findings and unclear RoB among studies
*Opiate Addiction**		
Craving Score	2 RCTs (N=138)[61,71]	Moderate SOE rTMS likely improves craving scores in opiate addicted adults compared to sham, but confidence is limited by unclear RoB among studies.

1 cohort study, Gaertner 2018, examined iTBS for chronic regional pain syndrome, not included in table
*All studies examined rTMS
**Defined as suicide attempt, suicide-related death, inpatient psychiatric hospitalization, or need for rTMS retreatment
Abbreviations: SOE= Strength of Evidence, RCT= Randomized controlled trial, rTMS=Repetitive transcranial magnetic stimulation, iTBS= Intermittent theta-burst stimulation, RoB=Risk of Bias, nRCT=non-randomized controlled trial, PTSD=Post traumatic stress disorder, sTMS=Synchronized TMS; TBI=Traumatic brain injury

GAPS AND FUTURE RESEARCH

Findings of this review suggest that it would be premature to conclude that TMS is an effective therapy for chronic pain, PTSD, TBI, and opiate addiction among Veteran populations. Additional studies with larger samples, robust methodology (*ie*, appropriate randomization and matching procedures), and standardized TMS parameters (*ie*, following various TMS guidance for specific patient populations, if available)[98] are needed to provide more conclusive evidence. To address limitations to the existing evidence on the effectiveness of TMS for conditions other than MDD, future studies should consider the following:

- Although many RCTs were identified, most were small. This may be an inherent limitation to studies due to the cost of neurotherapies. However, greater resource investment would be beneficial to clarify the effectiveness of TMS for chronic pain, PTSD, TBI, and opiate addiction.

- No studies examined the use of TMS specifically for sexual trauma, and studies in this area are needed to determine the effectiveness of TMS therapy among individuals who have experienced sexual trauma.

- Studies directly comparing novel TMS therapy such as theta-burst or EEG-guided TMS to rTMS are needed to determine if these therapies offer any advantage over rTMS.

CONCLUSIONS

rTMS therapy may reduce symptoms in people with chronic pain, PTSD, TBI, and opiate addiction and could be a treatment option for patients who have exhausted all other available options. However, findings are mixed and there is wide variability in patient and intervention characteristics among the included studies. Future research should focus on studies with larger samples, robust methodology, standardized TMS parameters, and direct comparisons of rTMS to novel TMS therapies (*eg*, iTBS, sTMS, or EEG-guided TMS). Practical aspects of more widely implementing TMS in a health care system, including patient and provider burden, cost, and accessibility, also need further consideration.

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Operational Partners

Operational partners are system-level stakeholders who have requested the report to inform decision-making. They recommend Technical Expert Panel (TEP) participants; assure VA relevance; help develop and approve final project scope and timeframe for completion; provide feedback on draft report; and provide consultation on strategies for dissemination of the report to field and relevant groups.

Christine Eickhoff
Health System Specialist
10P10 Office of Community Engagement (OCE)

Peer Reviewers

The Coordinating Center sought input from external peer reviewers to review the draft report and provide feedback on the objectives, scope, methods used, perception of bias, and omitted evidence. Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The Coordinating Center and the ESP Center work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Evidence Brief: Transcranial Magnetic Stimulation (TMS) for Chronic Pain, PTSD, TBI, Opioid Addiction, and Sexual Trauma

Supplementary Materials

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APPENDIX A: VA/DOD GUIDELINES

Year	Title	Condition	TMS-related guidance
2017	Management of Posttraumatic Stress Disorder and Acute Stress Reaction 2017	PTSD/Acute Stress Reaction	There is insufficient evidence to recommend for or against the following somatic therapies: repetitive transcranial magnetic stimulation (rTMS), electroconvulsive therapy (ECT), hyperbaric oxygen therapy (HBOT), stellate ganglion block (SGB), or vagal nerve stimulation (VNS).
2020	The Primary Care Management of Headache	Headache	There is insufficient evidence to recommend for or against the following for headache: •Transcranial magnetic stimulation •Transcranial direct current stimulation •External trigeminal nerve stimulation •Supraorbital electrical stimulation
2016	Management of Concussion-mild Traumatic Brain Injury (mTBI)	Concussion/mild Traumatic Brain Injury (mTBI)	There is no evidence to suggest for or against the use of any particular modality for the treatment (including rTMS) of tinnitus after mTBI.

APPENDIX B: SEARCHES

1. Search for current systematic reviews (limited to last 7 years) Date Searched: 08-06-2020			
A. Bibliographic Databases:	**#**	**Search Statement**	**Results:**
MEDLINE: Systematic Reviews **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R)** 1946 to February 05, 2020	1	Transcranial Magnetic Stimulation/	11013
	2	(transcranial magnetic stimulation$1 or rTMS or TMS).mp.	21201
	3	1 or 2	21201
	4	(systematic review.ti. or meta-analysis.pt. or meta-analysis.ti. or systematic literature review.ti. or this systematic review.tw. or pooling project.tw. or (systematic review.ti,ab. and review.pt.) or meta synthesis.ti. or meta-analy*.ti. or integrative review.tw. or integrative research review.tw. or rapid review.tw. or umbrella review.tw. or consensus development conference.pt. or practice guideline.pt. or drug class reviews.ti. or cochrane database syst rev.jn. or acp journal club.jn. or health technol assess.jn. or evid rep technol assess summ.jn. or jbi database system rev implement rep.jn. or (clinical guideline and management).tw. or ((evidence based.ti. or evidence-based medicine/ or best practice*.ti. or evidence synthesis.ti,ab.) and (((review.pt. or diseases category/ or behavior.mp.) and behavior mechanisms/) or therapeutics/ or evaluation studies.pt. or validation studies.pt. or guideline.pt. or pmcbook.mp.)) or (((systematic or systematically).tw. or critical.ti,ab. or study selection.tw. or ((predetermined or inclusion) and criteri*).tw. or exclusion criteri*.tw. or main outcome measures.tw. or standard of care.tw. or standards of care.tw.) and ((survey or surveys).ti,ab. or overview*.tw. or review.ti,ab. or reviews.ti,ab. or search*.tw. or handsearch.tw. or analysis.ti. or critique.ti,ab. or appraisal.tw. or (reduction.tw. and (risk/ or risk.tw.) and (death or recurrence).mp.)) and ((literature or articles or publications or publication or bibliography or bibliographies or published).ti,ab. or pooled data.tw. or unpublished.tw. or citation.tw. or citations.tw. or database.ti,ab. or internet.ti,ab. or textbooks.ti,ab. or references.tw. or scales.tw. or papers.tw. or datasets.tw. or trials.ti,ab. or meta-analy*.tw. or (clinical and studies).ti,ab. or treatment outcome/ or treatment outcome.tw. or pmcbook.mp.))) not (letter or newspaper article).pt.	382964
	5	3 and 4	717
	6	limit 5 to english language	686
	7	limit 6 to last 7 years	545
CDSR: Protocols and Reviews **EBM Reviews - Cochrane Database of Systematic Reviews** 2005 to February 4, 2020	1	Transcranial Magnetic Stimulation/	0
	2	(transcranial magnetic stimulation$1 or rTMS or TMS).mp.	68
	3	1 or 2	68
	4	limit 3 to last 7 years	47

2. Search for systematic reviews currently under development (includes forthcoming reviews & protocols) **Date Searched: 08-06-20**		
D. Under development:	**Evidence:**	**Results:**
PROSPERO (SR registry)	http://www.crd.york.ac.uk/PROSPERO/ Search: TMS; transcranial magnetic stimulation	0
DoPHER (SR Protocols)	http://eppi.ioe.ac.uk/webdatabases4/Intro.aspx?ID=9 Search: TMS; transcranial magnetic stimulation	0
Cochrane Database of Systematic Reviews: Protocols	http://www.ohsu.edu/xd/education/library/ See Cochrane search above	0

3. Search for primary literature **Date searched: 08-15-20**		
MEDLINE [Ovid MEDLINE(R) ALL 1946 to July 14, 2020]		
#	**Search Statement**	**Results**
1	Transcranial Magnetic Stimulation/	11396
2	(transcranial magnetic stimulation$1 or rTMS or TMS or (repetitive adj transcranial magnetic stimulation$1) or (single-pulse adj transcranial magnetic stimulation$1) or (paired?pulse adj transcranial magnetic stimulation$1)).ti,ab,kw.	20349
3	1 or 2	21918
4	Chronic Pain/	14451
5	(chronic adj1 pain).ti,ab,kw.	36934
6	4 or 5	43337
7	3 and 6	246
8	limit 7 to english language	236
9	limit 8 to yr=”2017-Current”	77
CINAHL [EBSCO]		
#	**Search Statement**	**Results**
1	(MH "Transcranial Magnetic Stimulation")	1234
2	TI ((transcranial magnetic stimulation# or rTMS or TMS or (repetitive N1 transcranial magnetic stimulation#) or (single-pulse N1 transcranial magnetic stimulation#) or (paired pulse N1 transcranial magnetic stimulation#))) OR AB ((transcranial magnetic stimulation# or rTMS or TMS or (repetitive N1 transcranial magnetic stimulation#) or (single-pulse N1 transcranial magnetic stimulation#) or (paired?pulse N1 transcranial magnetic stimulation#)))	3637
3	1 or 2	3896
4	(MH "Chronic Pain")	23575
5	TI (chronic N1 pain) OR AB (chronic N1 pain)	27466
6	4 or 5	38370
7	3 and 6	118

8	limit 7 to english language	116
9	limit 8 to 2017-Current	30

CCRCT [EBM Reviews - Cochrane Central Register of Controlled Trials June 2020]

#	Search Statement	Results
1	Transcranial Magnetic Stimulation/	1360
2	(transcranial magnetic stimulation$1 or rTMS or TMS or (repetitive adj transcranial magnetic stimulation$1) or (single-pulse adj transcranial magnetic stimulation$1) or (paired?pulse adj transcranial magnetic stimulation$1)).ti,ab,kw.	5643
3	1 or 2	5823
4	Chronic Pain/	2241
5	(chronic adj1 pain).ti,ab,kw.	8487
6	4 or 5	9437
7	3 and 6	139
8	limit 7 to english language	90
9	limit 8 to yr="2017-Current"	37

4. Search for primary literature - TMS-all + PTSD/TBI/Opioid addiction/MST
Date searched: 08-10-20

MEDLINE [Ovid MEDLINE(R) ALL 1946 to August 07, 2020]

#	Search Statement	Results
1	exp Transcranial Magnetic Stimulation/ or Magnetic Stimulation Therapy/	12590
2	(TMS or ((transcrani* or crani* or brain*) adj4 (electrostim* or electro-stim* or electrotherap* or electro-therap*)) or electrical stimulation or electrical treatment or ((brain* or cortex or cortical or transcranial* or cranial or magneti*) adj4 stimulat*) or (transcranial magnetic stimulation or rTMS or cranial electrostimulation or cranial electrotherapy)).ti,ab,kw.	95929
3	(MeRT or magnetic eResonance therapy or magnetic e-Resonance therapy).ti,ab,kw.	268
4	(magnetic EEG?EKG guidance resonance therapy or magnetic EEG guided resonance therapy or magnetic EEG-guided resonance therapy or magnetic EKG-guided resonance therapy or magnetic EKG-guided resonance therapy).ti,ab,kw.	0
5	(EEG?EKG guided TMS or EEG guided TMS or EEG-guided TMS or EKG guided TMS or EKG-guided TMS or EEG guided transcranial magnetic stimulation or EEG-guided transcranial magnetic stimulation or EKG guided transcranial magnetic stimulation or EKG guided transcranial magnetic stimulation or q-EEG or quantitative EEG).ti,ab,kw.	1402
6	or/1-5	99318
7	Stress Disorders, Post-Traumatic/ or exp Brain Injuries, Traumatic/ or exp Opioid-Related Disorders/ or Sexual Harassment/ or exp Sex Offenses/	96630
8	(PTSD or post-traumatic stress disorder or posttraumatic stress disorder or post-traumatic stress disorders or posttraumatic stress disorders or post-traumatic neuroses or posttraumatic neuroses or moral injury or moral injuries).ti,ab,kw.	34503
9	(TBI or TBIs or traumatic brain injury or traumatic brain injuries or brain trauma or brain traumas or traumatic encephalopathy or traumatic encephalopathies).ti,ab,kw.	44065
10	(opioid related disorders or opioid-related disorders or opioid addiction or opioid addictions or opioid dependence or opioid dependences or opiate abuse or opiate abuses or opiate dependence or opiate addiction or opioid abuse or opioid abuses).ti,ab,kw.	7202

11	((sexual* adj1 (trauma or abuse or violence or harassment or assault or assults or assulted) or (sex* adj1 offense or offenses) or rape or raped)).ti,ab,kw.	30052
12	or/7-11	160123
13	6 and 12	802
14	limit 13 to english language	770
15	limit 14 to yr=”2012-Current”	541

CINAHL [EBSCO]

#	Search Statement	Results
1	(MH "Transcranial Magnetic Stimulation")	1215
2	TI ((TMS or ((transcrani* or crani* or brain*) adj4 (electrostim* or electro-stim* or electrotherap* or electro-therap*)) or electrical stimulation or electrical treatment or ((brain* or cortex or cortical or transcranial* or cranial or magneti*) adj4 stimulat*) or (transcranial magnetic stimulation or rTMS or cranial electrostimulation or cranial electrotherapy))) OR AB ((TMS or ((transcrani* or crani* or brain*) adj4 (electrostim* or electro-stim* or electrotherap* or electro-therap*)) or electrical stimulation or electrical treatment or ((brain* or cortex or cortical or transcranial* or cranial or magneti*) adj4 stimulat*) or (transcranial magnetic stimulation or rTMS or cranial electrostimulation or cranial electrotherapy))) OR SU ((TMS or ((transcrani* or crani* or brain*) adj4 (electrostim* or electro-stim* or electrotherap* or electro-therap*)) or electrical stimulation or electrical treatment or ((brain* or cortex or cortical or transcranial* or cranial or magneti*) adj4 stimulat*) or (transcranial magnetic stimulation or rTMS or cranial electrostimulation or cranial electrotherapy)))	10359
3	TI ((MeRT or magnetic eResonance therapy or magnetic e-Resonance therapy)) OR AB ((MeRT or magnetic eResonance therapy or magnetic e-Resonance therapy)) OR SU ((MeRT or magnetic eResonance therapy or magnetic e-Resonance therapy))	40
4	TI ((magnetic EEG?EKG guidance resonance therapy or magnetic EEG guided resonance therapy or magnetic EEG-guided resonance therapy or magnetic EKG-guided resonance therapy or magnetic EKG-guided resonance therapy)) OR AB ((magnetic EEG?EKG guidance resonance therapy or magnetic EEG guided resonance therapy or magnetic EEG-guided resonance therapy or magnetic EKG-guided resonance therapy or magnetic EKG-guided resonance therapy)) OR SU ((magnetic EEG?EKG guidance resonance therapy or magnetic EEG guided resonance therapy or magnetic EEG-guided resonance therapy or magnetic EKG-guided resonance therapy or magnetic EKG-guided resonance therapy))	0
5	TI ((EEG?EKG guided TMS or EEG guided TMS or EEG-guided TMS or EKG guided TMS or EKG-guided TMS or EEG guided transcranial magnetic stimulation or EEG-guided transcranial magnetic stimulation or EKG guided transcranial magnetic stimulation or EKG guided transcranial magnetic stimulation or q-EEG or quantitative EEG)) OR AB ((EEG?EKG guided TMS or EEG guided TMS or EEG-guided TMS or EKG guided TMS or EKG-guided TMS or EEG guided transcranial magnetic stimulation or EEG-guided transcranial magnetic stimulation or EKG guided transcranial magnetic stimulation or EKG guided transcranial magnetic stimulation or q-EEG or quantitative EEG)) OR SU ((EEG?EKG guided TMS or EEG guided TMS or EEG-guided TMS or EKG guided TMS or EKG-guided TMS or EEG guided transcranial magnetic stimulation or EEG-guided transcranial magnetic stimulation or EKG guided transcranial magnetic stimulation or EKG guided transcranial magnetic stimulation or q-EEG or quantitative EEG))	226
6	S1 OR S2 OR S3 OR S4 OR S5	10622
7	(MH "Stress Disorders, Post-Traumatic+") OR (MH "Brain Injuries+") OR (MH "Sexual Harassment") OR (MH "Substance Use Disorders+")	214680
8	TI ((PTSD or post-traumatic stress disorder or posttraumatic stress disorder or post-traumatic stress disorders or posttraumatic stress disorders or post-traumatic	16203

	neuroses or posttraumatic neuroses or moral injury or moral injuries)) OR AB ((PTSD or post-traumatic stress disorder or posttraumatic stress disorder or post-traumatic stress disorders or posttraumatic stress disorders or post-traumatic neuroses or posttraumatic neuroses or moral injury or moral injuries)) OR SU ((PTSD or post-traumatic stress disorder or posttraumatic stress disorder or post-traumatic stress disorders or posttraumatic stress disorders or post-traumatic neuroses or posttraumatic neuroses or moral injury or moral injuries))	
9	TI ((TBI or TBIs or traumatic brain injury or traumatic brain injuries or brain trauma or brain traumas or traumatic encephalopathy or traumatic encephalopathies)) OR AB ((TBI or TBIs or traumatic brain injury or traumatic brain injuries or brain trauma or brain traumas or traumatic encephalopathy or traumatic encephalopathies)) OR SU ((TBI or TBIs or traumatic brain injury or traumatic brain injuries or brain trauma or brain traumas or traumatic encephalopathy or traumatic encephalopathies))	17087
10	TI ((opioid related disorders or opioid-related disorders or opioid addiction or opioid addictions or opioid dependence or opioid dependences or opiate abuse or opiate abuses or opiate dependence or opiate addiction or opioid abuse or opioid abuses)) OR AB ((opioid related disorders or opioid-related disorders or opioid addiction or opioid addictions or opioid dependence or opioid dependences or opiate abuse or opiate abuses or opiate dependence or opiate addiction or opioid abuse or opioid abuses)) OR SU ((opioid related disorders or opioid-related disorders or opioid addiction or opioid addictions or opioid dependence or opioid dependences or opiate abuse or opiate abuses or opiate dependence or opiate addiction or opioid abuse or opioid abuses))	3476
11	TI (((sexual* adj1 (trauma or abuse or violence or harassment or assault or assults or assulted) or (sex* adj1 offense or offenses) or rape or raped))) OR AB (((sexual* adj1 (trauma or abuse or violence or harassment or assault or assults or assulted) or (sex* adj1 offense or offenses) or rape or raped))) OR SU (((sexual* adj1 (trauma or abuse or violence or harassment or assault or assults or assulted) or (sex* adj1 offense or offenses) or rape or raped)))	6905
12	S7 or S8 or S9 or S10 or S11	228968
13	S6 and S12	283
14	limit 13 to english language	282
15	limit 14 to yr=”2012-Current”	191
CCRCT [EBM Reviews - Cochrane Central Register of Controlled Trials July 2020]		
#	**Search Statement**	**Results**
1	exp Transcranial Magnetic Stimulation/ or Magnetic Stimulation Therapy/	1537
2	(TMS or ((transcrani* or crani* or brain*) adj4 (electrostim* or electro-stim* or electrotherap* or electro-therap*)) or electrical stimulation or electrical treatment or ((brain* or cortex or cortical or transcranial* or cranial or magneti*) adj4 stimulat*) or (transcranial magnetic stimulation or rTMS or cranial electrostimulation or cranial electrotherapy)).ti,ab,kw.	17132
3	(MeRT or magnetic eResonance therapy or magnetic e-Resonance therapy).ti,ab,kw.	8
4	(magnetic EEG?EKG guidance resonance therapy or magnetic EEG guided resonance therapy or magnetic EEG-guided resonance therapy or magnetic EKG-guided resonance therapy or magnetic EKG-guided resonance therapy).ti,ab,kw.	0
5	(EEG?EKG guided TMS or EEG guided TMS or EEG-guided TMS or EKG guided TMS or EKG-guided TMS or EEG guided transcranial magnetic stimulation or EEG-guided transcranial magnetic stimulation or EKG guided transcranial magnetic stimulation or EKG guided transcranial magnetic stimulation or q-EEG or quantitative EEG).ti,ab,kw.	309
6	or/1-5	17606

7	Stress Disorders, Post-Traumatic/ or exp Brain Injuries, Traumatic/ or exp Opioid-Related Disorders/ or Sexual Harassment/ or exp Sex Offenses/	6821
8	(PTSD or post-traumatic stress disorder or posttraumatic stress disorder or post-traumatic stress disorders or posttraumatic stress disorders or post-traumatic neuroses or posttraumatic neuroses or moral injury or moral injuries).ti,ab,kw.	5644
9	(TBI or TBIs or traumatic brain injury or traumatic brain injuries or brain trauma or brain traumas or traumatic encephalopathy or traumatic encephalopathies).ti,ab,kw.	4539
10	(opioid related disorders or opioid-related disorders or opioid addiction or opioid addictions or opioid dependence or opioid dependences or opiate abuse or opiate abuses or opiate dependence or opiate addiction or opioid abuse or opioid abuses).ti,ab,kw.	2061
11	(sexual* trauma or sexual* abuse or sexual* violence or sex* offense or sex* offenses or sexual* harassment or sexual* assault or sexual* assaults or sexual* assaulted or rape or raped).ti,ab,kw.	1531
12	or/7-11	15898
13	6 and 12	418
14	limit 13 to english language	230
15	limit 14 to yr="2012-Current"	202
PsycINFO [Ovid, APA PsycInfo 1806 to August Wk 1 2020]		
#	**Search Statement**	**Results**
1	exp Transcranial Magnetic Stimulation/	8425
2	(TMS or ((transcrani* or crani* or brain*) adj4 (electrostim* or electro-stim* or electrotherap* or electro-therap*)) or electrical stimulation or electrical treatment or ((brain* or cortex or cortical or transcranial* or cranial or magneti*) adj4 stimulat*) or (transcranial magnetic stimulation or rTMS or cranial electrostimulation or cranial electrotherapy)).ti,ab,id.	31753
3	(MeRT or magnetic eResonance therapy or magnetic e-Resonance therapy).ti,ab,id.	25
4	(magnetic EEG?EKG guidance resonance therapy or magnetic EEG guided resonance therapy or magnetic EEG-guided resonance therapy or magnetic EKG-guided resonance therapy or magnetic EKG-guided resonance therapy).ti,ab,id.	0
5	(EEG?EKG guided TMS or EEG guided TMS or EEG-guided TMS or EKG guided TMS or EKG-guided TMS or EEG guided transcranial magnetic stimulation or EEG-guided transcranial magnetic stimulation or EKG guided transcranial magnetic stimulation or EKG guided transcranial magnetic stimulation or q-EEG or quantitative EEG).ti,ab,id.	848
6	or/1-5	32760
7	exp Posttraumatic Stress Disorder/ or exp Traumatic Brain Injury/ or exp "Opioid Use Disorder"/ or exp Sexual Harassment/ or exp Sex Offenses/	92255
8	(PTSD or post-traumatic stress disorder or posttraumatic stress disorder or post-traumatic stress disorders or posttraumatic stress disorders or post-traumatic neuroses or posttraumatic neuroses or moral injury or moral injuries).ti,ab,id.	42280
9	(TBI or TBIs or traumatic brain injury or traumatic brain injuries or brain trauma or brain traumas or traumatic encephalopathy or traumatic encephalopathies).ti,ab,id.	18909
10	(opioid related disorders or opioid-related disorders or opioid addiction or opioid addictions or opioid dependence or opioid dependences or opiate abuse or opiate abuses or opiate dependence or opiate addiction or opioid abuse or opioid abuses).ti,ab,id.	4358
11	(sexual* trauma or sexual* abuse or sexual* violence or sex* offense or sex* offenses or sexual* harassment or sexual* assault or sexual* assaults or sexual* assaulted or rape or raped).ti,ab,id.	42333
12	or/7-12	122224

13	6 and 12	488
14	limit 13 to english language	468
15	limit 14 to yr=”2012-Current”	314

5. Search for primary literature - TMS-all + Chronic pain-post2017
Date searched: 08-10-20

MEDLINE [Ovid MEDLINE(R) ALL 1946 to August 06, 2020]

#	Search Statement	Results
1	exp Transcranial Magnetic Stimulation/ or Magnetic Stimulation Therapy/	12590
2	(TMS or ((transcrani* or crani* or brain*) adj4 (electrostim* or electro-stim* or electrotherap* or electro-therap*)) or electrical stimulation or electrical treatment or ((brain* or cortex or cortical or transcranial* or cranial or magneti*) adj4 stimulat*) or (transcranial magnetic stimulation or rTMS or cranial electrostimulation or cranial electrotherapy)).ti,ab,kw.	95929
3	(MeRT or magnetic eResonance therapy or magnetic e-Resonance therapy).ti,ab,kw.	268
4	(magnetic EEG?EKG guidance resonance therapy or magnetic EEG guided resonance therapy or magnetic EEG-guided resonance therapy or magnetic EKG-guided resonance therapy or magnetic EKG-guided resonance therapy).ti,ab,kw.	0
5	(EEG?EKG guided TMS or EEG guided TMS or EEG-guided TMS or EKG guided TMS or EKG-guided TMS or EEG guided transcranial magnetic stimulation or EEG-guided transcranial magnetic stimulation or EKG guided transcranial magnetic stimulation or EKG guided transcranial magnetic stimulation or q-EEG or quantitative EEG).ti,ab,kw.	1402
6	or/1-5	99318
7	Chronic Pain/	14595
8	((chronic* or back or musculoskel* or intractabl* or neuropath* or phantom limb or fantom limb or neck or myofasc* or "temporomandib* joint*" or "temperomandib* joint*" or "tempromandib* joint*" or central or post*stroke or complex or regional or spinal cord) adj4 pain*) or (sciatica or back-ache or back*ache or lumbago or fibromyalg* or (trigemin* adj2 neuralg*) or (herp* adj2 neuralg*) or (diabet* adj2 neuropath*) or (reflex adj4 dystroph*) or (sudeck* adj2 atroph*) or causalg* or whip-lash or whip*lash or polymyalg* or (failed back adj4 surg*) or (failed back adj4 syndrome*)).ti,ab,kw.	207706
9	7 or 8	207706
10	6 and 9	2887
11	limit 10 to english language	2719
12	limit 11 to yr=”2017-current”	674

CINAHL [EBSCO]

#	Search Statement	Results
1	(MH "Transcranial Magnetic Stimulation")	1215
2	TI ((TMS or ((transcrani* or crani* or brain*) adj4 (electrostim* or electro-stim* or electrotherap* or electro-therap*)) or electrical stimulation or electrical treatment or ((brain* or cortex or cortical or transcranial* or cranial or magneti*) adj4 stimulat*) or (transcranial magnetic stimulation or rTMS or cranial electrostimulation or cranial electrotherapy))) OR AB ((TMS or ((transcrani* or crani* or brain*) adj4 (electrostim* or electro-stim* or electrotherap* or electro-therap*)) or electrical stimulation or electrical treatment or ((brain* or cortex or cortical or transcranial* or cranial or magneti*) adj4 stimulat*) or (transcranial magnetic stimulation or rTMS	10359

	or cranial electrostimulation or cranial electrotherapy))) OR SU ((TMS or ((transcrani* or crani* or brain*) adj4 (electrostim* or electro-stim* or electrotherap* or electro-therap*)) or electrical stimulation or electrical treatment or ((brain* or cortex or cortical or transcranial* or cranial or magneti*) adj4 stimulat*) or (transcranial magnetic stimulation or rTMS or cranial electrostimulation or cranial electrotherapy)))	
3	TI ((MeRT or magnetic eResonance therapy or magnetic e-Resonance therapy)) OR AB ((MeRT or magnetic eResonance therapy or magnetic e-Resonance therapy)) OR SU ((MeRT or magnetic eResonance therapy or magnetic e-Resonance therapy))	40
4	TI ((magnetic EEG?EKG guidance resonance therapy or magnetic EEG guided resonance therapy or magnetic EEG-guided resonance therapy or magnetic EKG-guided resonance therapy or magnetic EKG-guided resonance therapy)) OR AB ((magnetic EEG?EKG guidance resonance therapy or magnetic EEG guided resonance therapy or magnetic EEG-guided resonance therapy or magnetic EKG-guided resonance therapy or magnetic EKG-guided resonance therapy)) OR SU ((magnetic EEG?EKG guidance resonance therapy or magnetic EEG guided resonance therapy or magnetic EEG-guided resonance therapy or magnetic EKG-guided resonance therapy or magnetic EKG-guided resonance therapy))	0
5	TI ((EEG?EKG guided TMS or EEG guided TMS or EEG-guided TMS or EKG guided TMS or EKG-guided TMS or EEG guided transcranial magnetic stimulation or EEG-guided transcranial magnetic stimulation or EKG guided transcranial magnetic stimulation or EKG guided transcranial magnetic stimulation or q-EEG or quantitative EEG)) OR AB ((EEG?EKG guided TMS or EEG guided TMS or EEG-guided TMS or EKG guided TMS or EKG-guided TMS or EEG guided transcranial magnetic stimulation or EEG-guided transcranial magnetic stimulation or EKG guided transcranial magnetic stimulation or EKG guided transcranial magnetic stimulation or q-EEG or quantitative EEG)) OR SU ((EEG?EKG guided TMS or EEG guided TMS or EEG-guided TMS or EKG guided TMS or EKG-guided TMS or EEG guided transcranial magnetic stimulation or EEG-guided transcranial magnetic stimulation or EKG guided transcranial magnetic stimulation or EKG guided transcranial magnetic stimulation or q-EEG or quantitative EEG))	226
6	S1 OR S2 OR S3 OR S4 OR S5	10622
7	(MH "Chronic Pain")	12958
8	TI (((chronic* or back or musculoskel* or intractabl* or neuropath* or phantom limb or fantom limb or neck or myofasc* or "temporomandib* joint*" or "temperomandib* joint*" or "tempromandib* joint*" or central or post*stroke or complex or regional or spinal cord) adj4 pain*) or (sciatica or back-ache or back*ache or lumbago or fibromyalg* or (trigemin* adj2 neuralg*) or (herp* adj2 neuralg*) or (diabet* adj2 neuropath*) or (reflex adj4 dystroph*) or (sudeck* adj2 atroph*) or causalg* or whip-lash or whip*lash or polymyalg* or (failed back adj4 surg*) or (failed back adj4 syndrome*))) OR AB (((chronic* or back or musculoskel* or intractabl* or neuropath* or phantom limb or fantom limb or neck or myofasc* or "temporomandib* joint*" or "temperomandib* joint*" or "tempromandib* joint*" or central or post*stroke or complex or regional or spinal cord) adj4 pain*) or (sciatica or back-ache or back*ache or lumbago or fibromyalg* or (trigemin* adj2 neuralg*) or (herp* adj2 neuralg*) or (diabet* adj2 neuropath*) or (reflex adj4 dystroph*) or (sudeck* adj2 atroph*) or causalg* or whip-lash or whip*lash or polymyalg* or (failed back adj4 surg*) or (failed back adj4 syndrome*))) OR SU (((chronic* or back or musculoskel* or intractabl* or neuropath* or phantom limb or fantom limb or neck or myofasc* or "temporomandib* joint*" or "temperomandib* joint*" or "tempromandib* joint*" or central or post*stroke or complex or regional or spinal cord) adj4 pain*) or (sciatica or back-ache or back*ache or lumbago or fibromyalg* or (trigemin* adj2 neuralg*) or (herp* adj2 neuralg*) or (diabet* adj2 neuropath*) or (reflex adj4 dystroph*) or	5599

	(sudeck* adj2 atroph*) or causalg* or whip-lash or whip*lash or polymyalg* or (failed back adj4 surg*) or (failed back adj4 syndrome*)))	
9	S7 or S8	18008
10	S6 and S9	136
11	limit 10 to english language	136
12	limit 11 to yr="2017-current"	52
CCRCT [EBM Reviews - Cochrane Central Register of Controlled Trials July 2020]		
#	**Search Statement**	**Results**
1	exp Transcranial Magnetic Stimulation/ or Magnetic Stimulation Therapy/	1537
2	(TMS or ((transcrani* or crani* or brain*) adj4 (electrostim* or electro-stim* or electrotherap* or electro-therap*)) or electrical stimulation or electrical treatment or ((brain* or cortex or cortical or transcranial* or cranial or magneti*) adj4 stimulat*) or (transcranial magnetic stimulation or rTMS or cranial electrostimulation or cranial electrotherapy)).ti,ab,kw.	17132
3	(MeRT or magnetic eResonance therapy or magnetic e-Resonance therapy).ti,ab,kw.	8
4	(magnetic EEG/EKG guidance resonance therapy or magnetic EEG guided resonance therapy or magnetic EEG-guided resonance therapy or magnetic EKG-guided resonance therapy or magnetic EKG-guided resonance therapy).ti,ab,kw.	0
5	(EEG?EKG guided TMS or EEG guided TMS or EEG-guided TMS or EKG guided TMS or EKG-guided TMS or EEG guided transcranial magnetic stimulation or EEG-guided transcranial magnetic stimulation or EKG guided transcranial magnetic stimulation or EKG guided transcranial magnetic stimulation or q-EEG or quantitative EEG).ti,ab,kw.	309
6	or/1-5	17606
7	Chronic Pain/	2274
8	((chronic* or back or musculoskel* or intractabl* or neuropath* or phantom limb or fantom limb or neck or myofasc* or "temporomandib* joint*" or "temperomandib* joint*" or "tempromandib* joint*" or central or post*stroke or complex or regional or spinal cord) adj4 pain*) or (sciatica or back-ache or back*ache or lumbago or fibromyalg* or (trigemin* adj2 neuralg*) or (herp* adj2 neuralg*) or (diabet* adj2 neuropath*) or (reflex adj4 dystroph*) or (sudeck* adj2 atroph*) or causalg* or whip-lash or whip*lash or polymyalg* or (failed back adj4 surg*) or (failed back adj4 syndrome*)).ti,ab,kw.	45397
9	7 or 8	45397
10	6 and 9	1342
11	limit 10 to english language	806
12	limit 11 to yr="2017-current"	307
PsycINFO [Ovid, APA PsycInfo 1806 to August Wk 1 2020]		
#	**Search Statement**	**Results**
1	exp Transcranial Magnetic Stimulation/	8425
2	(TMS or ((transcrani* or crani* or brain*) adj4 (electrostim* or electro-stim* or electrotherap* or electro-therap*)) or electrical stimulation or electrical treatment or ((brain* or cortex or cortical or transcranial* or cranial or magneti*) adj4 stimulat*) or (transcranial magnetic stimulation or rTMS or cranial electrostimulation or cranial electrotherapy)).ti,ab,id.	31753
3	(MeRT or magnetic eResonance therapy or magnetic e-Resonance therapy).ti,ab,kw.	25

4	(magnetic EEG/EKG guidance resonance therapy or magnetic EEG guided resonance therapy or magnetic EEG-guided resonance therapy or magnetic EKG-guided resonance therapy or magnetic EKG-guided resonance therapy).ti,ab,id.	0
5	(EEG?EKG guided TMS or EEG guided TMS or EEG-guided TMS or EKG guided TMS or EKG-guided TMS or EEG guided transcranial magnetic stimulation or EEG-guided transcranial magnetic stimulation or EKG guided transcranial magnetic stimulation or EKG guided transcranial magnetic stimulation or q-EEG or quantitative EEG).ti,ab,id.	848
6	or/1-5	32760
7	exp Chronic Pain/	13491
8	(((chronic* or back or musculoskel* or intractabl* or neuropath* or phantom limb or fantom limb or neck or myofasc* or "temporomandib* joint*" or "temperomandib* joint*" or "tempromandib* joint*" or central or post*stroke or complex or regional or spinal cord) adj4 pain*) or (sciatica or back-ache or back*ache or lumbago or fibromyalg* or (trigemin* adj2 neuralg*) or (herp* adj2 neuralg*) or (diabet* adj2 neuropath*) or (reflex adj4 dystroph*) or (sudeck* adj2 atroph*) or causalg* or whip-lash or whip*lash or polymyalg* or (failed back adj4 surg*) or (failed back adj4 syndrome*))).ti,ab,id.	35688
9	7 or 8	36491
10	6 and 9	861
11	limit 10 to english language	821
12	limit 11 to yr=”2017-Current”	157

6. ClinicalTrials.gov* Date Searched: 08-27-20		
#	**Search Statement**	**Results**
1	Condition or disease: PTSD or post-traumatic stress disorder or posttraumatic stress disorder or traumatic brain injury or TBI or opioid or opioids or sexual trauma or sexual abuse or sexual violence or chronic pain Other terms: TMS or transcranial magnetic stimulation or MeRT or magnetic eResonance therapy or magnetic EEG/EKG guidance resonance therapy EEG guidance or EKG guidance or magnetic stimulation therapy	0
2	Condition or disease: PTSD or post-traumatic stress disorder or posttraumatic stress disorder Other terms: TMS or transcranial magnetic stimulation	26
3	Condition or disease: PTSD or post-traumatic stress disorder or posttraumatic stress disorder Other terms: MeRT	2
4	Condition or disease: traumatic brain injury or TBI or concussion Other terms: TMS or transcranial magnetic stimulation	3
5	Condition or disease: traumatic brain injury or TBI or concussion Other terms: MeRT	1
6	Condition or disease: opioid or opioids Other terms: TMS or transcranial magnetic stimulation	12
8	Condition or disease: chronic pain Other terms: TMS or transcranial magnetic stimulation	42

*No results for: sexual trauma and any intervention; EEG/EKG-guided resonance therapy and any condition; MeRT and opioid addiction, chronic pain

APPENDIX C: EXCLUDED STUDIES

Exclude reasons: 1=Ineligible population, 2=Ineligible intervention, 3=Ineligible comparator, 4=Ineligible outcome, 5=Ineligible timing, 6=Ineligible study design, 7=Ineligible publication type 8=Outdated or ineligible systematic review, 9=Non-prioritized pain area, 10=Unable to locate full-text

#	Citation	Exclude Reason
1	Aamir, A., et al. (2020). "Repetitive Magnetic Stimulation for the Management of Peripheral Neuropathic Pain: A Systematic Review." Advances in Therapy 37(3): 998-1012.	E7
2	Adamson, M., et al. (2020). "Repetitive transcranial magnetic stimulation for improving cognition in veterans with TBI: results from pilot clinical trial." Brain Stimulation **12**(2): 551-.	E4
3	Adamson, M., et al. (2020). "Repetitive transcranial magnetic stimulation for improving cognition in veterans with TBI: results from pilot clinical trial." Brain Stimulation **12**(2): 551-.	E6
4	Ansado, J., et al. (2019). "Impact of non-invasive brain stimulation on transcallosal modulation in mild traumatic brain injury: a multimodal pilot investigation." Brain Injury 33(8): 1021-1031.	E4
5	Akyuz, G. and E. Giray (2019). "Noninvasive neuromodulation techniques for the management of phantom limb pain: a systematic review of randomized controlled trials." International Journal of Rehabilitation Research **42**(1): 1-10.	E7
6	Baptista, A. F., et al. (2019). "Latin American and Caribbean consensus on noninvasive central nervous system neuromodulation for chronic pain management (LAC₂-NIN-CP)." The Pain Report **4**(1): e692.	E7
7	Berlim, M. T. and F. Van Den Eynde (2014). "Repetitive transcranial magnetic stimulation over the dorsolateral prefrontal cortex for treating posttraumatic stress disorder: an exploratory meta-analysis of randomized, double-blind and sham-controlled trials." Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie **59**(9): 487-496.	E7
8	Berlim, M. T. and F. Van Den Eynde (2014). "Repetitive transcranial magnetic stimulation over the dorsolateral prefrontal cortex for treating posttraumatic stress disorder: an exploratory meta-analysis of randomized, double-blind and sham-controlled trials." Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie **59**(9): 487-496.	E7
9	Bhatia, R., et al. (2017). "Transcranial magnetic stimulation of dorsolateral prefrontal cortex in chronic pain management." Brain Stimulation **10**(2): 434-435.	E6
10	Blanchard, D. and S. Bourgeois (2017). "Efficacy of non-invasive brain stimulation for people experiencing chronic pain." International Journal of Evidence-Based Healthcare **15**(2): 79-80.	E6
11	Bogdanova, Y., et al. (2015). "Sleep problems, treatment and recovery in veterans with blast exposure, TBI and PTSD." Archives of physical medicine and rehabilitation **96**(10): e3-e4.	E6
12	Bursali, C., et al. (2019). "Effectiveness of repetitive transcranial magnetic stimulation in patients with failed back surgery syndrome." Annals of the rheumatic diseases **78**.	E6
13	Castel-Lacanal, E., et al. (2014). "Transcranial magnetic stimulation in brain injury." Annales Francaises d Anesthesie et de Reanimation **33**(2): 83-87.	E7

14	Cervigni, M., et al. (2018). "Repetitive transcranial magnetic stimulation for chronic neuropathic pain in patients with bladder pain syndrome/interstitial cystitis." Neurourology & Urodynamics **37**(8): 2678-2687.	E9
15	Chan, P., et al. (2019). "The Role of Fast or Slow Repetitive Transcranial Magnetic Stimulation in Civilian Post-Traumatic Stress Disorder: a Randomized, Sham-Controlled Trial." Brain Stimulation **12**(4): e132-.	E6
16	Choi, G. S., et al. (2018). "Effect of high-frequency repetitive transcranial magnetic stimulation on chronic central pain after mild traumatic brain injury: A pilot study." Journal of Rehabilitation Medicine **50**(3): 246-252	E9
17	Cirillo, P., et al. (2019). "Transcranial magnetic stimulation in anxiety and trauma-related disorders: A systematic review and meta-analysis." Brain and Behavior **9**(6): e01284.	E7
18	Cogne, M., et al. (2017). "Seizure induced by repetitive transcranial magnetic stimulation for central pain: Adapted guidelines for post-stroke patients." Brain Stimulation **10**(4): 862-864.	E6
19	Cohen, B., et al. (2017). "Deep tms augmentation treatment for fibromyalgia: a safety and feasibility study." Brain stimulation. Conference: 2nd international brain stimulation conference. Spain **10**(2): 450.	E6
20	Coles, A., et al. (2018). "A review of brain stimulation methods to treat substance use disorders." American Journal on Addictions **27**(2): 71-91	E2
21	Cordero-Gessa, A. and L. Espejo-Antúnez (2019). "Eficacia de la estimulación magnética transcraneal de baja intensidad en mujeres diagnosticadas de fibromialgia. Un estudio piloto." Fisioterapia **41**(2): 99-106.	E8
22	Etoh, S. (2017). "Effect of the repetitive transcranial magnetic stimulation and motor imagery therapy on the central pain after stroke."	E10
23	Dhaliwal, S. K., et al. (2015). "Non-Invasive Brain Stimulation for the Treatment of Symptoms Following Traumatic Brain Injury." Frontiers in psychiatry Frontiers Research Foundation **6**: 119.	
24	Ferreira, N. R., et al. (2019). "The efficacy of transcranial direct current stimulation and transcranial magnetic stimulation for chronic orofacial pain: A systematic review." PLoS ONE [Electronic Resource] **14**(8): e0221110.	E7
25	Ferrulli, A., et al. (2019). "Deep transcranial magnetic stimulation in patients with obesity: italian safety data." Obesity facts **12**(11).	E6
26	Freire, R. C., et al. (2020). "Neurostimulation in Anxiety Disorders, Post-traumatic Stress Disorder, and Obsessive-Compulsive Disorder." Advances in Experimental Medicine & Biology **1191**: 331-346.	E6
27	Fryml, L. D., et al. (2018). "The role of rTMS for patients with severe PTSD and depression." Evidence-Based Mental Health 21(1): 39-40.	E5
28	Gao, F., et al. (2017). "Repetitive transcranial magnetic stimulation for pain after spinal cord injury: a systematic review and meta-analysis." Journal of Neurosurgical Sciences **61**(5): 514-522.	E7
29	Geraets, C. N. W., et al. (2019). "Lack of analgesic effects of transcranial pulsed electromagnetic field stimulation in neuropathic pain patients: A randomized double-blind crossover trial." Neuroscience Letters 699: 212-216.	E2
30	Geraets, C. N. W., et al. (2019). "Lack of analgesic effects of transcranial pulsed electromagnetic field stimulation in neuropathic pain patients: A randomized double-blind crossover trial." Neuroscience Letters 699: 212-216.	E1
31	Gertler, P., et al. (2015). "Non-pharmacological interventions for depression in adults and children with traumatic brain injury." Cochrane Database of Systematic Reviews(12): CD009871.	E7

32	Goudra, B., et al. (2017). "Repetitive Transcranial Magnetic Stimulation in Chronic Pain: A Meta-analysis." Albang Maqalat Wa Abhat Fi Altahdir Waalinas **11**(3): 751-757.	E7
33	Gouveia, F. V., et al. (2020). "Treating Post-traumatic Stress Disorder with Neuromodulation Therapies: Transcranial Magnetic Stimulation, Transcranial Direct Current Stimulation, and Deep Brain Stimulation." Neurotherapeutics **28**: 28.	E7
34	Hamid, P., et al. (2019). "Noninvasive Transcranial Magnetic Stimulation (TMS) in Chronic Refractory Pain: A Systematic Review." Cureus **11**(10): e6019.	E7
35	Hammoud, M. and M. Milad (2018). "Symptom Changes in Posttraumatic Stress Disorder and Major Depressive Disorder After Transcranial Magnetic Stimulation: Mechanisms of Where and How in the Brain." Biological Psychiatry **83**(3): 200-202.	E6
36	Hayashi, C., et al. (2019). "Abstract #77: repetitive Transcranial Magnetic Stimulation (rTMS) in chronic diffuse axonal injury: a randomized controlled trial." Brain Stimulation **12**(2): e27-.	E6
37	Henssen, D., et al. (2019). "Bilateral vs unilateral repetitive transcranial magnetic stimulation to treat neuropathic orofacial pain: A pilot study." Brain Stimulation **12**(3): 803-805.	E9
38	Herrero Babiloni, A., et al. (2018). "Non-invasive brain stimulation in chronic orofacial pain: a systematic review." Journal of pain research **11**: 1445-1457.	E7
39	Herrold, A., et al. (2014). "Transcranial magnetic stimulation: potential treatment for co-occurring alcohol, traumatic brain injury and posttraumatic stress disorders." Neural Regeneration Research **9**(19): 1712-1730.	E6
40	Hosomi, K., et al. (2019). "P74-S A randomized clinical trial of repetitive transcranial magnetic stimulation for neuropathic pain." Clinical Neurophysiology **130**(7): e114-.	E6
41	Hosomi, K., et al. (2019). "Exploratory study of optimal conditions of repetitive transcranial magnetic stimulation of the primary motor cortex for chronic pain." Brain Stimulation **12**(2): 454-.	E6
42	Kan, R. L. D., et al. (2020). "Non-invasive brain stimulation for posttraumatic stress disorder: a systematic review and meta-analysis." Transl Psychiatry Psychiatry **10**(1): 168.	E7
43	Kaplan, C. M., et al. (2020). "Targeting network hubs with noninvasive brain stimulation in patients with fibromyalgia." Pain **161**(1): 43-46.	E6
44	Karsen, E. F., et al. (2014). "Review of the effectiveness of transcranial magnetic stimulation for post-traumatic stress disorder." Brain Stimulation **7**(2): 151-157.	E7
45	Keays, A. C. (2020). "190 Treating Fibromyalgia Syndrome through Neuromodulation With Transcranial Magnetic Stimulation." Cns Spectrums **25**(2): 319.	E6
46	Kohutova, B., et al. (2017). "Theta burst stimulation in the treatment of chronic orofacial pain: a randomized controlled trial." Physiological Research **66**(6): 1041-1047.	E9
47	Kumar, A., et al. (2017). "Targeting motor cortex with neuronavigated repetitive transcranial magnetic stimulation in management of chronic migraine." Indian journal of physiology and 6pharmacology **1**(5): 115-116	E10
48	Kumru, H., et al. (2017). "Effectiveness of repetitive trancranial or peripheral magnetic stimulation in neuropathic pain." Disability & Rehabilitation **39**(9): 856-866.	E7
49	Lage, C., et al. (2016). "A systematic review of the effects of low-frequency repetitive transcranial magnetic stimulation on cognition." Journal of Neural Transmission **123**(12): 1479-1490.	E7

50	Larkin, M. B., et al. (2020). "Neurostimulation for treatment-resistant posttraumatic stress disorder: an update on neurocircuitry and therapeutic targets." Journal of Neurosurgery: 1-9.	E7
51	Lefaucheur, J. P., et al. (2020). "Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014-2018)." Clinical Neurophysiology **131**(2): 474-528.	E6
52	Leung, A., et al. (2020). "Transcranial Magnetic Stimulation for Pain, Headache, and Comorbid Depression: INS-NANS Expert Consensus Panel Review and Recommendation." Neuromodulation **23**(3): 267-290.	E6
53	Lin, J., et al. (2019). "Chronic repetitive transcranial magnetic stimulation (rTMS) on sleeping quality and mood status in drug dependent male inpatients during abstinence." Sleep Medicine 58: 7-12.	E1
54	Lopez-Trigo, J., et al. (2017). "Effect of repetitive high frequency transcranial magnetic stimulation on trigeminal neuralgia." Brain stimulation. Conference: 2nd international brain stimulation conference. Spain. Conference start:. 20170305 **Conference end: 20170308 10**(2): 532.	E6
55	Martino Cinnera, A., et al. (2016). "Clinical effects of non-invasive cerebellar magnetic stimulation treatment combined with neuromotor rehabilitation in traumatic brain injury. A single case study." Functional Neurology 31(2): 117-120.	E5
56	Mavromatis, N., et al. (2020). "Combination of cortical and peripheral TBS with physical therapy in chronic low back pain: after-effects on clinical and TMS outcomes." Clinical Neurophysiology **131**(4): e136-.	E6
57	Mo, J. J., et al. (2019). "Motor cortex stimulation: a systematic literature-based analysis of effectiveness and case series experience." BMC Neurology 19(1): 48.	E2
58	Mori, N., et al. (2019). "P75-S Exploratory study of optimal stimulus parameters of repetitive transcranial magnetic stimulation for neuropathic pain." Clinical Neurophysiology **130**(7): e114-.	E6
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APPENDIX D: STUDIES INCLUDED IN EXISTING SYSTEMATIC REVIEW (O'CONNELL 2018)

Author, Year	Methods	Participants	Interventions	Outcomes
Ahmed 2011[1]	Parallel, quasi-RCT	Country of study: Egypt Setting: Dept of Neurology, hospital-based Condition: chronic phantom limb pain Prior management details: unresponsive to various pain medications n = 27, 17 active and 10 sham Age, mean (SD): active group 52.01 (12.7) years, sham group 53.3 (13.3) years Duration of symptoms, mean (SD) months: active group 33.4 (39.3), sham group 31.9 (21.9) Gender distribution: active group 13 M, 4 F; sham group 6 M, 4 F	Stimulation type: rTMS Stimulation parameters: frequency 20 Hz; coil orientation not specified, number of trains 10; duration of trains 10 s; ITI 50 s; total number of pulses 2000 Stimulation location: M1 stump region Number of treatments: x 5, daily Control type: sham - coil angled away from scalp	Primary: pain VAS (anchors not reported), LANNS When taken: poststimulation session 1 and 5 and at 1 month and 2 months post-treatment Secondary: none relevant
Andre-Obadia 2006[2]	Cross-over RCT; 3 conditions	Country of study: France Setting: laboratory Condition: neuropathic pain (mixed central, peripheral and facial) Prior management details: refractory to drug management, candidates for invasive MCS n=14 Age: 31-66 years; mean 53 (SD 11) Duration of symptoms: mean 6.9 years (SD 4) Gender distribution: 10 M, 4 F	Stimulation type: rTMS figure-of-8 coil Stimulation parameters: Condition 1: frequency 20 Hz; coil orientation posteroanterior; 90% RMT; number of trains 20; duration of trains 4 s; ITI 84 s; total number of pulses 1600 Condition 2: frequency 1 Hz; coil orientation lateromedial; number of trains 1; duration of trains 26 min, total number of pulses 1600 Condition 3: sham - same as for condition 2 with coil angled away perpendicular to scalp Stimulation location: M1 contralateral to painful side Number of treatments: 1 for each condition	Primary: VAS 0-10 cm, anchors "no pain" to "unbearable pain" When taken: immediately poststimulation then daily for 1 wk Secondary: none
Andre-Obadia 2008[3]	Cross-over RCT; 3 conditions	Country of study: France Setting: laboratory-based Condition: neuropathic pain (mixed central, peripheral and facial) Prior management details: refractory to	Stimulation type: rTMS, figure-of-8 coil Stimulation parameters: Condition 1: frequency 20 Hz; coil orientation posteroanterior; 90% RMT; number of trains 20; duration	Primary: 0-10 NRS (anchors "no pain" to "unbearable pain") When taken: daily for 2 wks poststimulation Secondary: none

		drug management, candidates for invasive MCS n = 30 Age: 31-72 years, mean 55 (SD 10.5) Duration of symptoms: mean 5 years (SD 3.9) Gender distribution: 23 M, 7 F	of trains 4 s; ITI 84 s; total number of pulses 1600 Condition 2: frequency 20 Hz, coil orientation lateromedial; number of trains 20; duration of trains 4 s; ITI 84 s; total number of pulses 1600 Condition 3: sham - same as for active conditions with coil angled away perpendicular to scalp Stimulation location: M1 contralateral to painful side Number of treatments: 1 for each condition	
Andre-Obadia 2011[4]	Cross-over RCT; 3 conditions	Country of study: France Setting: laboratory-based Condition: chronic neuropathic pain (mixed) Prior management details: resistant to conventional pharmacological treatment n = 45 Age: 31-72 years (mean 55) Duration of symptoms: "chronic" Gender distribution: 28 M, 17 F	Stimulation type: rTMS Stimulation parameters: frequency 20 Hz; coil orientation not specified, number of trains 20; duration of trains 4 s; ITI 84 s; total number of pulses 1600 Stimulation location: M1 hand area Number of treatments: 1 per group Control type: sham coil - same sound and appearance, no control for sensory cues	Primary: pain NRS anchors 0 = no pain, 10 = unbearable pain When taken: daily for 2 wks following each stimulation Secondary: none relevant
Avery 2013[5]	Parallel RCT	Country of study: USA Setting: unclear Condition: chronic widespread pain Prior management details: not reported n = 19 Age mean (SD): active 54.86 (7.65) years, sham 52.09 (10.02) years Duration of symptoms (months mean (SD)): active group 11 (4.26), sham group 15.64 (6.93) Gender distribution: all F	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation not specified; 120% RMT; number of trains 75; duration of trains 4 s; ITI 26 s; total number of pulses 3000 Stimulation location: L DLPFC Number of treatments: 15 sessions over 4 wks Control type: sham coil - controls for visual, auditory and scalp sensory cues	Primary: pain NRS 0-10 anchors not reported When taken: end of treatment period, 1 month following and 3 months following Secondary: pain interference BPI QoL SF-36 AEs: multiple minor; no clear difference in incidence between active and sham stimulation
Borckardt 2009[6]	Cross-over RCT; 2 conditions	Country of study: USA Setting: laboratory Condition: peripheral neuropathic pain Prior management details: not specified n = 4 Age: 33-58 years; mean 46 (SD 11)	Stimulation type: rTMS, figure-of-8 coil Stimulation parameters: frequency 10 Hz; coil orientation not specified; 100% RMT; number of trains 40; duration of trains 10 s; ITI 20 s; total number of pulses 4000	Primary: average daily pain 0-10 Likert scale, anchors "no pain at all" to "worst pain imaginable" When taken: post-stimulation for each condition (unclear how many days post) and daily for 3 wks

		Duration of symptoms: 5-12 years; mean 10.25 (SD 3.5) Gender distribution: 1 M, 3 F	Stimulation location: L PFC Number of treatments: 3 over a 5-d period Control type: neuronetics sham coil (looks and sounds identical)	poststimulation Secondary: none
Boyer 2014[7]	Parallel RCT	Country of study: France Setting: specialised pain treatment centre Condition: fibromyalgia Prior management details: stable treatment for more than 1 month before enrolment n = 38 Age, mean (SD): active group 49.1(10.6) years, sham group 47.7 (10.4) years Duration of symptoms, mean (SD): active group 3.7 (4.5) years, sham group 3.6 (3.8) Gender distribution: 37 F, 1 M	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation anteroposterior; 90% RMT; number of trains 20; duration of trains 10 s; ITI 50 s; total number of pulses 2000 Stimulation location: L M1 Number of treatments: 14 sessions. 10 sessions in 2 wks followed by maintenance phase of 1 session at wks 4, 6, 8 and 10 Control type: sham coil - did not control for sensory cues	Primary: pain VAS 0 = no pain, 10 = maximal pain imaginable When taken: 2 wks, 11 wks Secondary: FIQ AEs
Carretero 2009[8]	Parallel RCT	Country of study: Spain Setting: outpatient clinic Condition: fibromyalgia (with major depression) Prior management details: unclear n = 26 Age: active group 47.5 (SD 5.7) years, sham group 54.9 (SD 4.9) years Duration of symptoms: unclear "chronic" Gender distribution: 2 M, 24 F	Stimulation type: rTMS Stimulation parameters: frequency 1 Hz; coil orientation not specified; 110% RMT; number of trains 20; duration of trains 60 s; ITI 45 s; number of pulses 1200 Stimulation location: R DLPFC Number of treatments: up to 20 on consecutive working days Control type: coil angled 45º from the scalp	Primary: Likert pain scale 0-10, anchors "no pain" to "extreme pain" When taken: 2 wks, 4 wks and 8 wks from commencement of study Secondary: none
Dall'Agnol 2014[9]	Parallel RCT	Country of study: Brazil Setting: not specified Condition: chronic myofascial pain in the upper body Prior management details: not reported n = 24 Age, mean (SD): active group 45.83 (9.63) years, sham group 44.83 (14.09) years Duration of symptoms: not reported Gender distribution: all F	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation 45º from midline, 80% RMT, number of trains 16; duration of trains 10 s; ITI 26 s; total number of pulses 1600 Stimulation location: L M1 Number of treatments: 10 sessions, timescale not specified Control type: sham coil - same sound and appearance and sensation	Primary: pain NRS anchors 0 = no pain, 10 = worst possible pain When taken: postintervention Secondary: AEs

de Oliveira 2014[10]	Parallel RCT	Country of study: Brazil Setting: neurology dept Condition: CPSP Prior management details: stable medication for 30 d preceding baseline n = 23 Age, mean (SD): active group 55 (9.67) years, sham group SD 57.8 (11.86) years Duration of symptoms, mean (SD): active group 64.18 (49.27) months, sham group 50.1 (28.04) Gender distribution: active group 45% M, sham group 50% M	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation not specified, 120% RMT, number of trains 25; duration of trains 5 s; ITI 25s; total number of pulses 1250 Stimulation location: L premotor/DLPFC Number of treatments: 10 sessions daily for 2 wks Control type: sham coil - same sound and appearance, no control for sensory cues	Primary: pain NRS anchors not reported When taken: end of intervention, 1, 2, and 4 wks postintervention Secondary: AEs, QoL (SF-36)
Defrin 2007[11]	Parallel RCT	Country of study: Israel Setting: outpatient department Condition: post-SCI central neuropathic pain Prior management details: refractory to drug, physical therapy and complementary therapy management n = 12 Age: 44-60 years; mean 54 (SD 6) Duration of symptoms: > 12 months Gender distribution: 7 M, 4 F	Stimulation type: rTMS, figure-of-8 coil Stimulation parameters: frequency 5 Hz; coil orientation not specified; 115% RMT; number of trains 500; duration of trains 10 s; ITI 30 s; total number of pulses 500 reported, likely to have been 25,000 judging by these parameters Stimulation location: M1 - midline Number of treatments: x 10, x 1 daily on consecutive days Control type: sham coil - visually the same and makes similar background noise	Primary: 15 cm 0-10 VAS pain intensity, anchors "no pain sensation" to "most intense pain sensation" When taken: pre and post each stimulation session Secondary: McGill pain questionnaire When taken: 2- and 6-wk follow-up period
Fregni 2005[12]	Cross-over RCT	Country of study: USA Setting: laboratory Condition: chronic pancreatitis pain Prior management details: not specified n = 5 Age: 44 (SD 11) Duration of symptoms: not specified, "chronic" Gender distribution: not specified	Stimulation type: rTMS, figure-of-8 coil Stimulation parameters: frequency 1 Hz or 20 Hz; coil orientation not specified; 90% RMT; number of trains not specified; duration of trains not specified; ITI not specified; total number of pulses 1600 Stimulation location: L and R SII Number of treatments: 1 for each condition Control type: sham, "specially designed sham coil". No further details	Primary: pain VAS, anchors not specified When taken: after each stimulation session Secondary: none

Fregni 2011[13]	Parallel RCT	Country of study: USA Setting: laboratory Condition: chronic visceral pain (chronic pancreatitis) Prior management details: most on continuous opioid therapy, most had received surgery for their pain n = 17, 9 in active group, 8 in sham group Age mean (SD): active group 41.11 (11.27) years, sham group 46.71 (13.03) years Duration of symptoms: > 2 years Gender distribution: 14 F, 3 M	Stimulation type: rTMS Stimulation parameters: frequency 1 Hz; coil orientation not specified, number of trains 1; duration of trains not specified; intensity 70% maximum stimulator output, total number of pulses 1600 Stimulation location: SII Number of treatments: 10, x 1 daily (wkdays only) Control type: sham rTMS coil	Primary: pain VAS; 0 = no pain, 10 = most intense pain imaginable When taken: daily pain logs for 3 wks pre-intervention, daily post-stimulation during intervention period and at 3-wk follow-up Secondary: none relevant
Hirayama 2006a[14]	Cross-over RCT; 5 conditions	Country of study: Japan Setting: laboratory Condition: intractable deafferentation pain (mixed central, peripheral and facial) Prior management details: intractable n = 20 Age: 28-72 years Duration of symptoms: 1.5-24.3 years, mean 6.4 (SD 6) Gender distribution: 13 M, 7 F	Stimulation type: rTMS, figure-of-8 coil Stimulation parameters: frequency 5 Hz; coil orientation not specified; 90% RMT; number of trains 10; duration of trains 10 s; ITI 50 s; total number of pulses 500 Stimulation location: condition 1: M1; condition 2: primary sensory cortex; condition 3: pre-motor area; condition 4: supplementary motor area; condition 5: sham Number of treatments: 1 for each condition Control type: coil angled 45º from scalp with synchronised electrical scalp stimulations to mask sensation	Primary: pain intensity VAS, anchors not specified When taken: 0, 30, 60, 90, 180 min poststimulation Secondary: None
Hosomi 2013[15]	Cross-over RCT	Country of study: Japan Setting: multicentre, laboratory-based Condition: mixed neuropathic pain Prior management details: pain persisted despite "adequate treatments" n = 70 of whom 64 analysed Age mean (SD): 60.7 (10.6) years Duration of symptoms: 58.2 (10.6) months Gender distribution: 40 M, 24 F	Stimulation type: rTMS Stimulation parameters: frequency 5 Hz; coil orientation parasagittal, number of trains 10; duration of trains 10 s; ITI 50 s, intensity 90% RMT, total number of pulses per session 500 Stimulation location: M1 corresponding to painful region Number of treatments: 10, x 1 daily (consecutive working days) Control type: sham coil	Current daily pain 0-100 VAS (anchors not reported), SF McGill, AEs

Irlbacher 2006[16]	Cross-over RCT; 3 conditions	Country of study: Germany Setting: laboratory Condition: PLP and CNP Prior management details: unclear n = 27 Age: (median) PLP 46.6 years, CNP 51.1 years Duration of symptoms: mean PLP 15.2 (SD 14.8), CNP 3.9 (SD 4.1) years. Gender distribution: 16 M, 11 F	Stimulation type: rTMS, figure-of-8 coil Stimulation parameters: Condition 1: frequency 1 Hz; coil orientation not specified; 95% RMT; number of trains not specified; duration of trains not specified; ITI not specified; total number of pulses 500 Condition 2: frequency 5 Hz; coil orientation not specified; 95% RMT; number of trains not specified; duration of trains not specified; ITI not specified; total number of pulses 500 Condition 3: sham frequency 2 Hz; coil orientation not specified; number of trains not specified; duration of trains not specified; ITI not specified; total number of pulses 500 Stimulation location: M1, contralateral to painful side Number of treatments: x 1 for each condition Control type: sham coil; mimics sight and sound of active treatment	Primary: 0-100 mm VAS pain intensity, anchors "no pain" and "most intense pain imaginable" When taken: pre- and post-stimulation Secondary: none
Jette 2013[17]	Cross-over RCT	Country of study: Canada Setting: outpatient rehabilitation centre Condition: post-SCI neuropathic pain Prior management details: almost all participants in various medications n = 18 Age: range 31-69 years, mean (SD) 50 (9) Duration of symptoms: not reported Gender distribution: 11 M, 5 F	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation 45º posterolateral, 90% RMT for hand, 110% RMTA for leg, number of trains 40; duration of trains 5 s; ITI 25 s; total number of pulses 2000 Stimulation location: M1 hand or leg area with neuronavigation Number of treatments: single session per condition, 1 session of sham Control type: sham coil - same sound and appearance and sensation	Primary: pain NRS anchors 0 = no pain, 10 = worst possible pain When taken: immediately poststimulation, 20 min poststimulation Secondary: AEs - though no formal assessment reported
Kang 2009[18]	Cross-over RCT	Country of study: South Korea Setting: university hospital outpatient setting Condition: post-SCI central neuropathic pain	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation angled 45º posterolaterally; 80% RMT; number	Primary: NRS average pain over last 24 h, anchors "no pain sensation" to "most intense pain sensation imaginable"

		Prior management details: resistant to drug, physical or complementary therapies n = 11 Age: 33-75 years, mean 54.8 Duration of symptoms: chronic Gender distribution: 6 M, 5 F	of trains 20; duration of trains 5 s; ITI 55 s; total number pulses 1000 Stimulation location: R M1, hand area Number of treatments: 5, x 1 daily Control type: coil elevated and angled away from the scalp	When taken: immediately after the 3rd and 5th treatments and 1, 3, 5, and 7 wks after the end of the stimulation period
Khedr 2005[19]	Parallel RCT	Country of study: Egypt Setting: university hospital neurology department Condition: neuropathic pain, mixed central (poststroke) and facial (trigeminal neuralgia) pain Prior management details: refractory to drug management n = 48 Age: poststroke 52.3 (SD 10.3) years, trigeminal neuralgia 51.5 (SD 10.7) years Duration of symptoms: poststroke 39 months (SD 31), trigeminal neuralgia 18 months (SD 17) Gender distribution: 8 M, 16 F	Stimulation type: rTMS Stimulation parameters: frequency 20 Hz; coil orientation not specified; 80% RMT; number of trains 10; duration of trains 10 s; ITI 50 s; total number of pulses 2000 Stimulation location: M1 contralateral to the side of worst pain Number of treatments: 5, x 1 on consecutive days Control type: coil elevated and angled away from scalp	Primary: pain VAS, anchors not specified When taken: post 1st, 4th, and 5th stimulation session and 15 days after the last session Secondary: none
Lee 2012[20]	Parallel RCT	Country of study: Korea Setting: outpatient clinic Condition: fibromyalgia Prior management details: none reported n = 22 Age mean (SD): low-frequency group 45.6 (9.6) years, high-frequency group 53 (4.2) years, sham group 51.3 (6.2) years Duration of symptoms (months mean (SD)): low-frequency group: 47.2 (20.1), high-frequency group 57.1 (6.4), sham group 44.7 (10.3) Gender distribution: all F	Stimulation type: rTMS Stimulation parameters: Low-frequency group: frequency 1 Hz; coil orientation not specified, number of trains 2; duration of trains 800 s; ITI 60 s; total number of pulses 1600 High-frequency group: frequency 10 Hz; coil orientation not specified, number of trains 25; duration of trains 8 s; ITI 10 s; total number of pulses 2000 Stimulation location: right DLPFC (low-frequency), L M1 (high-frequency) Number of treatments: 10, x 1 daily (wkdays only) for 2 wks Control type: sham - coil orientated away from scalp	Primary: 0-100 mm pain VAS; 0 = none, 100 = an extreme amount of pain When taken: post-treatment and at 1 month follow-up Secondary: FIQ

Lefaucheur 2001a[21]	Cross-over RCT	Country of study: France Setting: laboratory Condition: intractable neuropathic pain (mixed central and facial) Prior management details: refractory to drug management n = 14 Age: 34-80 years, mean 57.2 Duration of symptoms: not specified "chronic" Gender distribution: 6 M, 8 F	Stimulation type: rTMS, figure-of-8 coil Stimulation parameters: frequency 10 Hz; coil orientation not specified; 80% RMT; number of trains 20; duration of trains 5 s; ITI 55 s; total number of pulses 1000 Stimulation location: M1, contralateral to painful side Number of treatments: x 1 for each condition Control type: sham coil used (inert)	Primary: 0-10 VAS, anchors not specified When taken: daily for 12 days poststimulation Secondary: none
Lefaucheur 2001b[22]	Cross-over RCT	Country of study: France Setting: laboratory Condition: neuropathic pain (mixed central and peripheral) Prior management details: refractory to drug management n = 18 Age: 28-75 years, mean 54.7 Duration of symptoms: not specified "chronic" Gender distribution: 11 M, 7 F	Stimulation type: rTMS, figure-of-8 coil Stimulation parameters: Condition 1: frequency 10 Hz; coil orientation posteroanterior; 80% RMT; number of trains 20; duration of trains 5 s; ITI 55 s; total number of pulses 1000 Condition 2: frequency 0.5 Hz; coil orientation posteroanterior; number of trains 1; duration of trains 20 min; total number of pulses 600 Condition 3: sham - same as for condition 1 with sham coil Stimulation location: M1 contralateral to painful side Number of treatments: x 1 for each condition	Primary: 0-10 VAS pain, anchors not specified When taken: 5-10 min poststimulation Secondary: none
Lefaucheur 2004[23]	Cross-over RCT	Country of study: France Setting: laboratory Condition: neuropathic pain (mixed central, peripheral and facial) Prior management details: refractory to drug management n = 60 Age: 27-79 years, mean 54.6 Duration of symptoms: not specified "chronic" Gender distribution: 28 M, 32 F	Stimulation type: rTMS, figure-of-8 coil Stimulation parameters: frequency 10 Hz; coil orientation posteroanterior; 80% RMT; number of trains 20; duration of trains 5 s; ITI 55 s; total number of pulses 1000 Stimulation location: M1 contralateral to painful side Number of treatments: x 1 for each condition Control type: sham coil	Primary: 0-10 VAS pain, anchors not specified When taken: 5 min poststimulation Secondary: none

Lefaucher 2006[24]	Cross-over RCT; 3 conditions	Country of study: France Setting: laboratory Condition: unilateral chronic neuropathic pain (mixed central and peripheral) Prior management details: refractory to drug management n = 22 Age: 28-75 years, mean 56.5 (SD 2.9) Duration of symptoms: 2-18 years, mean 5.4 (SD 4.1) Gender distribution: 12 M, 10 F	Stimulation type: rTMS, figure-of-8 coil Stimulation parameters: Condition 1: frequency 10 Hz; coil orientation posteroanterior; 90% RMT; number of trains 20; duration of trains 6 s; ITI 54 s; total number of pulses 1200 Condition 2: frequency 1 Hz; coil orientation posteroanterior; 90% RMT; number of trains 1; duration of trains 20 min; total number of pulses 1200 Condition 3: sham coil Stimulation location: M1 contralateral to painful side Number of treatments: x 1 for each condition	Primary: 0-10 VAS pain, anchors not specified When taken: pre- and poststimulation Secondary: none
Lefaucher 2008[25]	Cross-over RCT; 3 conditions	Country of study: France Setting: laboratory Condition: neuropathic pain (mixed central, peripheral and facial) Prior management details: refractory to drug management for at least 1 year n = 46 Age: 27-79 years, mean 54.2 Duration of symptoms: chronic > 1 year Gender distribution: 23 M, 23 F	Stimulation type: rTMS, figure-of-8 coil Stimulation parameters: Condition 1: frequency 10 Hz; coil orientation posteroanterior; 90% RMT; number of trains 20; duration of trains 6 s; ITI 54 s; total number of pulses 1200 Condition 2: frequency 1 Hz; coil orientation posteroanterior; 90% RMT; number of trains 1; duration of trains 20 min; total number of pulses 1200 Condition 3: sham coil Stimulation location: M1 contralateral to painful side Number of treatments: x 1 for each condition	Primary: 0-10 VAS, anchors not specified When taken: pre- and poststimulation Secondary: none
Malavera 2013[26]	Parallel RCT	Country of study: Colombia Setting: rehabilitation department Condition: phantom limb pain Prior management details: no difference across groups in use of NSAIDS, physical rehabilitation or psychological	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation 45° angle from midline, 90% RMT number of trains 20; duration of trains 6 s; ITI 54 s; total number of pulses 1200	Primary: pain NRS anchors 0 = no pain, 10 = worst pain possible When taken: 15 d and 30 d after treatment Secondary: AEs

		therapy n = 54 Age, mean (SD): active group 33.1 (6.6) years, sham group 8.2 (6.3) years Duration of symptoms: not reported Gender distribution: 50 M, 4 F	Stimulation location: M1 contralateral to painful side, no neuronavigation Number of treatments: 10 sessions x 1 per work day for 2 wks Control type: sham coil - same sound and appearance, no control for sensory cues	
Medeiros 2016[27]	Factorial RCT	Country of study: Brazil Setting: not specified Condition: chronic myofascial pain syndrome Prior management details: not reported n = 46, of which 23 relevant to this review Age, mean (SD): active group 45.83 (9.63) years, sham group 46.73 (13.09) years Duration of symptoms: not reported Gender distribution: all F	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation 45° from midline, 80% RMT, number of trains not reported; duration of trains not reported; ITI s not reported; total number of pulses 1600 Stimulation location: L M1 Number of treatments: 10 days of stimulation Control type: sham coil - no details provided	Primary: pain NRS anchors 0 = no pain, 10 = worst possible pain When taken: at end of intervention Secondary: none relevant
Mhalla 2011[28]	Parallel RCT	Country of study: France Setting: laboratory Condition: fibromyalgia Prior management details: not reported but concomitant treatments allowed n = 40 Age, mean (SD): active group 51.8 (11.6) years, sham group 49.6 (10) years Duration of symptoms (mean (SD) years): active group 13 (12.9), sham group 14.1 (11.9) Gender distribution: all F	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation posteroanterior, number of trains 15; duration of trains 10 s; ITI 50 s, intensity 80% RMT, total number of pulses 1500 Stimulation location: L M1 Number of treatments: 14, x 1 daily for 5 days, x 1 wkly for 3 wks, x 1 every two wks for 6 wks, x 1 monthly for 3 months Control type: sham coil, did not control for sensory cues	Primary: pain NRS; 0 = no pain, 10 = maximal pain imaginable When taken: day 5, 3 wks, 9 wks, 21 wks, 25 wks Secondary: BPI interference scale, FIQ
Nardone 2017[29]	Parallel RCT	Country of study: Italy and Austria Setting: laboratory Condition: below level post SCI, predominantly neuropathic pain Prior management details: > 4/10 pain despite rehabilitation and pharmacological treatment. All participants previously treated with antidepressant, anticonvulsants and analgesics for a	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation AP direction, 120% RMT, number of trains 25; duration of trains 5 s; ITI 25s; total number of pulses 1250 Stimulation location: L PFC (no neuronavigation) Number of treatments: 10 sessions daily	Primary: pain VAS anchors not reported When taken: postintervention, 1 month postintervention Secondary: none relevant AEs

		minimum period of 6 months n = 12 Age, mean (range): active group 43.7 (26-56) years, sham group 42.5 (24-62) years Duration of symptoms: not reported Gender distribution: 9 M, 3 F	x 5 per wk for 2 wks Control type: sham coil - same sound and appearance, no control for sensory cues	
Nurmikko 2016[30]	Cross-over RCT	Country of study: UK Setting: laboratory Condition: mixed refractory neuropathic pain Prior management details: no benefit from medication or other stimulation approaches n = 40 (27 after loss to follow-up) Age, range: 27-79 years Duration of symptoms: not reported Gender distribution: 23 M, 17 F	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation AP direction, 90% RMT, number of trains 20; duration of trains 10 s; ITI 1 min; total number of pulses 2000 Stimulation location: Site A: M1 hotspot, Site B M1 reorganised area, Site C (sham) occipital fissure Number of treatments: 3-5 sessions per wk for 5 sessions Control type: sham active stimulation of occipital fissure	Primary: pain NRS anchors 0 = no pain 10 = worst pain imagined When taken: postintervention, 3 wks postintervention Secondary: none relevant AEs
Onesti 2013[31]	Cross-over RCT	Country of study: Italy Setting: laboratory n = 25 Condition: neuropathic pain from diabetic neuropathy Prior management details: resistant to standard therapies for at least 1 year Age mean (SD): 70.6 (8.5) years Duration of symptoms (months mean (SD)): not reported Gender distribution: 9 F, 14 M	Stimulation type: rTMS using H-coil Stimulation parameters: frequency 20 Hz; coil orientation H coil, number of trains 30; duration of trains 2.5 s; ITI 30 s, intensity 100% RMT, total number of pulses 1500 Stimulation location: M1 lower limb (deep in central sulcus) Number of treatments: 5 per condition on consecutive days Control type: sham coil, controlled for scalp sensory, auditory and visual cues	Primary: pain VAS 0-100, no pain to worst possible pain When taken: immediately poststimulation, 3 wks poststimulation Secondary: none relevant

Passard 2007[32]	Parallel RCT	Country of study: France Setting: laboratory Condition: fibromyalgia Prior management details: unclear n = 30 Age: active group: 52.6 (SD 7.8) years, sham group 55.3 (SD 8.9) years Duration of symptoms: active group: 8.1 (SD 7.9), sham group: 10.8 (SD 8.6) Gender distribution: 1 M, 29 F	Stimulation type: rTMS, figure-of-8 coil Stimulation parameters: frequency 10 Hz; coil orientation posteroanterior; 80% RMT; number of trains 25; duration of trains 8 s; ITI 52 s; total number of pulses 2000 Stimulation location: M1 contralateral to painful side Number of treatments: 10, x 1 daily for 10 working days Control type: sham rTMS coil. Mimics sight and sound of active treatment	Primary: 0-10 NRS of average pain intensity over last 24 h, anchors "no pain" to "maximal pain imaginable" When taken: daily during treatment period and at 15, 30, and 60 days post-treatment follow-up Secondary: FIQ When taken: as for primary outcome
Picarelli 2010[33]	Parallel RCT	Country of study: Brazil Setting: laboratory Condition: CRPS type I Prior management details: refractory to best medical treatment n = 23 Age mean (SD): active group 43.5 (12.1) years, sham group 40.6 (9.9) years Duration of symptoms (months mean (SD)): active group 82.33 (34.5), sham group 79.27 (32.1) Gender distribution: 14 F, 9 M	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation posteroanterior, number of trains 25; duration of trains 10 s; ITI 60 s, intensity 100% RMT, total number of pulses 2500 Stimulation location: M1 contralateral to painful limb Number of treatments: 10, x 1 daily on consecutive wkdays Control type: sham coil - did not control for sensory cues	Primary: pain VAS; 0 = "no pain", 10 = "most severe pain" When taken: after first and last session then 1 and 3 months post-treatment Secondary: QoL SF-36, not reported
Pleger 2004[34]	Cross-over RCT	Country of study: Germany Setting: laboratory Condition: CRPS type I Prior management details: drug management ceased for 48 h prior to study n = 10 Age: 29-72 years, mean 51 Duration of symptoms: 24-72 months, mean 35 Gender distribution: 3 M, 7 F	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation unspecified; 110% RMT; number of trains 10; duration of trains 1.2 s; ITI 10 s; total number of pulses 120 Stimulation location: M1 hand area Number of treatments: 1 for each condition Control type: coil angled 45º away from scalp	Primary: 0-10 VAS current pain intensity, anchors "no pain" to "most extreme pain" When taken: 30 s, 15, 45, and 90 min poststimulation Secondary: none When taken: 30 s, 15, 45, and 90 min poststimulation

Rollnik 2002[35]	Cross-over RCT	Country of study: Germany Setting: pain clinic Condition: chronic pain (mixed musculoskeletal and neuropathic) Prior management details: "intractable" n = 12 Age: 33-67 years, mean 51.3 (SD 12.6) Duration of symptoms: mean 2.7 (SD 2.4) Gender distribution: 6 M, 6 F	Stimulation type: rTMS, circular coil for arm symptoms, double cone coil for leg symptoms Stimulation parameters: frequency 20 Hz; coil orientation not specified; 80% RMT; number of trains 20; duration of trains 2 s; ITI not specified; total number of pulses 800; treatment duration 20 min Stimulation location: M1 (midline) Number of treatments: x 1 for each condition Control type: coil angled 45º away from the scalp	Primary: 0-100 mm VAS pain intensity, anchors "no pain" to "unbearable pain" When taken: 0, 5, 10, and 20 min post-stimulation Secondary: none
Saitoh 2007[36]	Cross-over RCT; 4 conditions	Country of study: Japan Setting: laboratory Condition: neuropathic pain (mixed central and peripheral) Prior management details: intractable n = 13 Age: 29-76 years, mean 59.4 Duration of symptoms: 2-35 years, mean 10.2 (SD 9.7) Gender distribution: 7 M, 6 F	Stimulation type: rTMS figure-of-8 coil Stimulation parameters: Condition 1: frequency 10 Hz; coil orientation not specified; 90% RMT; number of trains 5; duration of trains 10 s; ITI 50 s; total number of pulses 500 Condition 2: frequency 5 Hz; coil orientation not specified; 90% RMT; number of trains 10; duration of trains 10 s; ITI 50 s; total number of pulses 500 Condition 3: frequency 1 Hz; coil orientation not specified; 90% RMT; number of trains 1; duration of trains 500 s; total number of pulses 500 Condition 4: sham, coil angled 45º from scalp with synchronised electrical scalp stimulations to mask sensation Stimulation location: M1 over the representation of the painful area Number of treatments: 1 for each condition	Primary: VAS pain, anchors not specified When taken: 0, 15, 30, 60, 90, and 180 minutes poststimulation Secondary: none

Tzabazis 2013[37]	Unclear, likely parallel RCT (for 1 Hz only), 10 Hz data open-label therefore excluded from this review	Country of study: USA Setting: not reported, likely laboratory Condition: fibromyalgia Prior management details: "moderate to severe despite current and stable treatment regime" n = unclear, abstract report (Schneider 2012 (see Tzabazis 2013)) stated 45, but full paper stated 16 Age mean (SD): 53.2 (8.9) years Duration of symptoms, years mean (SD): not reported Gender distribution: 14 F, 2 M	Stimulation type: rTMS 4-coil configuration Stimulation parameters: frequency 1 Hz; no of trains not reported; duration of trains not reported; ITI not reported, intensity 110% RMT, total number of pulses per session 1800, stimulation duration 30 min Stimulation location: targeted to the anterior cingulate cortex Number of treatments: 20, x 1 daily (working days) for 4 wks Control type: sham coil	Primary: BPI average pain last 24 h, NRS, anchors not reported When taken: end of treatment, 4 wks post-treatment Secondary: FIQ
Short 2011[38]	Parallel RCT	Country of study: USA Setting: laboratory Condition: fibromyalgia Prior management details: naive to TMS n = 20 Age mean (SD): active group 54.2 (8.28) years, sham group 51.67 (18.19) years Duration of symptoms, years mean (SD): active group 12.1 (7.75), sham group 10.10 (12.81) Gender distribution: 84% F	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation parasagittal, number of trains 80; duration of trains 5 s; ITI 10 s, intensity 120% RMT, total number of pulses per session 4000 Stimulation location: L DLPFC Number of treatments: 10, x 1 daily (working days) for 2 wks Control type: sham coil	Primary: pain VAS; 0 = "no pain", 10 = "worst pain" When taken: after 1 and 2 wks of treatment, then 1 wk and 2 wks posttreatment Secondary: FIQ, BPI function scale
Tekin 2014[39]	Parallel RCT	Country of study: Turkey Setting: Rehabilitation outpatient unit Condition: fibromyalgia Prior management details: no analgesic use for 1 month prior to enrolment n = 51 Age mean (SD): active group 42.4 (78.63) years, sham group 46.5 (8.36) years Duration of symptoms: mean (SD) active group 10.81 (6.31) years, sham group 13.33 (6.65) Gender distribution: 47 F, 4 M	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation 45º angle from the midline, 100% RMT number of trains 30; duration of trains 5 s; ITI 12 s; total number of pulses 1500 Stimulation location: M1 midline, no neuronavigation Number of treatments: 10 sessions daily - unclear whether only work days Control type: sham coil - same sound and appearance, no control for sensory cues	Primary: pain NRS anchors 0 = no pain, 10 = most severe pain When taken: end of intervention Secondary: WHQoL-BREF

Umezaki 2016[40]	Parallel RCT	Country of study: USA Setting: not reported Condition: burning mouth syndrome Prior management details: not reported n = 26 Age mean (SD): active group 63.36 (10.78) years, sham group 64.42 (8.35) years Duration of symptoms, mean (SD): active group 61.57 (32.10) months, sham group 65.58 (55.52) Gender distribution: active group 93% F, sham group 92% F	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation not specified, 100% RMT, number of trains 10; duration of trains 5 s; ITI 10 s; total number of pulses 3000 Stimulation location: L DLPFC Number of treatments: 10 x 1 daily on work days Control type: sham coil - same sound and appearance and sensory cues	Primary: pain NRS anchors 0 = no pain, 10 = extreme amount When taken: end of stimulation and 15, 30, 60 days after start of treatment Secondary: AEs
Yagci 2014[41]	Parallel RCT	Country of study: Turkey Setting: not reported Condition: fibromyalgia Prior management details: no improvement in cases of using medical treatment for fibromyalgia for at least 3 months n = 28 Age mean (SD): active group 45.25 (9.33) years, sham group 43 (7.63) years Duration of symptoms, mean(SD): active group 53 (29.15) months, sham group 54.92 (30.44) Gender distribution: all F	Stimulation type: rTMS Stimulation parameters: frequency 1 Hz; coil orientation not reported, 90% RMT, number of trains 20; duration of trains 60 s; ITI 45 s; total number of pulses 1200 Stimulation location: L M1, no neuronavigation Number of treatments: 10 sessions, wkdays for 2 wks Control type: sham coil - same sound and appearance, no control for sensory cues	Primary: pain NRS anchors 0 = no pain, 10 = maximum pain imaginable When taken: end of intervention, 1 month, 3 months Secondary: FIQ, AEs

Yilmaz 2014[42]	Parallel RCT	Country of study: Turkey Setting: rehabilitation unit Condition: post-SCI below lesion neuropathic pain Prior management details: pain that is resistant to pharmacological (anticonvulsants, antidepressants, narcotics) and interventional treatments n = 17 Age mean (SD): active group: 40 (5.1) years, sham group 36.94 (8) years Duration of symptoms mean (SD): active group 32.3 (25.9) months, sham group 35.4 (17.9) Gender distribution: all M	Stimulation type: rTMS Stimulation parameters: frequency 10 Hz; coil orientation handle pointing posteriorly, number of trains 30; duration of trains 5 s; ITI 25 s; total number of pulses 1500 Stimulation location: M1 midline Number of treatments: daily for 10 wkdays Control type: coil angled away - same sound and appearance, did not control for visual or sensory cues	Primary: pain NRS anchors 0 = no pain, 10 = worst pain imaginable When taken: end of intervention, 6 wks, 6 months postintervention Secondary: none relevant

Visual analogue scale (VAS), Numeric rating scale (NRS), Leeds assessment of neuropathic symptoms and signs (LANSS), World Health Organization Quality of Life – BREF (WHQoL-BREF), rTMS (repetitive transcranial magnetic stimulation), Brief pain inventory (BPI), Fibromyalgia Impact Questionnaire (FIQ), rTMS (repetitive transcranial magnetic stimulation), Resting motor threshold (RMT), Hz (Hertz), Dorsolateral prefrontal cortex (DLPFC), Adverse events (AE)

APPENDIX E: ONGOING STUDIES

Opioid Use Disorder

NCT Number	Title	Status	Conditions	Interventions	Completion Date
NCT03653169	Use of Transcranial Magnetic Stimulation to Reduce Craving for Individuals With Opioid Use Disorder Taking Buprenorphine	Enrolling by invitation	Opioid-use Disorder	TMS	7/1/2020
NCT04231708	Effects of Pharmacological Stress and rTMS on Executive Function in Opioid Use Disorder	Not yet recruiting	Opioid Use Disorder	rTMS + pharmacotherapy	12/31/2022
NCT04181515	Using rTMS to Explore Neural Mechanisms of Stress-Induced Opioid Use	Not yet recruiting	Opioid-use Disorder	rTMS + pharmacotherapy	6/1/2025
NCT04336293	sTMS for Substance Use-disordered Veterans	Not yet recruiting	Opioid Addiction	sTMS	5/31/2022
NCT03821337	Transcranial Magnetic Stimulation (rTMS) as a Tool to Decrease Pain and Improve Functioning	Active, not recruiting	Opioid Use Disorder	rTMS	5/31/2021
NCT03653169	Use of Transcranial Magnetic Stimulation to Reduce Craving for Individuals With Opioid Use Disorder Taking Buprenorphine	Enrolling by invitation	Opioid Use Disorder	TMS	7/1/2020
NCT04231708	Effects of Pharmacological Stress and rTMS on Executive Function in Opioid Use Disorder	Not yet recruiting	Opioid Use Disorder	rTMS + pharmacotherapy	12/31/2022
NCT04181515	Using rTMS to Explore Neural Mechanisms of Stress-Induced Opioid Use	Not yet recruiting	Opioid-use Disorder	rTMS + pharmacotherapy	6/1/2025
NCT04336293	sTMS for Substance Use-disordered Veterans	Not yet recruiting	Opioid Addiction	sTMS	5/31/2022
NCT03804619	Accelerated Intermittent Theta-Burst Stimulation for Opiate Use Disorder	Not yet recruiting	Opiate Dependence, Depression	rTMS (theta burst)	12/1/2022
NCT04432493	Using Combined EEG and Non-invasive Brain Stimulation to Examine and Improve Reward Functioning in Opioid Use Disorder	Recruiting	Opioid-use Disorder	rTMS	3/31/2022
NCT04157062	An Open-Label Trial of Repetitive Transcranial Magnetic Stimulation for Opioid Use Disorder	Recruiting	Opioid-use Disorder	rTMS	10/1/2021
NCT03229642	Repetitive Transcranial Magnetic Stimulation in Patients With Opioid Use Disorders	Recruiting	Opioid Dependence	rTMS	7/31/2020

NCT03538444	Repetitive Transcranial Magnetic Stimulation for Opiate Use Disorder	Recruiting	Opiate Dependence, Chronic Pain	rTMS	6/1/2021

PTSD

NCT Number	Title	Status	Conditions	Interventions	Completion Date
NCT01806168	rTMS in the Treatment of PTSD	Active, not recruiting	PTSD	rTMS	3/1/2019
NCT02158663	Study Testing if Fast or Slow rTMS is Better for the Treatment of Posttraumatic Stress Disorder (PTSD)	Completed	PTSD/Depression	rTMS	3/14/2019
NCT02584894	Potentiation of Trauma Exposure in Post-traumatic Stress Disorder by Repeated Transcranial Magnetic Stimulation	Completed	PTSD	rTMS	4/17/2020
NCT03932773	Multi-site Confirmatory Efficacy Treatment Trial of Combat-related PTSD	Recruiting	PTSD	rTMS + cognitive processing therapy	7/31/2023
NCT03114891	Accelerated TMS to a Novel Brain Target in MDD and PTSD	Recruiting	PTSD/Depression	rTMS (theta burst)	5/1/2021
NCT04325087	Reduction of Trauma-induced Intrusions and Amygdala Hyperreactivity Via Non-invasive Brain Stimulation	Recruiting	PTSD	rTMS (theta burst)	5/30/2020
NCT00134446	Transcranial Magnetic Stimulation for Post-Traumatic Stress Disorder	Unknown status	PTSD	TMS	

Traumatic Brain Injury (TBI)

NCT Number	Title	Status	Conditions	Interventions	Completion Date
NCT03819608	Neuromodulation and Neurorehabilitation for mTBI Plus PTSD	Recruiting	mTBI/PTSD	rTMS	3/1/2024
NCT03523507	fMRI-neuronavigated rTMS Treatment for Symptoms of Depression Associated With Concussive TBI in the Military Population	Recruiting	TBI/Depression	rTMS	2/1/2022
NCT02458521	Transcranial Magnetic Stimulation (TMS) to Treat mTBI and PTSD	Unknown status	TBI/PTSD	rTMS	5/1/2019

Pain

NCT Number	Title	Status	Conditions	Interventions	Completion Date
NCT03576781	Developing rTMS Treatment Strategies for Pain in Opiate Dependence	Completed	Chronic Pain, Opioid Dependence	rTMS (theta burst)	11/12/2019
NCT03576781	Developing rTMS Treatment Strategies for Pain in Opiate Dependence	Completed	Chronic Pain, Opioid Dependence	rTMS (theta burst)	11/12/2019
NCT03994991	Transcranial Magnetic Stimulation (TMS) for Thoracic Surgery	Not yet recruiting	Chronic Pain	TMS	8/1/2022
NCT03984201	Accelerated Theta Burst in Chronic Pain: A Biomarker Study	Not yet recruiting	Chronic Pain	rTMS (theta burst)	8/1/2023
NCT04203199	H-coil TMS to Reduce Pain: A Pilot Study Evaluating Relative Efficacy of the H1 vs H7 Coil	Not yet recruiting	Chronic Pain, Opioid Use	rTMS	7/1/2022
NCT02687360	Imaging the Effects of rTMS on Chronic Pain	Recruiting	Chronic Pain, Opioid Dependence	rTMS	10/1/2021
NCT02572726	An Exploration of the Neuroplasticity of Endogenous Analgesia in Health and Chronic Pain	Recruiting	Pain | Fibromyalgia	rTMS	12/1/2020
NCT03681769	Developing Brain Stimulation as a Treatment for Chronic Pain in Opiate Dependent	Recruiting	Chronic Pain, Opiate Dependence	rTMS (theta burst)	7/1/2021
NCT04283643	Noninvasive Brain Stimulation for Pain Relief	Recruiting	Acute Pain, Chronic Pain	TMS	4/1/2021

NCT02687360	Imaging the Effects of rTMS on Chronic Pain	Recruiting	Chronic Pain, Opioid-use Disorder	rTMS	10/1/2021
NCT04156802	Project Relief: Developing Brain Stimulation as a Treatment for Chronic Pain	Recruiting	Chronic Pain, Opioid Use	rTMS (theta burst)	12/1/2021
NCT03973788	Effects of Repetitive Transcranial Magnetic Stimulation on Pain Thresholds in Patients With Chronic Low Back Pain	Recruiting	Low Back Pain	rTMS	8/31/2020
NCT03076294	Repetitive Transcranial Magnetic Stimulation Associated With Manual Therapy in Knee Osteoarthritis Pain	Unknown status	Pain, Knee Osteoarthritis	TMS	3/1/2019

Alcohol Use Disorder

NCT Number	Title	Status	Condition	Intervention	Completion Date
NCT03995173	Pilot rTMS for AUD+mTBI	Recruiting	Alcohol Use Disorder, mTBI, PTSD	rTMS	11/1/2020
NCT04043442	rTMS Target Identification for Functional Disability in AUD+mTBI	Recruiting	Alcohol Use Disorder, mTBI	rTMS	9/30/2023

APPENDIX F: DATA ABSTRACTION

CONTROLLED STUDIES

Pain

Author Year Study Design N	Population Patient characteristics: Mean age	Intervention Study Follow-up	Comparator	TMS Protocol: Location Frequency (Hz) Intensity (% RMT) Sessions	Symptom Improvement	Other Outcomes	Harms
Neurological							
Ahmed 2020[1] RCT N=30	Patients with a diagnosis of diabetic neuropathy (stages 2a or 2b) Age: 50.8 % male: 36.67 % white: NR	rTMS and aerobic training exercises 1 wk	Transcutaneous electrical nerve stimulation (TENS) and aerobic training exercises.	Location: Precentral motor cortex (hemisphere contralateral to pain) Frequency: 20 Hz Intensity: 80-90% RMT Sessions: 5 session (daily)	Decrease in pain severity at 1 wk from baseline ($p<0.05$) in both groups, but no differences between groups.	NR	NR
Andre-Obadia, 2018[43] Randomized crossover trial N=35	Patients with upper limb or facial neuropathic pain for at least 1 year Age: 18-80 % male: NR % white: NR	rTMS NR	Sham rTMS: sham coil mimicking sounds and vibrations	Location: Hand or facial motor cortex Frequency: 20 Hz Intensity: 90% RMT Sessions: 3 sessions (2 active, 1 sham, separated by 2 wks)	rTMS targeted over the hand motor cortex had greater pain relief than rTMS targeted over facial cortex face rTMS ($p=0.002$) and sham ($p=0.005$).	NR	NR
Galhardoni 2019[44] RCT N=100	Patients with chronic (> 3 months) CNP due to stroke or spinal cord lesions	Deep TMS 12 wks	Sham deep TMS: coil mimicking sounds and vibrations	Location: Anterior cingulate cortex (ACC) or posterior superior insula (PSI) Frequency: 10 Hz Intensity: 90% RMT Sessions: 16 sessions (daily for 5 days (induction) then 1 session/wk for 11 wks)	NRS score was not significantly different between groups at any point during the study.	Active dTMS treatments had no significant effects on pain interference with daily activities (Brief Pain Inventory), or	Pain (mostly headaches) after each dTMS was the most prevalent adverse event

	Age: 55.02 % male: NR % white: NR					quality of life (SF-36).	
Hosomi, 2020[45] RCT N=144	Adult patients with neuropathic pain for more than 6 months Age: 61.9 % male: 64.6 % white: NR	rTMS 5 wks	Sham rTMS: sham coil mimicking sounds and vibrations	Location: Primary motor cortex (M1) targeting part of the body with the worst pain Frequency: 5 Hz Intensity: 90% RMT Sessions: 5 sessions (daily), then 1 session/wk for 4 wks (responders only - open-label)	Pain improvement not significantly different (p=0.58) between the rTMS (-8.0) and sham (-9.2) during the daily sessions. No difference in number of responders (≥ 10mm decrease VAS) between rTMS (31%) and sham (37%). The patients enrolled in the continuous wkly rTMS achieved more pain relief in with rTMS compared with the sham (p<0.01).	No difference in quality of life scores over time or between groups.	No serious adverse events were observed
Kim, 2020[46] RCT N=30	Patients with CNP Age: 61.9 % male: 64.6 % white: NR	Intermittent theta-burst stimulation (iTBS) 5 days	ham iTBS: coil turned away from skull at 90°	Location: Ipsilateral hemisphere Frequency: 50 Hz Intensity: 80% RMT Sessions: 5 sessions (daily)	S-LANSS decreased more in iTBS (-4.53) vs sham (-0.8) (p=0.002). NRS decreased more in iTBS (-2.13) vs sham (-0.86) (p=0.029).	NR	No adverse events were reported
Quesada, 2020[47] Randomized crossover trial N=42	Adult patients with medically refractory chronic CNP for at least 6 months Age: 62.8 % male: 63.3 % white: NR	rTMS 7 months	sham rTMS	Location: Primary motor cortex contralateral to the patient's pain Frequency: 20 Hz Intensity: 80% RMT Sessions: 8 sessions (4 sessions each stimulation) over 9 wks (3 wks between sessions and 8 wk washout)	Percent of pain relief (%R) was greater after rTMS phase (33.8%) compared to sham phase (13%). 54% (rTMS) vs 21% (sham) achieved ≥30% pain relief and 35% (rTMS) vs 12% (sham) achieved ≥50% pain relief. Significant decrease in VAS after rTMS phase but not sham phase.	Quality of life (EQ5-D) did not change over time or between groups.	One patient left due to pain exacerbation during both active rTMS and sham.

Sun, 2019[48] RCT N=21	Right-handed inpatient rehab patients with neuropathic pain following SCI % male: 88 % white: NR	rTMS 6 wks	Sham rTMS: coil turned away from skull at 90°	Location: Left primary motor cortex Frequency: 10 Hz Intensity: 80% RMT Sessions: Daily sessions for 6 wks, with one-day interval per wk	Pain intensity decreased from baseline to 6 wks in rTMS group (5 vs 1.5* NRS) and sham group (4.5 vs 3* NRS). Pain intensity decreased more in rTMS group compared to sham and the difference became significant at wk 2. *Estimated from Figure 4	NR	No patients complained of discomfort during or after treatment and no pathologic effects were reported.
Complex Regional Pain							
Gaertner, 2018[49] Cohort N=21	People who met "Budapest" Clinical Diagnostic Criteria for CRPS and had pain greater than 3/10 average on a numerical rating scale (NRS). Age: 44 % male: 9.5 % white: NR	iTBS followed by TMS 2 wks	1 TMS session group vs 5 TMS session group	Location: targeted over motor cortex to stimulate CPRS affected region Frequency: 50 Hz (iTBS) then 10 Hz Intensity: 70% (iTBS) then 80% Sessions: 1 or 5 sessions over 5 days	Both groups demonstrated significant pain reduction after 1 wk posttreatment; but no differences between groups. Treatment response (≥30% reduction in pain from baseline): 60% of participants with 1 session responded at wk 1. 58% and 50% of participants responded at wks 1 and 2 with 5 sessions.	NR	One subject withdrew due to adverse head pain. No serious adverse events occurred. Headache and nausea were the most common side effects.
Fibromyalgia							
Abd Elghany, 2019[50] Non-randomized controlled trial N=120	Outpatients with FMS according to ACR 2010 diagnostic criteria Age: NR % male: 0 (all female) % white: NR	rTMS One month	Regenerative injection therapy (RIT) (3 injections, 2 wks apart)	Location: DLPFC Frequency: 10 Hz Intensity: NR Sessions: 15 sessions (every other day for 1 month)	Significant decrease in mean VAS score with rTMS immediately after treatment (-20) and at 1 month (-24.3) and with injection therapy immediately after treatment (-25.2) and at 1 month (-49). Injection therapy had lower pain scores at baseline	Significant decrease in mean Fibromyalgia Impact Questionnaire Revised (FIQR) score with rTMS (-7.29) and injection therapy (-30.7) at 1 month. Injection therapy had lower	NR

					(p=0.002) and 1 month compared to rTMS (p<0.001).	FIQR scores at 1 month compared to rTMS (p<0.001).	
Atlas, 2019[51] RCT N=30	Right-handed, female patients with FMS according to ACR 2010 Diagnostic Criteria Age: 50 % male: 26.3 % white: NR	rTMS 3 wks	Sham rTMS: reverse position coil at 0.1 Hz, 1% RMT	Location: left primary motor cortex (M1) or Left DLPFC Frequency: 10 Hz Intensity: 90% RMT Sessions: 15 sessions (sessions/wk for 3 wks)	Significant improvements from baseline in VAS score in M1 (-2.8), DLPFC (-2.2) and sham (-1.7). Decrease in VAS significantly greater in Group M1 vs sham (p=0.028), but not DLPFC vs sham (p=.238) or M1 vs DLPFC (p=0.237)	Significant improvements from baseline in FIQ score in M1 (-14.7), DLPFC (-12.3) and sham (-12.4). No differences in decrease in FIQ amongst groups. Significant improvements from baseline in SF-36 physical functioning score in M1 (25), DLPFC (19.5) and sham (4). SF-36 physical functioning improvement greater in M1 vs sham (p=0.002), and DLPFC vs sham (p=.004), but not M1 vs DLPFC (p=0.62	No adverse events
Bilir, 2020[52] RCT N=20	Adult patients with diagnosis of FMS according to 2016 Fibromyalgia diagnostic criteria Age: 45.25 % male: 0 % white: NR	rTMS 6 wks	Sham rTMS: reverse position coil at 1% RMT	Location: Left DLPFC Frequency: 10 Hz Intensity: 90% RMT Sessions: 14 sessions (5 days/wk for 2 wks (induction phase), then 1 session/wk for 4 wks)	There was no significant difference in VAS-pain over time or between groups (p>0.05).	FIQ decreased at wk 2 vs baseline in rTMS group but not sham group. No differences compared to baseline at wk 6 in either group. No differences at any time between groups	No adverse events were reported

Cheng, 2019[53] RCT N=20	Patients with FMS according to ACR-2010 diagnostic criteria and DSM-IV MDD Age: 50 % male: 26.3 % white: NR	rTMS 2 wks	Sham rTMS: sham coil mimicking sounds and vibrations	Location: Left DLPFC Frequency: 10 Hz Intensity: 100% RMT Sessions: 10 sessions (5 sessions/wk for 2 wks)	Decrease in pain score (VAS) with rTMS (wk 2 vs wk 1, -0.7, p=0.021), but not with sham (wk 2 vs wk 1, +0.1, p=0.585). No significant difference between groups at wk 1 (p=0.975) or wk 2 (p=0.950)	NR	One participant complained of mild dizziness with no other adverse events reported.
Fitzgibbon, 2018[54] RCT N=26	Patients with FMS according to ACR-2010 diagnostic criteria Age: 45.6 % male: 8.3 % white: NR	rTMS 1 month	Sham rTMS: sham coil mimicking sounds and vibrations	Location: Left DLPFC Frequency: 10 Hz Intensity: 120% (RMT) Sessions: 20 sessions (5 consecutive session/wk for 4 wks)	Pain improved at 1 month vs baseline in both rTMS and sham groups on all pain measures. No significant differences between groups was observed. rTMS group significantly more likely to respond (achieve a minimum 30% improvement in pain intensity ratings) 7 rTMS vs 1 sham (p=0.024).	Both groups improved at 1 month vs baseline on FIQ, no differences between groups were observed.	5 participants reported site discomfort, 7 reported headaches, 2 reported neck pain, 3 reported nausea, 1 reported dizziness, and 2 reported other adverse events
Guinot, 2019[55] RCT N=39	Patients with FMS according to ACR-2010 diagnostic criteria Age: 44.6 % male: 8.9 % white: NR	rTMS 6 months	Sham rTMS (sham coil mimicking sounds and vibrations) + multicomponent therapy (aerobic, strength, relaxation training)	Location: Left DLPFC Frequency: 10 Hz Intensity: 90% RMT Sessions: 14 sessions (5 days/wk for 2 wks (induction phase), then 1 session/wk for 4 wks)	There was no significant difference in VAS-pain over time or between groups (p>0.05).	FIQ improved after therapy (wk 14) and at 6 month follow-up for both rTMS and sham groups (p<0.001). No differences in pain reduction between groups	No adverse effects were recorded during the study

Headache							
Mattoo, 2019[56] RCT N=30	Right-handed CTTH patients with history of headache >15 days a month for 3 months or more Age: 35.7 % male: NR % white: NR	rTMS 4 Wks after completion	sham rTMS: coil placed perpendicular to right DLPFC	Location: Right DLPFC Frequency: NR Intensity: 110% RMT Sessions: 20 sessions (5 sessions/wk for 4 wks)	NRS score decreased significantly (P<0.001) in the rTMS group compared to placebo.	rTMS group improved significantly more than sham group in Headache Impact Test-6 (HIT-6) (p<0.001), but not WHO QOL score	NR
Sahu, 2019[57] RCT N=41	Right-handed patients with a diagnosis of migraine with or without aura according to the international Classification of Headache Disorders-II	Intermittent theta-burst stimulation (iTBS) 12 Wks	sham iTBS: coil placed perpendicular to left DLPFC	Location: Left DLPFC Frequency: 50 Hz Intensity: 80 Sessions: 10 session (2x/day for 5 days)	There was a greater decrease in frequency, duration, and severity of migraine in the active group compared to the sham group over the study period (p<0.001).	There was a greater decrease in MIDAS score compared to sham group over the study period (p<0.001).	There were no significant adverse effects observed during the entire period of study

Abbreviations: rTMS, (Repetitive Trancranial Magnetic Stimulation), Dorsolateral prefrontal cortex (DLPFC), World Health Organization Quality of Life assessment (WHO QOL), Migraine Disability Assessment Score (MIDAS), Chronic tension-type headache (CTTH), Fibromyalgia Impact Questionnaire (FIQ), Numerical rating scale (NRS), Resting motor threshold (RMT), Hertz (Hz)

PTSD

Author Year Study Design N	**Population** Patient characteristics: Mean age	**Intervention** Study Follow-up	**Comparator**	**TMS Protocol:** Location Frequency (Hz) Intensity (% RMT) Sessions	**Symptom Improvement**	**Other Outcomes**	**Harms**
Ahmadizadeh, 2018[58] RCT N=65	Veterans with current combat-related PTSD symptoms Age: 50.45 % male: 100 % white: NR	rTMS 4 wks	Sham rTMS: sham coil mimicking sounds and vibrations	Location: bilateral (left and right) or right DLPFC Frequency: 20 Hz Intensity: 100 % RMT Sessions: 10 session (3 sessions/wk for 2 wks; 2 sessions/wk for 2 wks)	Greater proportion of responders (≥ 2 std from mean PCL) in rTMS (bilateral (62.5%) and unilateral (41.2%)) groups compared to sham (0%) (p=0.0001) and no difference was found between bilateral and unilateral groups. Significant mean improvement in PCL in unilateral and bilateral rTMS vs sham after all sessions.	NR	2 patients withdrew due to headache and 1 patient withdrew due to discomfort (both patients in bilateral rTMS group).
Fryml, 2019[59] RCT N=8	Veterans (OIF/OEF) with combat-related PTSD Age: 28.1 % male: 87.5 % white: NR	rTMS and Prolonged exposure therapy (PE) 8 wks	Sham rTMS (details NR)	Location: Right or left prefrontal cortex Frequency: 10 Hz Intensity: 120% RMT Sessions: 8 (1 session/wk for 8 wks)	Reduction in CAPS scores was 55% (90% CI 18.5-53.5) with rTMS compared to 40% (90% CI 13.6-73.0) with sham at session 5.	NR	No adverse events or serious adverse events occurred during the study.
Isserles, 2013[60] RCT N=30	Veterans with PTSD Age: 43.4 % male: 76.9 % white: NR	deep TMS + traumatic or positive imagery 4 wks	Sham deep TMS + traumatic imagery	Location: Prefrontal cortex Frequency: 20 Hz Intensity: 120% Sessions: 12 sessions (3 sessions/wk for 4 wks)	CAPS score improved significantly in rTMS + trauma imagery group (-27, p<.0.05), but not in rTMS + positive imagery group (-10, p>.0.05), or sham group (-10, p>0.05)	NR	A few patients had mild headaches

Kozel, 2018[61] RCT N=103	Veterans deployed to combat regions, 2001-present Age: NR (range 18-60) % male	rTMS + cognitive processing therapy	sham rTMS (inactive coil) + cognitive processing therapy	Location: right DLPFC Frequency: 1 Hz Intensity: 110% motor threshold Sessions: 12 sessions (1session/wk for 12 wks)	Total CAPS score had a greater decrease from baseline in rTMS (-48) compared to sham (-36) group (p<0.023)	NR	3 participants withdrew due to headaches (2 rTMS, 1 sham rTMS)
Kozel, 2019[62] RCT N=35	Veterans suffering from PTSD with and without depressive symptoms	rTMS 3 months	10 Hz. vs 1 Hz rTMS	Location: Right DLPCF Frequency: 1 Hz or 10 Hz Intensity: 110% RMT Sessions: 36 sessions (timing NR)	CAPS response: 29% 1 Hz vs 31% 10 Hz (p=1.0) after 30 sessions CAPS remission: 21% 1 Hz. vs 33% 10 Hz (p=0.67) after 30 sessions Improved CAPS score with 1 Hz (-9.4) and `0 Hz (-10.9) rTMS after 30 sessions. No significant difference between groups.	No difference in Inventory of Psychosocial Functioning (IPF) score with 1 Hz (-.4) or 10 Hz (-0.5) rTMS after 30 sessions	There were no seizures and no continuing complications. Two participants could not tolerate treatment at the first visit (10 Hz group)
Leong, 2020[63] RCT N=31	Civilians with non-combat related PTSD (most common type of trauma was sexual violence 52%) Age: 43,7 % male: 17.1 % white: NR	rTMS 3 months	sham rTMS: sham coil (1 Hz or 10 Hz) mimicking sounds	Location: Right DLPFC Frequency: 1 Hz or 10 Hz Intensity: 120% RMT Sessions: 10 sessions (5 sessions/wk for 2 wks)	PTSD symptoms improved at the end of treatment with 1 Hz rTMS (p=0.021) compared to sham, but not with 10 Hz rTMS (p=.065) compared to sham. There was a significant time x treatment effect over the 3 month follow-up (p=0.046).	NR	On participant withdrew due to suicidal ideation.
Nam, 2013[64] RCT N=18	Patients with non-military related PTSD Age: 34.3 % male: 37.5 % white: NR	rTMS 8 wks	Sham rTMS: coil turned away from skull at 90°	Location: right prefrontal cortex Frequency: 1 Hz Intensity: 100% RMT Sessions: 15 sessions (5 consecutive sessions/wk for 3 wks)	PTSD symptoms (CAPS-total) improved for all groups (p<0.001) but no significant effect of treatment group (p=0.147). Significant	NR	Mild adverse effects, such as headache (3 rTMS, 2 sham), dizziness (1 rTMS, 1 sham), and difficulty

					effect of time x treatment (p=0.008).		concentrating (1 sham)
Petrosino, 2020*[65] RCT N=46	Veterans with PTSD	Intermittent theta-burst stimulation (iTBS)	sham iTBS (details NR)	Location: right DLPFC Frequency: 50 Hz Intensity: 80% RMT Sessions: 10 sessions (5 consecutive sessions/wk for 2 wks)	Overall, 47.8% of patients had clinical relapse (1 patient (2.1%) overdose death, 3 patients (6.5%) inpatient hospitalization, and 18 patients (39.1%) TMS retreatment). Fewer patients in active iTBS group (33.3%) had relapse compared to sham (63.6%) (OR relapse = 3.5, 95% CI 1.04 to 11.79).	NR	NA
Philip, 2019[66] RCT N=23	People with PTSD and MDD Age: 51 % male: 84.8 %: 88 % white: NR	Synchronized TMS (sTMS) (rotating magnets synchronized to individuals intrinsic alpha frequency (IAF))	Sham sTMS: sham device with no rotating magnets 1 year	Location: NR Frequency: NR Intensity: NR Sessions: 20 (5 sessions/wk for 4 wks)	All participants demonstrated significant reductions in PTSD and MDD symptoms (p< 0.001). No significant difference in PTSD symptoms (PCL total score) (p=0.083) or MDD symptoms (QIDS-SR total score) (p=0.091) between groups, but greater improvement in "PTSD threshold symptoms" in sTMS group (p=0.011).	NR	2 participants (sTMS)reported headaches, and 1 participant (sTMS) reported nausea
Philip, 2019[67] (iTBS)* RCT N=50	Veterans with PTSD (90% with comorbid depression) Age: 50.5 % male: 84 % white: 84	Intermittent theta-burst stimulation (iTBS) 1 month	Sham iTBS (details NR)	Location: right DLPFC Frequency: 50 Hz Intensity: 80% RMT Sessions: 10 sessions (5 consecutive sessions/wk for 2 wks)	No difference in PTSD symptoms (CAPS) between groups (p=0.31) after treatment (2 wks). At 1 month (after unblinded phase) iTBS had greater PTSD symptom improvement compared to sham	Statistically significant improvement on Social and Occupational Functioning Assessment Scale (SOF) (p=0.04) after 2	NR

					(p<0.001). More patients responded (≥ 12 point CAPS reductions) with iTBS (81%) compared to sham (67%) (p<0.001).	wks of iTBS compared to sham.	
Watts, 2012[68] RCT N=20	People with PTSD Age: 55.9 % male: 90 % white: 100	rTMS 10 wks	Sham rTMS: sham coil mimicking sounds and vibrations	Location: Right DLPFC Frequency: 1 Hz Intensity: 90% RMT Sessions: 10 sessions (5 consecutive days/wk for 2 wks)	rTMS group had significant reduction in PTSD symptoms compared with sham after treatment (2 wks) (p=0.009 CAPS, p=0.002 PCL). CAPS scores remained significantly improved from baseline at 2 months post-treatment, but 6/10 participants had ≥ 10 point worsening in PTSD symptoms from post-treatment to 2 months).	NR	NR

Abbreviations: Post-traumatic stress disorder (PTSD), PTSD checklist-military version (PCL-M), Clinician Administered PTSD Scale (CAPS), PTSD Checklist (PCL), rTMS (repetitive Transcranial Magnetic Stimulation), Intermittent theta-burst stimulation (iTBS), Dorsolateral Prefrontal Cortex (DLPFC), Resting motor threshold (RMT), Operation Iraqi Freedom / Operation Enduring Freedom (OIF/OEF), Migraine Disability Assessment Score (MIDAS), Adverse events(AE)

TBI

Author Year Study Design N	**Population** Patient characteristics: Mean age	**Intervention** Study Follow-up	**Comparator**	**TMS Protocol:** Location Frequency (Hz) Intensity (% RMT) Sessions	**Symptom Improvement**	**Other Outcomes**	**Harms**
Choi 2018[69] RCT N=12	Adults with mild TBI and pain lasting at least 6 months Age: 42.6 % male: 50 % white: NR	rTMS 6 wks	Sham rTMS: coil turned away from skull at 90°	Location: Primary motor cortex Frequency: 10 Hz Intensity: 90% RMT Sessions: 10 sessions (5 per wk for 2 wks)	Changes in NRS over time were significantly different between groups (p<0.001). NRS score significantly lower in rTMS group compared to sham group at each follow-up point.	SF-36 physical component scores increased more in rTMS group compared to sham group at each time point, but SF-36 mental component scores did not change significantly over time.	No adverse events reported during study.
Hoy, 2019[70] RCT N=21	People with TBI (≥ 6 wks post TBI) experiencing current moderate severity depressive episode Age: 46.3 % male: 47.6 % white: NR	rTMS 4 wks	Sham treatment: coil turned away at 45°	Location: Left or right DLPFC Frequency: 1 Hz (right), 10 Hz (left) Intensity: 110% RMT Sessions: 20 sessions (over 4 wks)	Significant improvement in depressive symptoms (MADRS) for both groups (p=0.002), but no differences between groups.	Improvement in Trail Making Test (B) with rTMS, but no difference between groups.	More patients reported side effects with rTMS compared to sham (72% vs 30%), but statistically insignificant (p=0.146).
Lee, 2018[71] RCT N=13	Patients with TBI (≥ 6 months) without severe depression Age: 41.9 % male: 69 % white: NR	rTMS + neurodevelopmental therapy 2 wks	Sham treatment + neuro-developmental therapy	Location: Right DLPFC Frequency: 1 Hz Intensity: 100% RMT Sessions: 10 sessions (5 consecutive sessions/wk for 2 wks)	Significant improvements in depressive symptoms after rTMS (p<0.05) but not after sham. Improvement with rTMS vs sham: MADRS (-6.86 vs -0.34),	Improvement in function after rTMS but not after sham. Improvement with rTMS vs sham: TMT (-6.03 vs -1.20), and SCWT (-19.99 vs -3.00).	No adverse effects reported.

Leung, 2016[72] RCT N=24	Veterans with mild traumatic brain injury (MBTI) and post-traumatic headache Age: 41 % male: 87.5 % white: NR	rTMS (targeted by neuronavigated TMS) 4 wks	Sham treatment: coil turned away at 180°	Location: Left motor cortex Frequency: 10 Hz Intensity: 80% RMT Sessions: 3 sessions (within 1 wk)	More patients in rTMS group had ≥ 50% headache reduction compared to sham (58.3% vs 16.6%, p=0.035). Composite score of debilitating headache exacerbation significantly reduced in rTMS group at 4 wks while sham did not.	No difference in Conner's Continuous Performance (CPT) at wks 1 or 4 between groups. Significant interaction of visit and treatment at 1 wk, with an increase in CPT score with rTMS, but decrease in CPT score with sham.	One patient (rTMS) reported local tenderness at treatment site. Two subjects (one from each group) reported mild transient dizziness
Leung, 2018[73] RCT N=29	Veterans with mild traumatic brain injury related headache (MTBI-HA) Age: 34.1 % male: 79.3 % white: NR	rTMS (targeted by neuronavigated TMS) 4 wks	Sham treatment: coil turned away at 180°	Location: Left prefrontal cortex Frequency: 10 Hz Intensity: 80% RMT Sessions: 4 sessions (within 1 wk)	Signification reduction (p<0.0001) in average daily persistent headache intensity with rTMS but not sham at 1-wk (-25.3% vs -<1%) and 4-wks (-23% vs -2.3%). Significant reduction (p=0.009) in % of patients no longer experiencing persistent headaches with rTMS but not sham at 1-wk (50% vs 7%) and 4-wks (57% vs 29%).	No overall interaction between group and time on Conner's Continuous Performance (CPT).	No side effects reported.
Manko, 2013[74] Non-randomized controlled trial N=40	People with severe TBI and prolonged coma undergoing long-term rehab Age: NR % male: NR % w white: NR	rTMS NR	Relative beta training - biofeedback and neurofeedback	Location: NR Frequency: NR Intensity: NR Sessions: NR	Mental and physical comfort significantly improved with rTMS (p<0.001) but not in control group (p=.0797).	NR	NR

Neville, 2019[75] RCT N=36	People with chronic (>12 months post-injury) TBI Age: 31.1 % male: 90 % white: NR	rTMS 90 days	Sham rTMS: sham coil mimicking sounds and vibrations	Location: Left DLPFC Frequency: 10 Hz Intensity: 110% RMT Sessions: 10 sessions (daily)	No differences in executive function between groups or in time x group interactions. rTMS group improved significantly at 90-days compared to baseline ($p<0.05$).	NR	Greater frequency of mild adverse events with rTMS compared to sham (70.6% vs 46.2%).
Rao, 2019[76] RCT N=34	People with TBI and major depressive disorder Age: 40 % male: 53.3 % white: 63.3	rTMS 16 wks	Sham rTMS: sham coil mimicking sounds and vibrations	Location: Right DLPFC Frequency: 1 Hz Intensity: 110% RMT Sessions: 20 session (5 consecutive sessions/wk for 4 wks)	No statistically significant differences between groups in changes in HAM-D scores or on rates of remission or response. HAM-D scores varied widely, favoring rTMS at some time points (8 and 16 wks) and sham at others (4 and 12 wks).	Effects on neuropsychological functioning varied and favored rTMS for some measures and sham for others.	Two participants withdrew (rTMS) due to headaches. Common side effects included headache, worsening mood, dizziness, discomfort at stimulation site, insomnia, other general effects. No difference between groups.
Siddiqi, 2019[77] RCT N=15	People TBI and treatment-resistant depression Age: 45.8 % male: 73.3 % white: NR	rTMS (targeted by resting-state network mapping) NR (study terminated for "logistical reasons")	Sham rTMS: sham coil mimicking sounds and vibration	Location: Left and right DLPFC Frequency: 1 Hz (right), 10 Hz (left) Intensity: 120% RMT Sessions: 20 sessions (over 5 wks)	Mean MADRS improvement was greater with rTMS (56%) than with sham (27%). Hypothesis testing not completed due to study termination.	No clear differences in NIH Toolbox cognitive. Emotional composite scores.	No significant adverse events

Stilling, 2020[78] RCT N=20	People with persistent post-traumatic headache and post-concussion symptoms after TBI Age: 36 % male: 10 % white: NR	rTMS 6 months	Sham rTMS: sham coil mimicking sounds and vibrations	Location: Left DLPFC Frequency: 10 Hz Intensity: 70 % RMT Sessions: 10 sessions (5 consecutive sessions/wk for 2 wks)	Significant overall time effect for average headache severity (p=0.03) but no effect of treatment group at 1-month post-treatment.	Significant time effect for quality of life (Quality of Life after Brain Injury (QOLIBRI), p = 0.020). There were no significant interactions, time effects, or treatment effects for cognition.	Side effects reported included mild aggravation of headache, scalp discomfort, toothache, and dizziness. No serious adverse effects.

Abbreviations: Numerical Rating Scale (NRS), Montgomery Asberg Depression Rating Scale (MADRS), Trail Making Test (TMT), Stroop Word Color Test (SCWT), Hamilton Depression Rating Scale (HAM-D), Dorsolateral prefrontal cortex (DLPFC), rTMS (repetitive transcranial magnetic stimulation), Traumatic brain injury (TBI), Quality of Life after Brain Injury (QOLIBRI), Montreal Cognitive Assessment (MoCA), Conner's Continuous Performance (CPT), Resting motor threshold (RMT), Hertz (Hz)

Opiate Addiction

Author Year Study Design N	**Population** Patient characteristics: Mean age	**Intervention** Study Follow-up	**Comparator**	**TMS Protocol:** Location Frequency (Hz) Intensity (% RMT) Sessions	**Symptom Improvement**	**Other Outcomes**	**Harms**
Liu, 2020[79] RCT N=118	Male heroin use disorder patients referred to addiction rehabilitation centers Age: 39 % male: 100 % white: NR	rTMS 90 days	Wait list	Location: Left DLPFC Frequency: 10 Hz or 1 Hz Intensity: 100% RMT Sessions: 20 sessions over 28 days	Craving scores decreased more in first 30 days in both 1 Hz (-25.3 points) and 10 Hz groups (-29 points), compared to control (-11.6 points). All groups had significantly reduced craving score at 30, 60, and 90 days compared to baseline. No group had significant change in craving score at 60 or 90 days compared to 30 days.	None	Mild side effects reported (dizziness, headache, neck pain, insomnia, *etc*). Six subjects discontinued treatment for insomnia and headache.
Shen, 2016[80] RCT N=20	Heroin addicted adults Age: range 30-54 % male: 100 % white: NR	rTMS 5 days	Sham rTMS: coil turned away from skull at 90°	Location: Left DLPFC Frequency: 10 Hz Intensity: 100% RMT Sessions: 5 sessions (daily)	Craving score reduction of 20 points (60 vs 40) from baseline after rTMS (p=0.015) and 0 points (62 vs 62) from baseline after sham rTMS (p>0.05).	None	No subject reported any side effects

Abbreviations: Repetitive transcranial magnetic stimulation (rTMS), Dorsolateral prefrontal cortex (DLPFC), Motor threshold (MT), Hertz (Hz), Resting motor threshold (RMT), Not reported (NR)

CASE SERIES

Author Year	Condition	Intervention Study follow-up	Primary Outcome Measure	Symptom Improvement	Harms
Mrabet, 2019[81] N=19	Pain	rTMS One wk	Pain intensity via verbal rating scale (VRS)	Statistically significant difference was observed in the VRS score before and after the rTMS sessions with a median decrease of 3 points in the intensity of pain	No serious side effects were noted and in particular no epileptic seizures were observed. Less than 1% of rTMS sessions produced headache.
Quesada, 2018[47] N=80	Pain: neuropathic	rTMS One year	Percentage of pain relief (%R), duration of pain relief (DPR), numeric rating scale (NRS), neuropathic pain symptom inventory (NPSI), and pain relief score (PRS).	%R was 28% and DPR (11 days after the first 4 sessions. After 12 months of treatment (15 sessions) a cumulative effect on %R (48%), DPR (20 days). This effect reached significance after 4 sessions and was further maintained over 12 months.	No adverse events occurred
Lawson, 2018[82] N=50	Pain: Neuropathic	rTMS 6 wks	Visual analogue scale (VAS) for pain intensity	8/46 patients reported a significant level of pain relief (P < 0.001).	31/48 patients in the cohort suffered from atypical facial pain
Hodaj, 2020[83] N=57	Pain: orofacial, neuralgia, neuropathic	rTMS NR	VNS scores for pain, Analgesic effect, Neuropathic Pain Symptom Inventory (NPSI)	Analgesic response (pain intensity) decrease > 30% compared to baseline, observed in 39 patients (68%).	No serious adverse events reported
Pinot-Monange, 2019[84] N=12	Pain: pelvic pain	rTMS 4 wks	Patient Global Impression of Change	75% reported improvement on the Patient Global Impression of Change with a reduction in both pain intensity and pain interference	No serious adverse effects. 50% of patients reported light headaches and 25% described asthenia
Nikkola, 2020[85] N=11	Pain: pelvic pain	rTMS 12 wks	Numerical rating scale (NRS) for pain relief	Decreased pain was observed on the NRS after treatment and at 1 and 8 wks (P=0.019, P=0.006, P=0.042, respectively).	Mild transient tension headache reported by 2 patients. No adverse events or increase in pain occurred

Carpenter, 2018[86] N=40	PTSD/MDD	rTMS NR	PTSD Checklist (PCL) and Inventory of Depressive Symptomatology, Self-Report (IDS-SR) for PTSD and MDD symptoms.	Stimulation significantly reduced PTSD symptoms (PCL baseline mean ± SD score 52.2 ± 13.1 versus endpoint 34.0 ± 21.6; p<.001). MDD symptoms also improved significantly (IDSSR baseline 47.8 ± 11.9 to endpoint 30.9 ± 18.9; p<.001); 15 patients (42.9%) demonstrated categorical response and 12 (34.3%) remitted.	Four patients experienced serious adverse events; 3 required hospitalization for worsening symptoms with suicidality, and 1 for suicidality and substance abuse. One patient withdrew due to exacerbation of migraine. Fourteen (40%) experienced at least mild activation of PTSD symptoms; all but 1 of these was taking stimulants or bupropion.
Taghva, 2015[87] N=16	PTSD	EEG-guided magnetic resonance therapy NR	PTSD checklist (PCL-M),	Clinical improvements on the PCL-M were seen in all 16 patients, with an average pre-treatment score of 54.9 and post-treatment score of 31.8 (P < 0.001).	No adverse events were reported
Oznur, 2014[88] N=20	PTSD/ Depression	rTMS NR	Impact of Event Scale (IES), Beck Depression Inventory, Beck Anxiety Inventory	Statistically significant decreases in IES hyperarousal scores (from 21.4+-4.7 to 19.0 +-4.2, p=0.02). No statistically significant differences between total IES scores, IES intrusion scores, IES avoidance scores, Beck Depression Inventory, and Beck Anxiety Inventory scores	NR
Woodside, 2017[89] N=14	PTSD/Eating disorders	rTMS NR	PTSD checklist-Civilian (PCL-C) and Difficulties in Emotional Regulation Scale (DERS)	PCL-C scores reduced by 51.99% +-27.24% overall (p<0.001). DERS scores improved by 36.02% +-24.24% overall.	No adverse events aside from transient headaches during first treatments
Philip, 2016[90] N=10	PTSD /Depression	rTMS NR	PTSD Checklist (PCL), Quick Inventory of Depressive Symptamatology (QIDS)	Significant reduction in PTSD symptoms (p=0.003, effect size=1.12) and depression symptoms (p=0.005, effect size=1.09).	No adverse events

Nursey, 2020[91] N=8	PTSD	Intermittent theta-burst stimulation 3 months	Clinician-Administered PTSD Scale for DSM-5 (CAPS-5), Hamilton Depression Rating Scale (HAM-D)	Reductions in both PTSD (effect size= -1.78) and depression (effect size=-1.16) symptom severity post-treatment. Continued further modest decline at 3-month follow-up.	No serious adverse events aside from mild to moderate cranial pain and headaches
Seagly, 2016[92] N=7	PTSD	Low-frequency TMS 1 wk	Clinician-Administered PTSD Scale (CAPS), PTSD Checklist-Military (PCL-M), Treatment Outcome PSTD Scale (TOP-8)	PCL-M scores significantly lower post-treatment (38.71 +- 13.91) and one wk post-treatment (33.29 +-16.62) than baseline (33.29 +-16.62). TOP-8 scores significantly lower post-treatment (11.57 +-6.21) and one wk post-treatment (11.14 +-8.84) than baseline (24 +-5.23). Decrease in depression and anxiety symptom severity.	No adverse events aside from brief scalp irritation
Koski, 2015[93] N=12	TBI	rTMS NR	PCS Scale	PCS scores declined on average by 14.6 points (p=0.009)	Two participants withdrew because of worsening symptoms. Side effects included increased headache, greater sleep disturbance.
Leung, 2016[72] N=6	TBI	rTMS NR	Numerical rating scale (NRS) for pain relief	Average pre and post-rTMS NRS scores were 5.50 +- 1.38 and 2.67 +-1.75, respectively. Average headache exacerbation frequency (episodes per wk) reduced by 78.97% (+- 19.88).	None reported

Abbreviations: Verbal rating scale (VRS), Duration of pain relief (DPR), Numeric rating scale (NRS), Neuropathic pain symptom inventory (NPSI), Pain relief score (PRS), Visual analogue scale (VAS), Visual numerical scale (VNS), Clinician-Administered PTSD Scale (CAPS), PTSD Checklist-Military (PCL-M), Treatment Outcome PSTD Scale (TOP-8), PTSD Checklist (PCL), Quick Inventory of Depressive Symptomatology (QIDS), Emotional Regulation Scale (DERS), Impact of Event Scale (IES), Difficulties in Emotional Regulation Scale (DERS), Self-Report (IDS-SR), Major depression disorder (MDD)

APPENDIX G: QUALITY ASSESSMENT TABLES

QUALITY ASSESSMENT OF RCTS

Author, Year	Risk of bias from randomization process	Risk of bias from deviation from intended interventions (assignment)	Risk of bias from deviation from intended interventions (adherence)	Risk of bias from missing outcome data	Risk of bias in measurement of the outcome	Risk of bias in selection of the reported results	Overall bias (High, Low, Unclear)
Altas, 2019[51]	Unclear Computer generated blocked random allocation sequence. Statistically significant differences between groups at baseline in visual analog scale, fatigue severity scale, physical functioning, bodily pain. Unclear allocation concealment.	Low Participants and researchers blind to allocation. Unclear blinding of rTMS provider.	Low Participants and researchers unaware of assignment. All participants completed treatment.	Low No reported missing data.	Unclear Outcome assessor blinded but outcome self-report.	Unclear Protocol not readily accessible.	Unclear
Cheng, 2019[53]	Low Computerized random number generator with block randomization method. Independent research assistant performed randomization. Researchers and patients blind to block size. Baseline characteristics similar.	Low Participants and outcome assessors blind to assignments. Unclear if blinding of rTMS provider	Low Participants blind to assignments. All but 1 participant completed treatment.	Low No reported missing data. One participant withdrew from study.	Unclear Outcome assessor blinded but outcome self-report.	Low All outcomes listed in protocol were reported.	Low

Fitzgibbon, 2018[54]	Low Computer number sequence by independent researcher. Blinded allocation. Baseline characteristics similar.	Low Participants and outcome assessors blind to assignments. Unclear if blinding of rTMS provider	Low Participants blind to assignments. >95% of participants received allocated intervention.	Low >85% completed follow-up. Intent-to-treat analysis.	Unclear Outcome assessor blinded but outcome self-report.	Low All outcomes listed in protocol were reported.	Low
Guinot, 2019[55]	Unclear Computer-generated randomization. Researchers and physiotherapists blind to allocation. Baseline characteristics similar, except control group had 21% men while the intervention had 0%. Unclear allocation concealment.	Low Participants and outcome assessors blind to assignments. rTMS provider not blinded.	Unclear Participants blind to assignments. ~14% withdrew during treatment.	Low ~85% completed follow-up. Intent-to-treat analysis.	Unclear Outcome assessor blinded but outcome self-report.	Low Didn't use Covi Anxiety Scale to measure anxiety. Other outcomes measures consistent with trial registration.	Unclear
Bilir, 2020[52]	Low Computer generated block randomization. Independent researcher performed allocation. Participants blinded to allocation. Baseline characteristics similar.	Low Participants and outcome assessors blind to assignments. rTMS provider not blinded, but independent from others in the study.	Low Participants blind to assignments. All participants received allocated intervention.	Low No missing data reported, no participants withdrew/excluded.	Unclear Outcome assessor blinded but outcome self-report.	Low All outcomes listed in protocol were reported.	Low

Mattoo, 2019[56]	Low Computer-generated random numbers in blocks of 10. Participants blinded to assignments. Different investigators performed randomization, evaluation, and assignment. Baseline characteristics similar.	Low Participants and assessors blind to assignments. Unclear blinding of rTMS providers.	Low Participants blind to assignments. No flow diagram but appears all participants completed intervention.	Low No missing data reported. No participants withdrew/ excluded.	Unclear Outcome assessor blinded but outcome self-report.	Low All outcomes listed in protocol were reported.	Low
Sahu, 2019[57]	Unclear Alternate allocation. Says "double-blind", but limited information on blinding methods. Baseline characteristics similar.	Low Participants and assessors likely blinded. Unclear blinding of rTMS providers.	High 21% had to be dropped out of the study, unclear timing of drop-out.	High 21% had to be dropped out of the study, no information on handling of missing data.	Unclear Outcome assessor blinded but outcome self-report.	Unclear Protocol not readily accessible.	Unclear
Ahmed 2020[1]	Low Computer-generated randomization card by blinded research assistant. Allocation blinded. Baseline characteristics similar.	Unclear Unclear if participants or researchers blind to assignment.	Low No flow diagram, but appears that all participants completed the intervention.	Low No missing data reported. No participants withdrew/excluded.	Unclear Unclear if outcome assessors blind to assignments.	Unclear Protocol not readily accessible.	Unclear
Andre-Obadia 2018[43]	Unclear No information about randomization process or allocation concealment. No comparison of baseline characteristics.	Unclear Only participants blinded. Outcome assessors and rTMS providers not blinded.	Unclear Participants blinded. No information on adherence to interventions.	Unclear No information on withdrawal or missing data.	High Outcome assessor unblinded and outcome self-report	Unclear Protocol not readily accessible.	High

Galhardoni 2019[44]	Low Randomization performed with electronic software (randomizer.com). Allocation concealed. Baseline characteristics similar.	Low Participants and researchers blind to assignments. rTMS providers not blinded.	Low ~2% didn't complete intervention	Low 3 participants withdrew. Missing data imputation performed using k-nearest neighbor algorithm (n=5).	Unclear Outcome assessor blinded but outcome self-report.	Low All outcomes listed in protocol were reported.	Low
Hosomi, 2020[45]	Low Computer randomization using minimization method. Allocated concealed using allocation function of EDC system. Participants blind to assignment. Baseline characteristics similar.	Low Participants and assessors blind to assignments. rTMS providers unblinded.	Low 97% completed interventions.	Low 95% completed follow-up. Missing data handled without imputation. Intent-to-treat and per-protocol analysis.	Unclear Outcome assessor blinded but outcome self-report.	Low All outcomes listed in protocol were reported.	Low
Kim, 2020[46]	Low A randomization sequence of blocks was generated by a computer and concealed using opaque envelopes. No baseline differences between groups.	Low Patients and assessors likely blinded. Unclear blinding of providers.	Low All participants received intervention/sham condition as allocated (1 withdrew due to unrelated injury).	Low No participants lost to follow-up. >95% completed follow-up (1 withdrew due to unrelated injury).	Unclear Outcome assessor blinded but outcome self-report.	Unclear Protocol not readily accessible.	Low

Quesada, 2020[47]	Unclear Randomization and data collection were performed using REDCap electronic data capture tools. Allocation concealment not described (but appeared to be carried out within REDCap).	Low Patients, assessors, and providers blinded to intervention condition. Patients assessed for awareness of intervention receipt (guessing protocol).	Low All participants received intervention/sham condition as allocated (14% of each group lost/withdrew after treatment).	Unclear Relatively low missing data (14% of each group lost to follow-up/ withdrew) but single imputation (last/baseline observation carried forward) used to facilitate ITT analysis.	Unclear Outcome assessor blinded but outcome self-report.	Low All outcomes listed in protocol were reported.	Unclear
Shimizu, 2017[94]	Unclear Randomization mechanism not described. Independent data center determined the order of stimulation. Allocation concealed using unlabeled magnetic card that changed mode of operation of TMS device. Baseline differences not examined.	Unclear Patients were blinded to condition, but may have been able to distinguish between different types of TMS because of different coils (received more than one type because crossover trial). Patients assessed for awareness of intervention receipt (guessing protocol). Unclear blinding of providers.	Low All participants received intervention/sham condition as allocated.	Low No missing outcome data.	Unclear Outcome assessor blinded but outcome self-report.	Low All outcomes listed in protocol were reported.	Unclear

Sun, 2019[48]	Unclear Computer generated randomization method. No baseline differences between groups. Unclear allocation concealment	Low Participants and assessors blinded to treatment group. Unclear if rTMS delivered by independent researchers.	Unclear Participants blinded. ~80% completed protocol	Unclear 3 participants in rTMS group and 1 from sham group withdrew during the trial. No description of handling of missing data.	Unclear Outcome assessor blinded but outcome self-report.	Unclear Protocol not readily accessible.	Unclear
Ahmadizadeh, 2018[58]	Unclear Randomization conducted by statistician (unclear mechanism). Allocation concealment not described. No baseline differences between groups on demographic or clinical variables.	Low Patients and assessors were blinded to condition. Providers (rTMS technician) unblinded to condition.	Unclear 25% withdrew or were lost to follow-up.	High Moderate loss to follow up and use of last observation carried forward.	Unclear Outcome assessor blinded but some outcomes self-reported.	Unclear Protocol not readily accessible.	Unclear
Fryml, 2019[59]	Unclear Randomization mechanism not described. Allocation concealed using unlabeled magnetic card that changed mode of operation of TMS device. Higher CAPS score and lower depression score in experimental group (no statistical testing).	Low Patients and assessors were blinded to condition. Unclear blinding of providers.	Low All participants received intervention/sham as allocated.	High Reported outcomes appear to have complete data, but several outcomes not reported because of incomplete data. No attempt to handle missing data.	Unclear Outcome assessor blinded but some outcomes self-reported.	High Several outcomes not reported due to incomplete data.	High

Isserles, 2013[60]	Unclear Randomization and allocation concealment procedures not described. No baseline differences between groups.	Low Patients and assessors were blinded to condition. Providers appear to have been unblinded.	Low ~10% of patients withdrew from each group, but all interventions delivered as allocated. Results presented for all patients (ITT), those reaching treatment criterion, and completers.	Unclear Results provided for ITT (all patients regardless of assessments completed) but unclear how missing data for non-completers were handled.	Unclear Outcome assessor blinded but outcome self-report.	Low All outcomes listed in protocol were reported.	Unclear
Kozel, 2018[61]	Low Randomization was generated using computer randomization procedure. Assignments recorded on cards and placed in sealed envelopes that were sequentially numbered by an investigator not involved with the participants. Baseline differences between groups evaluated for completers and noncompleters.	Low Patients and assessors were blinded to condition. TMS providers unblinded but "were isolated from other study staff members and only had minimal interaction with participants during TMS treatment".	Unclear Substantial withdrawal after allocation. Significantly different baseline characteristics and outcomes for those who completed therapy versus those who withdrew, but differences were not specific to group.	Unclear ITT analyses conducted with missing data handled via maximum likelihood. High level of missing data.	Unclear Outcome assessor blinded but outcome self-report.	Low All outcomes listed in protocol were reported.	Unclear
Kozel, 2019[62]	Low Randomization was generated using a computer randomization. Assignments placed in envelopes prior to trial. No baseline differences between groups.	High Patients and providers unblinded to condition. Assessors blinded.	Unclear ~25% lost to follow up or withdrew, but all interventions delivered as allocated.	Unclear Patients who withdrew after allocation were not analyzed (6); patients lost to follow up (2) were retained.	Unclear Outcome assessor blinded but outcome self-report.	Low All outcomes listed in protocol were reported.	Unclear

Leong, 2020[63]	Low Participants were randomized by random sequence generation 2:2:1:1 with allocation concealment by the envelope method. No baseline differences between groups.	Low Patients and assessors blinded but providers unblinded.	Unclear Minimal but significantly different withdrawal/attrition between groups.	Unclear Minimal loss to follow-up/ withdrawal, but 3-month outcomes not reported due to differential attrition.	Unclear Outcome assessor blinded but outcome self-report.	Unclear Protocol not readily accessible. Three-month outcomes not reported due to differential attrition.	Unclear
Nam, 2013[64]	Unclear Random sequence and allocation concealment method not described. No baseline differences between groups.	Low Patient blinded but provider unblinded (though provider was "blind to all subject information and blocked from communicating about subjects with raters. Prior to the study, the experimenter was trained to maintain a consistent and neutral attitude toward each practice to minimize biases.")	Low ~90% received treatment as allocated (2 withdrew from treatment group).	Low All assessments complete with the exception of 2 withdrawals after allocation.	Unclear Outcome assessor blinded but outcome self-report.	Unclear Protocol not readily accessible.	Low
Philip, 2019[66]	Unclear Random sequence and allocation concealment method not described. Baseline differences not evaluated.	Unclear Patients blinded to condition. Patients assessed for awareness of intervention receipt (guessing protocol). Unclear blinding of	Low Appears that all patients received treatment as allocated.	Low No missing outcome data.	Unclear Unclear assessor blinding and outcome self-report.	Low All outcomes listed in protocol were reported.	Unclear

		providers and assessors.					
Philip, 2019 (iTBS)[67]	Unclear Randomization performed by uninvolved study member (mechanism not described). Staff uninvolved in treatment delivery selected coil to conceal randomization. No baseline differences between groups.	Low Patients and assessors blinded to condition. Patients assessed for awareness of intervention receipt (guessing protocol). Unclear blinding of providers.	Low <10% withdrew; CONSORT diagram suggests that all patients received treatment as allocated.	Low Missing outcome data were addressed using multiple imputation.	Unclear Blinded assessors but outcome self-report (neuroimaging outcomes in convenience subgroup).	Low All outcomes listed in protocol were reported.	Low
Watts, 2012[68]	Unclear Subjects randomly assigned, but no details on methods of randomization. Unclear allocation concealment. Appears that rTMS group may have more comorbidities, but no statistical test performed.	Low Participants and outcome assessors masked to intervention assignment.	Unclear No data on intervention adherence.	Unclear No information on handling of missing data.	Unclear Outcome assessor blinded but outcome self-report.	Unclear Protocol not readily accessible.	Unclear
Choi 2018[69]	Unclear Computer generated random number sequence. No baseline differences between groups. Unclear method of allocation concealment.	Low Participants and outcome assessors masked to intervention assignment.	Low Study states that all patients completed rTMS sessions.	Low No missing outcome data.	Unclear Outcome assessor blinded but outcome self-report.	Unclear Protocol not readily accessible.	Unclear
Hoy, 2019[70]	Unclear Computer generated random number sequence. No baseline differences between	Low Participants and outcome assessors masked to intervention	Unclear 14% of patients withdrew, no other information on	Unclear 14% of patients withdrew, no information on	Unclear Outcome assessor blinded but outcome self-report.	Low All outcomes listed in protocol were reported.	Unclear

	groups, except use of antidepressant medication. Unclear method of allocation concealment.	assignment. Neither able to guess treatment group.	adherence to interventions.	handling of missing data.			
Lee, 2018[71]	Unclear Unclear randomization method. Allocation concealed by sealed envelopes. No baseline differences between groups, except weight.	Unclear Participants blinded but unclear if outcome assessors masked to intervention assignment.	Low Flow diagram states that all subjects completed the trial.	Low No missing outcome data.	Unclear Outcome assessment appropriate but unclear if outcome assessors were blinded to intervention assignment and outcome self-report.	Unclear Protocol not readily accessible.	Unclear
Leung, 2016[72]	Unclear Computer generated random number sequence. No baseline differences between groups. Unclear method of allocation concealment.	Unclear Participants blinded but unclear if outcome assessors masked to intervention assignment (participants self-rated headache outcomes, but other outcomes unclear).	Unclear >80% received allocated intervention.	High Missing data on 5 (17%) subjects excluded from analysis. Complete case analysis carried out with relatively substantial amount of missing data.	Unclear Outcome assessment appropriate but unclear if outcome assessors were blinded to intervention assignment (participants self-rated headache outcomes, but other outcomes unclear).	Unclear Protocol not readily accessible.	Unclear

Leung, 2018[73]	Unclear Computer generated random number sequence. No baseline differences between groups. Unclear method of allocation concealment.	Unclear Participants blinded but unclear if outcome assessors masked to intervention assignment (participants self-rated headache outcomes, but other outcomes unclear).	Low >90% received allocated intervention.	Unclear Missing data on 3 (9.4%) subjects excluded from analysis. Complete case analysis carried out, but relatively small amount of missing data.	Unclear Outcome assessment appropriate but unclear if outcome assessors were blinded to intervention assignment (participants self-rated headache outcomes, but other outcomes unclear).	Unclear Protocol not readily accessible.	Unclear
Neville, 2019[75]	Low Computer generated random number sequence. No significant differences between groups at baseline. Allocation concealed using opaque envelope	Low Participants and outcome assessors masked to intervention assignment. Unclear blinding of rTMS providers.	Unclear >80% received allocated intervention.	High 6 participants (16.6%) did not complete study and were excluded from analysis. Complete case analysis carried out with relatively substantial amount of missing data.	Low Outcome assessment appropriate. Outcome assessors blinded to intervention assignment.	Low All outcomes listed in protocol were reported.	Unclear
Rao, 2019[76]	Unclear Computer generated random number sequence. No baseline differences between groups, except for higher fatigue in control group. Unclear method of allocation concealment.	Unclear Participants blinded but unclear if outcome assessors masked to intervention assignment.	Unclear >80% received allocated intervention.	Low Missing values imputed, but unclear use on imputations. Missing data only in treatment group.	Unclear Outcome assessment appropriate but unclear if outcome assessors were blinded to intervention assignment.	Unclear Protocol not readily accessible.	Unclear

Siddiqi, 2019[77]	Unclear Computer generated random number sequence. No baseline differences between groups. Unclear method of allocation concealment.	Low Participants, outcome assessors, and other study researchers were blinded, except those administering TMS.	Unclear 2 subjects (15%) did not complete the treatment (1 in each group).	Unclear No information on handling of missing data.	Unclear Outcome assessor blinded but outcome self-report.	Unclear Secondary outcome listed in protocol (tinnitus) not reported	Unclear
Stilling, 2020[78]	Low Computer generated random number sequence. No significant differences between groups at baseline (sham group older with less preventive medications). Allocation concealed using opaque envelope	Low Participants, outcome assessors, and other study researchers were blinded, except those administering TMS.	Low Flow diagram states that all subjects completed the trial.	Low No missing outcome data.	Unclear Outcome assessor blinded but outcome self-report.	Low All outcomes listed in protocol were reported.	Low
Liu, 2020[79]	Low Computer generated random number sequence. No baseline differences between groups. Unclear allocation concealment.	Low Participants blinded to treatment group. rTMS delivered by independent researchers	Unclear >80% received allocated intervention.	Unclear >80% followed-up at 90 days. No description of handling of missing data.	Unclear Outcome assessors different from those delivering intervention, unclear blinding and outcomes self-report.	Low All outcomes listed in protocol were reported.	Unclear
Shen, 2016[80]	Unclear No information about randomization process.	Unclear No information about blinding or deviations from protocol.	Unclear No information about blinding of participants or researchers. No information about intervention adherence.	Unclear No information on loss to follow-up or handling of missing data.	Unclear Unknown if outcome assessors were different from those delivering intervention, unclear blinding, and outcomes self-report.	Low All outcomes listed in protocol were reported.	Unclear

Petrosino 2020 not rated, same study as Philip 2019

QUALITY ASSESSMENT OF COHORT STUDIES

Author Year	Selection bias	Bias in classification of interventions	Bias due to departures from intended interventions	Bias due to measurement of outcomes	Bias due to confounding	Bias due to missing data	Bias in the selection of reported results	Overall bias (High, Low, Unclear)
Abd Elghany 2019[50]	Unclear Minimal info on how participants were selected. Study indicates groups were matched in age, sex, and disease duration, but no data presented. No adjustment for other potential confounders.	Unclear No info on how participants were placed into intervention groups.	Unclear No info on intervention adherence or potential co-interventions	Unclear Subjective outcome measures may be influenced by knowledge of intervention. Unclear masking of outcome assessors.	High Potential for confounding based on disease severity, unclear balance of disease severity across groups. Very limited controlling for confounding.	Unclear No description of handling of missing data.	Unclear Protocol not readily accessible.	High
Manko, 2013[74]	High Unclear how patients were selected into study. No information on baseline characteristics of patients. No adjustment for potential confounders.	Unclear Patients divided numerically into intervention groups. No other information on how participants were selected into groups.	Unclear No info on intervention adherence or potential co-interventions	Unclear Subjective outcome measures may be influenced by knowledge of intervention. Unclear masking of outcome assessors.	High Potential for confounding based on patient and disease characteristics and unclear balance of characteristics across groups. No controlling for confounding.	Unclear No description of handling of missing data.	Unclear Protocol not readily accessible.	High

Gaertner, 2018[49]	Unclear Minimal info on how participants were selected. Unclear if groups were balanced at baseline.	Unclear Patients self-selected into intervention groups. Unclear if patient or disease characteristics related to outcome may influence selection.	High Differential attrition between groups. 19% did not complete full protocol.	Unclear Subjective outcome measures may be influenced by knowledge of intervention. Unclear masking of outcome assessors.	High Potential for confounding based on patient and disease characteristics and unclear balance of characteristics across groups. No controlling for confounding.	Unclear No description of handling of missing data.	Low All outcomes listed in protocol were reported	High

APPENDIX H: STRENGTH OF EVIDENCE

Author, Year N	Primary Outcome(s)	Findings	Quality	Strength of Evidence
Complex Regional Pain Syndrome				
Gaetner, 2018[49] 21	Pain: VAS, NRS	Both groups demonstrated significant pain reduction after 1-wk posttreatment; but no differences between groups.	High	Very Low SOE It is unclear whether TMS may improve pain compared to sham. Very limited confidence due to 1 small cohort with high RoB.
Fibromyalgia				
Abd Elghany, 2019*[50] 120	Pain: VAS, SF-MPQ, NRS	Significant decrease in mean VAS score with rTMS immediately after treatment and at 1 month and with injection therapy immediately after treatment and at 1 month. Injection therapy had lower pain scores at baseline and 1 month compared to rTMS.	High	Low SOE TMS may be no better than sham in pain improvement. Limited confidence due 6 small studies with low to high RoB.
Atlas, 2019[51] 30		Significant improvements from baseline in VAS score in M1, DLPFC, and sham groups. Decrease in VAS significantly greater in Group M1 vs sham, but not DLPFC vs sham, or M1 vs DLPFC.	Unclear	
Bilir, 2020[52] 26		There was no significant difference in VAS-pain over time or between groups.	Low	
Cheng, 2019[53] 20		Decrease in pain score (VAS) with rTMS, but not with sham. No significant difference in pain between groups at wk 1 or wk 2.	Low	
Fitzgibbon, 2018[54] 26		Pain improved at 1 month vs baseline in both rTMS and sham groups on all pain measures. No significant differences between groups was observed. rTMS group significantly more likely to respond (achieve a minimum 30% improvement in pain intensity ratings) than sham.	Low	
Guinot, 2019[55] 26		Pain improved after therapy (wk 14) and at 6-month follow-up for both rTMS and sham groups. No differences in pain reduction between groups.	Low	
Headache				
Mattoo, 2019[56] 30	Pain: NRS, Headache symptoms	NRS score decreased significantly in the rTMS group compared to placebo.	Low	Moderate SOE TMS probably improves headache pain and symptoms compared to sham. Limited confidence due to small studies with low to unclear RoB.
Sahu, 2019[57] 41		There was a greater decrease in frequency, duration, and severity of migraine in the active group compared to the sham group over the study period.	Unclear	

Neuropathic				
Ahmed, 2020[1] 30	Pain: VAS, NRS	Decrease in pain severity at 1 wk from baseline in both groups, but no differences between groups.	Unclear	Low SOE TMS may improve pain compared to sham. Limited confidence due to inconsistent findings and low to high RoB.
Andre-Obadia, 2018[43] 35		rTMS targeted over the hand motor cortex had greater pain relief than rTMS targeted over facial cortex face rTMS and sham.	High	
Galhardoni, 2019[44] 100		NRS score was not significantly different between groups at any point during the study.	Low	
Hosomi, 2020[45] 144		Pain improvement not significantly different between the rTMS and sham groups during the daily sessions. No difference in number of responders (≥ 10mm decrease VAS) between rTMS and sham.	Low	
Kim, 2020[46] 30		S-LANSS decreased more in iTBS vs sham groups. NRS decreased more in iTBS vs sham.	Low	
Quesada, 2020[47] 42		Percent of pain relief (%R) was greater after rTMS phase compared to sham phase. 54% (rTMS) vs 21% (sham) achieved ≥30% pain relief and 35% (rTMS) vs 12% (sham) achieved ≥50% pain relief. Significant decrease in VAS after rTMS phase but not sham phase.	Low	
Shimizu, 2017[94] 18		VAS improved significantly immediately after deep rTMS and 1-hour after deep rTMS compared with sham. No significant pain improvement with rTMS immediately after or 1-hour compared with sham. No significant long-term effects on VAS scores for any type of stimulation.	Unclear	
Sun, 2019[48] 21		Pain intensity decreased from baseline to 6 wks in rTMS group and sham group. Pain intensity decreased more in rTMS group compared to sham and the difference became significant at wk 2.	Unclear	
PTSD				
Ahmadizadeh, 2018[58] 65	PTSD symptoms: PCL, CAPS	Greater proportion of responders (≥ 2 std from mean PCL) in rTMS groups compared to sham and no difference between bilateral and unilateral groups. Significant mean improvement in PCL in unilateral and bilateral rTMS vs sham after all sessions	Unclear	Low SOE TMS may improve PTSD symptoms compared to sham. Limited confidence due to inconsistent findings and low to high RoB.
Fryml, 2019[59] 8		No difference in reduction in CAPS scores with rTMS compared with sham at session 5.	High	
Isserles, 2013[60] 30		CAPS score improved significantly in rTMS + trauma imagery group, but not in rTMS + positive imagery group, or sham group.	Unclear	

Kozel, 2018[61] 103		Total CAPS score had a greater decrease from baseline in rTMS compared to sham group.	Unclear	
Kozel, 2019[62] 35		No difference in CAPS response or remission after 30 sessions. Improved CAPS score with 1 Hz and 10 Hz rTMS after 30 sessions. No significant difference between groups.	Unclear	
Leong, 2020[63] 31		PTSD symptoms improved at the end of treatment with 1 Hz rTMS compared to sham, but not with 10 Hz rTMS compared to sham. There was a significant time x treatment effect over the 3-month follow-up.	Unclear	
Nam, 2013[64] 18		PTSD symptoms improved for all groups but no significant effect of treatment group. Significant effect of time x treatment.	Low	
Philip, 2019[67] (iTBS) 50		No difference in PTSD symptoms (CAPS) between groups after treatment (2 wks). At 1-month (after unblinded phase) iTBS had greater PTSD symptom improvement compared to sham. More patients responded (≥ 12-point CAPS reductions) with iTBS compared to sham.	Low	
Philip, 2019[66] 23		All participants demonstrated significant reductions in PTSD and MDD symptoms. No significant differences between groups.	Unclear	
Watts, 2012[68] 20		rTMS group had significant reduction in PTSD symptoms compared with sham after treatment (2 wks). CAPS scores remained significantly improved from baseline at 2 months post-treatment, but 6/10 participants had ≥ 10-point worsening in PTSD symptoms from post-treatment to 2 months.	Unclear	
Petrosino, 2020[65] 46	Clinical relapse*	Overall, 47.8% of patients had clinical relapse. Fewer patients in active iTBS group had relapse compared to sham (OR relapse = 3.5, 95% CI 1.04 to 11.79).	Low	Low SOE TMS may improve clinical relapse compared to sham in PTSD patients. Limited confidence due to single study.
TBI				
Choi, 2011[69] 12	Pain: Numerical rating scale (NRS)	Changes in NRS over time were significantly different between groups. NRS score significantly lower in rTMS group compared to sham group at each follow-up point.	Unclear	Low SOE: TMS may improve pain compared to sham. Limited confidence due to single, small study with unclear RoB.
Hoy, 2019[70] 21	Depressive symptoms: MADRS, HAM-D	Significant improvement in depressive symptoms (MADRS) for both groups, but no differences between groups.	Unclear	Low SOE: TMS may improve depressive symptoms compared to sham. Limited
Lee, 2018[71] 13		Significant improvements in depressive symptoms after rTMS, but not after sham.	Unclear	

Rao, 2019[76] 35		No statistically significant differences between groups in changes in HAM-D scores or on rates of remission or response. HAM-D scores varied widely, favoring rTMS at some time points and sham at others.	Unclear	confidence due to inconsistent findings and unclear RoB.
Siddiqi, 2019[77] 15		Mean MADRS improvement was greater with rTMS than with sham. Hypothesis testing not completed due to study termination.	Unclear	
Leung, 2016[72] 24	Headache symptoms: headache diary	More patients in rTMS group had ≥ 50% headache reduction compared to sham. Composite score of debilitating headache exacerbation significantly reduced in rTMS group at 4 wks while sham did not.	Unclear	Low SOE: TMS may improve headache symptoms compared to sham. Limited confidence due to inconsistent findings and low to unclear RoB.
Leung, 2018[73] 29		Signification reduction in average daily persistent headache intensity with rTMS but not sham at 1- and 4-wks. Significant reduction in % of patients no longer experiencing persistent headaches with rTMS but not sham at 1- and 4-wks.	Unclear	
Stilling, 2020[78] 20		Significant overall time effect for average headache severity but no effect of treatment group at 1-month post-treatment.	Low	
Choi, 2018[69] 12	Quality of Life: SF-36, Quality of Life Evaluation Scale, Quality of Life after Brain Injury Questionnaire	SF-36 physical component scores increased more in rTMS group compared to sham group at each time point, but SF-36 mental component scores did not change significantly over time.	Unclear	Low SOE: Unclear whether TMS improves quality of life. Limited by inconsistent findings and low to high RoB.
Manko, 2013[74] 40		Mental and physical comfort significantly improved with rTMS (p<0.001) but not in control group (p=.0797).	High	
Stilling, 2020[78] 20		There was a significant time effect for quality of life, but no differences between groups.	Low	
Hoy, 2019[70] 21	Function: Trail Making Test, Conner's Continuous Performance Test	Improvement in Trail Making Test (B) with rTMS, but no difference between groups.	Unclear	Low SOE: Unclear if rTMS improves function compared to sham. Confidence limited by inconsistent findings and unclear RoB.
Leung, 2016[72] 24		No difference in Conner's Continuous Performance (CPT) at wks 1 or 4 between groups. Significant interaction of visit and treatment at 1 wk, with an increase in CPT score with rTMS, but decrease in CPT score with sham	Unclear	
Leung, 2018[73] 29		No overall interaction between group and time on Conner's Continuous Performance (CPT).	Unclear	
Neville, 2019[75] 36		No differences in executive function between groups or in time x group interactions. rTMS group improved significantly at 90-days compared to baseline.	Unclear	
Rao, 2019[76] 34		Effects on neuropsychological functioning varied and favored rTMS for some measures and sham for others.	Unclear	

Opioids				
Liu, 2020[79] 118	Craving score: subjective 0-100 scale	Craving scores decreased more in first 30 days in both 1 Hz and 10 Hz groups, compared to control. All groups had significantly reduced craving score at 30, 60, and 90 days compared to baseline.	Unclear	Moderate SOE: TMS may improve craving scores compared to sham. Limited by unclear RoB.
Shen, 2016[80] 20		Significant reduction in craving score after rTMS but not after sham rTMS.	Unclear	

*defined as suicide (attempt or otherwise), inpatient psychiatric hospitalization, or need for rTMS retreatment)
Abbreviations: iTBS=intermittent theta-burst stimulation; rTMS=repetitive transcranial magnetic stimulation; VAS=visual analog scale; NRS=numerical rating scale; PCL=PTSD symptom checklist; SF-MPQ=Short-Form McGill Pain Questionnaire; MADRS=Montgomery-Asberg Depression Rating Scale; HAM-D=Hamilton Depression Rating Scale; CAPS=Clinician administered PTSD scale; RoB=Risk of bias; S-LANSS=Leeds assessment of neuropathic symptoms and signs; SF-36=short form 36

PEER REVIEW COMMENTS TABLE

Comment #	Reviewer #	Comment	Author Response
Are the objectives, scope, and methods for this review clearly described?			
1	1	Yes	*None*
2	2	Yes	*None*
Is there any indication of bias in our synthesis of the evidence?			
3	1	No	*None*
4	2	No	*None*
Are there any published or unpublished studies that we may have overlooked?			
5	1	No	*None*
6	2	Yes - This depends on the scope of TBI being discussed. Please see below.	*We have clarified the scope of TBI. We did not limit to any severity of TBI but have specified the TBI severity in the included studies.*
Additional suggestions or comments can be provided below. If applicable, please indicate the page and line numbers from the draft report.			
7	1	I think it would be helpful to provide more detail for each indication what type of TMS has been researched as a treatment for the indication. For instance, under each indication there is a call-out box with the number of studies, level of SOE, number and mean of of participants, and summary of findings. It might be helpful to include in these boxes what type of TMS were used in the studies for each of the indications. This would make it easier for the audience to see for which conditions different types of TMS have been explored.	*We have specified in summary statements and in the individual descriptions, which studies are rTMS and which studies are other forms of TMS. We have clarified that most studies are in rTMS throughout.*
8	1	I think it would also be helpful in the Summary and Discussion section to include more context for the results, namely that since rTMS was the more commonly utilized protocol of TMS, the results should be understood in the appropriate context. In this section, the authors state "TMS therapy may be effective for treating chronic pain, PTSD, TBI, and opiate addiction" but there is very little evidence to support this conclusion in the context of iTMS, sTMS, and MERT compared to rTMS or deep TMS. Another way to clarify the context might be to include another figure similar to figure 2 (pg 9 line 13) to show the breakdown of the different types of TMS included in the review, perhaps even broken down to show which were studied and in how many papers for each condition (which would also address my previous	*We have clarified throughout the report that most of the evidence was for rTMS. We have specified in summary statements and in the individual descriptions, which studies are rTMS and which studies are other forms of TMS. We have updated Figure 2 to reflect the number of studies in rTMS and other TMS therapies.*

		point). For each indication, broad statements that "TMS may be effective for x" are used but I think the context of WHICH TMS may be effective is important since some varieties have been much more thoroughly studied than others.	
9	2	The review was very well-written and I have a few suggestions for additional clarity for other readers. Please note that page numbers below refer to the PDF page number and not the page number of the document.	*None.*
10	2	Page 6 - line 24: It would be more accurate to mention here (as you do later in the document), that TMS stimulation passes through the scalp/skull to stimulate the brain at the cortex.	*Changed.*
11	2	Page 8 - line 59: While it is true that any stimulation above 100% of resting motor threshold (RMT) increases the risk for seizure. The typical prescription for MDD is to treat at 120% of RMT. Given that this is common practice, it can be confusing for readers and this detail should be included for completeness.	*We have added this detail for clarity.*
12	2	Page 9 - line 24-25: It is true that the FDA approves the use of a new technology prior before it being used to treat a specific condition. To the best of my knowledge, the FDA approves the initially proposed device. Any additional devices with similar evidence, etc. then must demonstrate the equivalency of their device and it is then "cleared" by the FDA rather than approved.	*This wording has been changed for clarity.*
13	2	Page 20 - Summary Box: I am not sure if there is a typo in this box or if the age range is just flipped. It is odd to read the lower end of the age range on the right.	*This was an error, and the end age range has been fixed.*
14	2	General comments: PAGE 21 - PTSD versus sexual trauma This is a particularly interesting differentiating as it explicitly suggests a couple of differing things: (1) sexual trauma is different from PTSD and/or (2) PTSD resultant from sexual trauma as the criterion A event may manifest itself in a completely different way than other criterion A events. Overall, this implies that the potential underlying neuroanatomical substrates might differ based on type of trauma. The literature does not necessarily support this, but it does suggest that there are other factors which are associated with the incidence of specific types of trauma. All this to say, it is curious as to why sexual trauma is being discussed as a distinct condition.	*We agree that there is the potential for these two patient groups to overlap. We included studies of PTSD, regardless of the traumatic event. Patients with sexual trauma may have been included in these studies, but as the traumatic events were not commonly reported, we do not know if, or how many. Since people with sexual trauma may or may not have a diagnosis of PTSD, and may seek treatment without a diagnosis of PTSD, we feel it makes sense to leave sexual trauma in its own category. Moreover, the legislation motivating the request for this review differentiates PTSD from sexual trauma. We have added a couple of sentences to the discussion section to clarify this potential overlap.*

15	2	PAGE 22 - TBI symptoms and severity In order to fully elaborate on this area, it is important to indicate what severity level of TBI you are discussing. Is the evidence limited to mild to moderate TBI, or does it include information regarding severe TBI. Also, does the scope of the question include treating severe TBI resulting in minimally conscious persons? Reading of this gives the impression that only mild TBI is covered. If so, that should be explicitly stated. The description of symptoms treated is also vague and it is unclear what about TBI is being considered. Does the key question want to focus on cognitive sequelae, mood sequelae, those measured and identified on the Neurobehavioral Symptom Inventory (NSI). Additionally, post-concussive symptoms (PCS) could also be considered a separate condition in itself and has a variety of subsequent considerations. In sum, there is a lack of specificity in this area which makes this section less useful than it could be.	*We agree that more detail is useful in describing the results of the effect of TMS on TBI. We included any study that examined the use of TMS on TBI symptoms (any post-TBI symptoms and any TBI severity). We have added detail on TBI severity in the specific studies. We have added a sentence to clarify that we were looking at any post-TBI symptoms.*

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