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# 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](mailto: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=replicative 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”.<sup>1</sup>

### 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.<sup>2</sup> TMS was introduced in 1985,<sup>3</sup> and has been used in a variety of applications, including for intraoperative neurologic monitoring,<sup>4</sup> to investigate nerve conduction, to diagnose neurologic conditions,<sup>5</sup> 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.<sup>6</sup> 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.<sup>3,7</sup> This induced activity may alter synaptic plasticity, or the ability of nerve cell connections to strengthen or weaken over time.<sup>8</sup> 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.<sup>3</sup>

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.<sup>9</sup> 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.<sup>10</sup> 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.<sup>11,12</sup>

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 ( $\geq 5$  Hz) stimulation has excitatory effects.<sup>9</sup> 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.<sup>3</sup> However, typically MDD TMS protocols treat at 100-120% of RMT without significant side effects in most patients.<sup>13</sup> 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.<sup>14</sup>

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.<sup>5</sup> Another form of EEG-guided TMS, Magnetic eResonance Therapy (MeRT<sup>SM</sup>),<sup>15</sup> 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,<sup>16</sup> and several other devices have since been cleared for this use.<sup>17</sup> 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.<sup>7,18</sup> 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.<sup>3</sup> 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.<sup>13</sup> 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.<sup>13</sup>

Since approval for MDD, rTMS has been investigated for treatment of other conditions, including TBI,<sup>19-21</sup> PTSD,<sup>22-27</sup> pain,<sup>28,29</sup> schizophrenia,<sup>24,30</sup> dementia,<sup>22</sup> and substance use disorder.<sup>22,31,32</sup> The FDA expanded the approved marketing of rTMS for treatment of certain headaches in 2013 and for obsessive-compulsive disorder (OCD) in 2018.<sup>17</sup> 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.<sup>33</sup> 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.<sup>34</sup> 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,<sup>34</sup> mild TBI (tinnitus after mild TBI, update in progress),<sup>34</sup> and headache<sup>34</sup> 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:

- P**opulation: 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

- Setting: Any
- Study 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<sup>35</sup> 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.<sup>36-38</sup> 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,<sup>39</sup> 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.

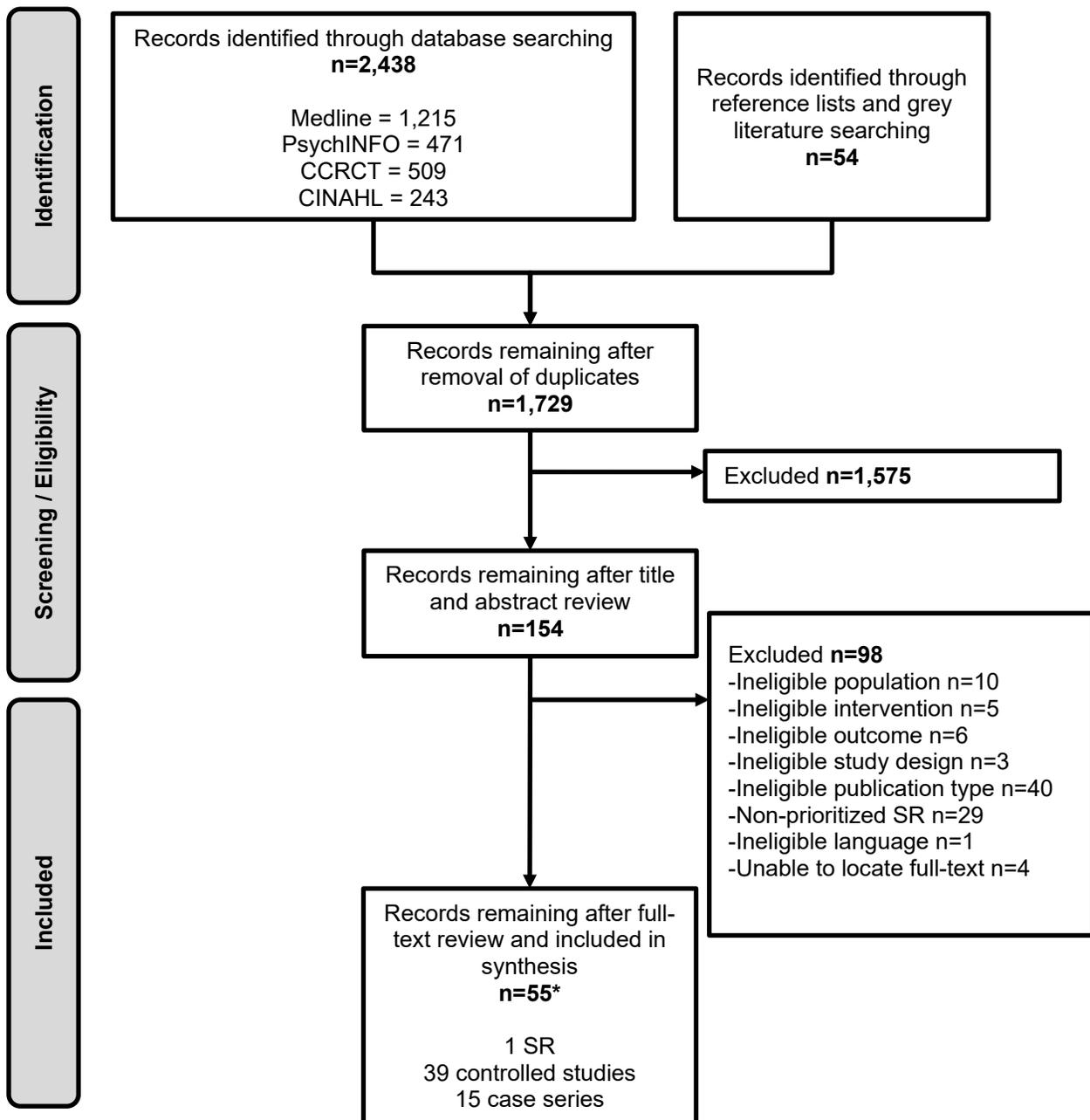
A draft version of this report was reviewed by peer reviewers as well as clinical leadership (see supplemental materials for disposition of peer review comments). The complete description of our full methods can be found on the PROSPERO international prospective register of systematic reviews (<http://www.crd.york.ac.uk/PROSPERO/>; registration number CRD420202648).

## 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**

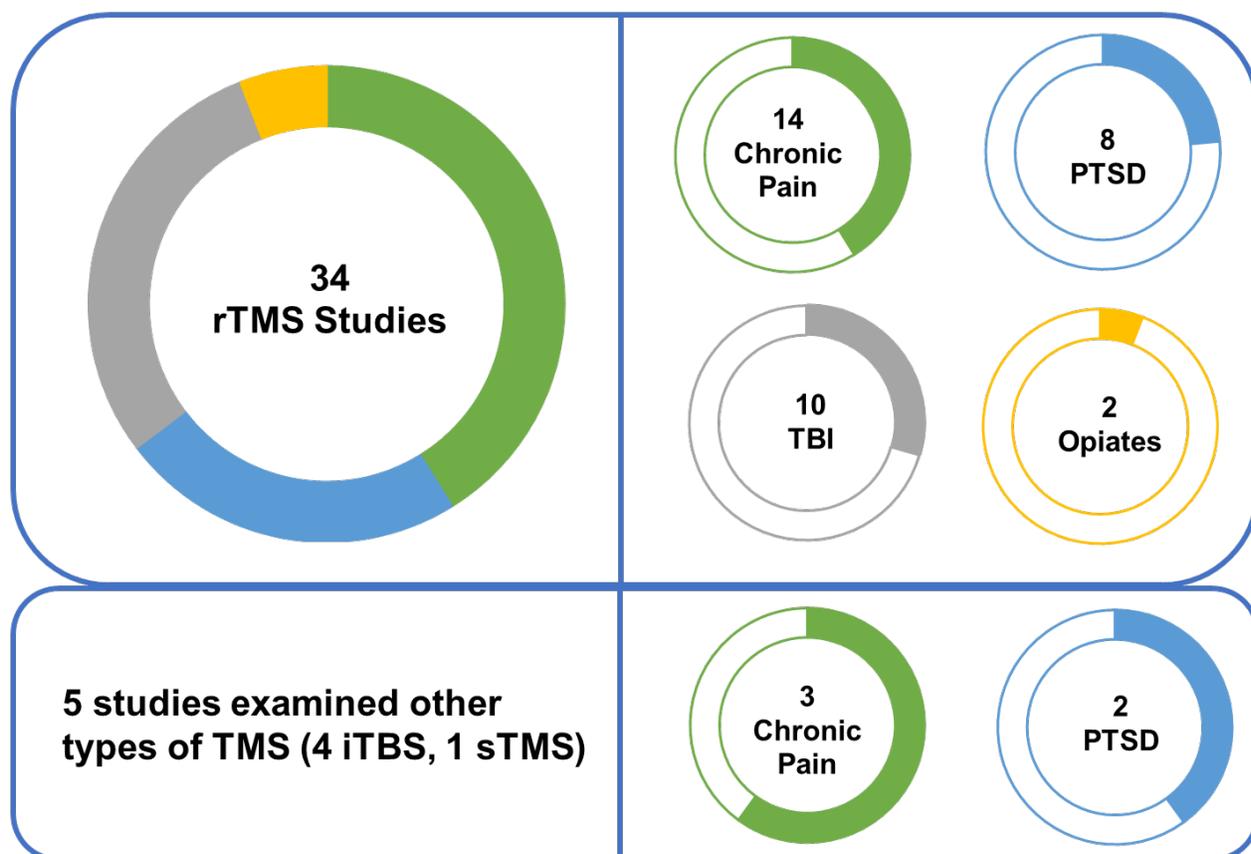


\*In 56 publications (1 study with 2 publications)

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),<sup>35</sup> 39 controlled studies (in 40 publications),<sup>40-79</sup> and 15 case series.<sup>80-94</sup> 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,<sup>71,95</sup> 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)<sup>54,70,48,67</sup> or synchronized TMS (sTMS)<sup>65</sup> (Figure 2).

**Figure 2. Overview of Included Controlled Studies**



Abbreviations: rTMS=repertive 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
<i>Chronic Pain: Neuropathic</i>							
Ahmed, 2020 <sup>41</sup> 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 <sup>43</sup> 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 <sup>49</sup> 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 <sup>51</sup> 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 <sup>54</sup> N=30	RCT 7 months	Patients with CNP	iTBS	Pain	Ipsilateral hemisphere	50 Hz 80% RMT	5 sessions (daily)
Quesada, 2020 <sup>68</sup> 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 <sup>72</sup> 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 <sup>79</sup> 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
<i>Chronic Pain: Fibromyalgia</i>							
Abd Elghany, 2019 <sup>76</sup> N=120	nRCT 1 month	Outpatients with FMS	rTMS	Pain	DLPFC	10 Hz NR	15 sessions (every other day for 1 month)

Atlas, 2019 <sup>42</sup> 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 <sup>44</sup> 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 <sup>45</sup> 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 <sup>77</sup> 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 <sup>50</sup> 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
<b>Chronic Pain: Headache</b>							
Mattoo, 2019 <sup>63</sup> 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 <sup>70</sup> 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)
<b>Chronic Pain: Complex Regional Pain Syndrome</b>							
Gaertner, 2018 <sup>48</sup> 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
<b>PTSD</b>							
Ahmadizadeh, 2018 <sup>40</sup> 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)

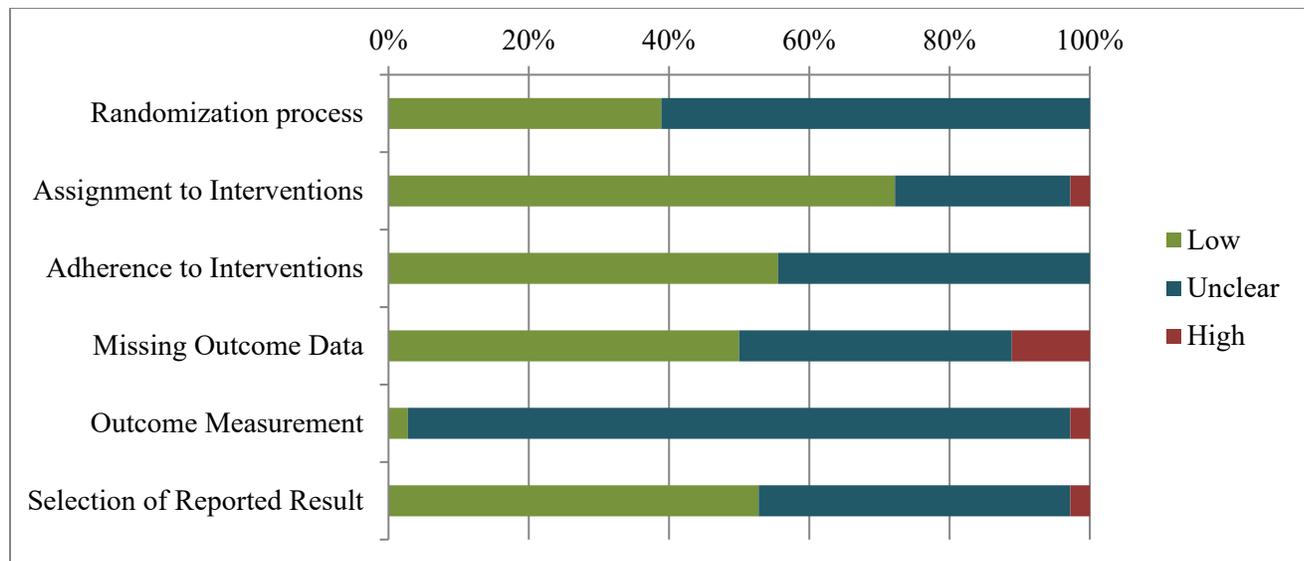
Fryml, 2019 <sup>47</sup> N=8	RCT 8 weeks	Veterans (OIF/OEF) with combat-related PTSD	rTMS and Prolonged exposure therapy (PE)	PTSD symptoms	Right or left prefrontal cortex	10 Hz 120% RMT	8 (1 session/wk for 8 wks)
Isserles, 2013 <sup>53</sup> N=30	RCT 4 weeks	Veterans with PTSD	Deep rTMS + traumatic imagery	PTSD symptoms	Prefrontal cortex	20 Hz 120% RMT	12 (3 sessions/wk for 4 wks)
Kozel, 2018 <sup>55</sup> 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 <sup>56</sup> 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 <sup>58</sup> 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 <sup>64</sup> 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 <sup>65*</sup> 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 <sup>67*</sup> 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 <sup>66</sup> 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 <sup>75</sup> 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)
<b>TBI</b>							
Choi, 2018 <sup>46</sup> 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 <sup>52</sup> 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 <sup>57</sup> 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 <sup>59</sup> 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 <sup>60</sup> 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 <sup>62</sup> N=40	nRCT NR	People with severe TBI and prolonged coma	rTMS	Mental and physical comfort	NR	NR NR	NR
Neville, 2019 <sup>78</sup> 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 <sup>69</sup> N=34	RCT 16 weeks	People with TBI and MDD	rTMS	Depressive symptoms	Right DLPFC	1 Hz 110% RMT	20 (5 consecutive sessions/wk for 4 wks)
Siddiqi, 2019 <sup>73</sup> 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 <sup>74</sup> 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)
<i>Opiate Addiction</i>							
Liu, 2020 <sup>61</sup> 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 <sup>71</sup> 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<sup>35</sup> 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.<sup>35</sup> 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<sup>43,54,68,72,79</sup> reported reduction in pain with TMS compared to sham TMS, while 3 studies<sup>41,49,51</sup> reported no significant difference in pain between TMS and sham groups. In the 2 largest trials (N=100;<sup>49</sup> N=144<sup>51</sup>), 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,<sup>49</sup> 2 studies pain reduction<sup>68,72</sup> compared to sham). A single study compared iTBS to sham iTBS,<sup>54</sup> 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,<sup>49,72</sup> 1 study intermittent theta-burst TMS<sup>54</sup>) and TMS protocols (target location, frequency, intensity, and number of sessions). Evidence from 3 case series<sup>88,89,92</sup> 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).<sup>42,44,45,76,50,77</sup> 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),<sup>42</sup> 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),<sup>45</sup> 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).<sup>77</sup> 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.<sup>50</sup> All studies used rTMS and targeted either the primary motor cortex<sup>42,50</sup> or the left DLPFC<sup>42,44,45,77</sup> 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,<sup>63,70</sup> but the evidence is limited by small sample sizes, and non-random allocation and unclear handling of missing data in 1 study.<sup>70</sup> Two studies reported decreases in pain (using NRS)<sup>63</sup> or migraine frequency, severity, and duration<sup>70</sup> at 8 to 12 weeks with rTMS therapy targeted to the right DLPFC<sup>63</sup> or iTBS therapy targeted to the left DLPFC<sup>70</sup> 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<sup>48</sup> 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<sup>91,93</sup> and general pain (from multiple conditions)<sup>90</sup> over time with TMS therapy. These studies are limited by a study design without a control group.

## POST TRAUMATIC STRESS DISORDER



10 controlled studies  
Low SOE



8-103 participants  
mean age 28-56



4 studies: reduction in PTSD symptoms  
6 studies: no reduction in PTSD symptoms (compared to control)

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),<sup>40,47,53,55,56,64-67,75,58</sup> 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<sup>40</sup> 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,<sup>40,47,53,55,56,67</sup> the largest of which (N=113)<sup>55</sup> 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.<sup>56,58</sup> Two studies compared different frequencies of rTMS stimulation: 1 study<sup>55</sup> found improved CAPS score with both 1 Hz and 10 Hz stimulation, but no significant difference between groups, while another study<sup>58</sup> found improved CAPS score with 1 Hz rTMS compared to sham, but not with 10 Hz rTMS compared to sham. Several case series<sup>80,82,84-87,94</sup> 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)<sup>65,67</sup> or synchronized TMS (sTMS),<sup>66</sup> 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.<sup>65</sup> One case series<sup>82</sup> examined EEG-guided magnetic resonance therapy (MeRT<sup>SM</sup>) and reported improvement in PTSD symptoms after treatment. We also identified 1 RCT (abstract only)<sup>96</sup> that reported improvement in PTSD symptoms in 8 subjects with use of MeRT<sup>SM</sup>, but there was no significant difference in outcomes between MeRT<sup>SM</sup> and sham therapy.

## TRAUMATIC BRAIN INJURY



10 controlled studies  
Low SOE



12-40 participants  
mean age 31-46



5 studies: improvement in symptoms after TBI  
5 studies: no difference (compared to control)

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,<sup>46,57,59,60,69,73,74</sup> but 3 studies<sup>52,62,78</sup> included patients with severe TBI exclusively or along with other TBI severity levels.

rTMS therapy improved headache symptoms,<sup>60,74,83</sup> and overall pain (using NRS)<sup>46</sup> compared to sham therapy in patients with TBI. Two studies in Veterans<sup>60,83</sup> 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.<sup>74</sup> Four studies<sup>52,57,69,73</sup> 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<sup>69</sup> 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.<sup>52,57,60,69,74,78,83</sup> Most studies found some improvement in function, but only 2 studies reported differences between rTMS and sham groups.<sup>57,83</sup> Several studies<sup>46,62,74</sup> 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.<sup>62</sup>

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.<sup>69,74,78</sup> All studies examined rTMS, but varied in target location, frequency, intensity, and number of sessions. Two case series<sup>81,83</sup> generally agreed with these findings, reporting improvements in post-concussive symptoms and pain with rTMS therapy over time.

## OPIATE ADDICTION



2 controlled studies  
Moderate SOE



20-118 participants  
mean age 30-39



All studies: Reduction in opioid craving (compared to control)

In adults with heroin addiction, rTMS therapy likely improves craving scores compared to sham therapy.<sup>61,71</sup> 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<sup>71</sup> to 90 days after treatment.<sup>61</sup>

## 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<sup>40,48,55,56,58,61,68,69</sup> 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<sup>56,69,77</sup> which examined symptom response or remission reported no significant difference between treatment and control groups in fibromyalgia pain,<sup>77</sup> PTSD,<sup>56</sup> or TBI<sup>69</sup> symptom response or remission. Further, only 2 studies evaluated the efficacy of rTMS for opiate addiction,<sup>61,71</sup> 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*).<sup>97</sup> 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<sup>35</sup> 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
<i>Chronic Pain: Neuropathic</i>		
Pain	8 RCTs (N=420) 7 rTMS, <sup>41,43,49,51,68,72,79</sup> 1 iTBS <sup>54</sup>	Low SOE rTMS may decrease pain compared to sham, but confidence is limited by inconsistent findings and low to high RoB among studies.
<i>Chronic Pain: Fibromyalgia*</i>		
Pain	5 RCTs (N=135) <sup>42,44,45,50,77</sup> and 1 nRCT (N=120) <sup>76</sup>	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.
<i>Chronic Pain: Headache</i>		
Headache pain and symptoms	2 RCTs (N=71) 1 rTMS, <sup>63</sup> 1 iTBS <sup>70</sup>	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.
<i>PTSD</i>		
PTSD symptoms	10 RCTs (N=383) 8 rTMS, <sup>40,47,53,55,56,58,64,75</sup> 1 iTBS, <sup>67</sup> 1 sTMS <sup>66</sup>	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 <sup>65</sup>	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
<i>TBI*</i>		
Pain	1 RCTs (N=12) <sup>46</sup>	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) <sup>52,57,69,73</sup>	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) <sup>60,74,83</sup>	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 <sup>46,74</sup> (N=32) and 1 nRCT (N=12) <sup>62</sup>	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) <sup>52,57,60,69,74,78,83</sup>	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
<i>Opiate Addiction*</i>		
Craving Score	2 RCTs (N=138) <sup>61,71</sup>	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)<sup>98</sup> 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  
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### 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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