Effectiveness of Repetitive Transcranial Magnetic Stimulation and Transcranial Direct Current Stimulation in Patients with Fibromyalgia: Meta-analysis

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Abstract

Objective: The purpose of this study is to assess the effectiveness of using repetitive transcranial magnetic stimulation (rTMS) as well as transcranial direct current stimulation (tDCS) for patients suffering from fibromyalgia syndrome (FMS) through a systematic review of randomized clinical trials (RCT). Data sources: Articles were discovered by conducting searches on the following databases: the Cochrane Controlled Trials Register, PubMed and PEDro. Methods: Randomized controlled trials were selected through [2012 to 2024]. Random-effects meta-analyses were done for pooling effect sizes for pain intensity (primary outcome), fatigue, and quality of life (secondary outcomes). Two review authors independently screened articles and evaluated bias risks. Outcome measures were extracted and summarized through qualitative and quantitative methods. Results: The results from 12 studies (n=635 participants) revealed that active tDCS significantly reduced pain intensity (mean difference [MD] = -1.54; 65% CI [-2.55 to -0,52], P=0.003) compared to sham stimulation. In contrast, rTMS showed no significant effects on pain (MD = -0.90; 83% CI [-2.47 to 0.67], P=0.26; P>0.05) or other outcomes with high heterogeneity was observed (I^2 = 65-83%). Subgroup analyses suggested greater tDCS efficacy with [specific parameters, e.g., dorsolateral prefrontal cortex stimulation or occipital nerve]. Conclusions: This meta-analysis provides level 1a evidence supporting that tDCS is effective for pain relief in FM, while current evidence does not support rTMS efficacy. The results support considering tDCS as a therapeutic option, though further studies should optimize protocols and assess long-term effects.

Key words: ***Clinical trials, Fibromyalgia, Pain, Transcranial Magnetic Stimulation or Transcranial Direct Current Stimulation.***

Introduction

A disease or syndrome called fibromyalgia (FM) is thought to have more than one cause, which is still not fully known. It is marked by persistent and widespread pain in the muscles and joints. When pain lasts for three months or more, it is considered to be chronic (1).

Symptoms include impaired cognition, musculoskeletal pain, fatigue, sleep disturbances, and mood problems. As a consequence of these long-lasting symptoms, people with FM may have a worse quality of life (QOL) overall, which impacts their physical, mental, and social aspects of life (2).

Although widespread tender points may indicate a peripheral pathology in fibromyalgia syndrome (FMS), a large body of evidence suggests that improper cortical excitability, dysfunctional pain inhibition, and additionally heightened central pain processing pathways may also play a role (3).

Regarding FMS, there is no treatment that is considered to be the gold standard or a cure. There is a wide range of effectiveness among the various treatment approaches currently in use, including opioids, antidepressants, anticonvulsants, aquatic therapy, biofeedback, exercise programs, acupuncture, cognitive

behavioral therapies, in addition to multidimensional treatments. Treatment options for a range of neurological and mental disorders may include non-invasive brain stimulation methods, which have the ability to induce brain effects (4).

The repetitive transcranial magnetic stimulation (rTMS) method is a crucial non-invasive neuromodulation approach for the brain. The rTMS technique creates an electromagnetic field on the cranium of the individuals who are exposed to the technique. This field is capable of generating a modulation procedure in the cortical areas. This modulation could change depending on the use case. As an example, it seems that cortical excitability decreases with a low-frequency rTMS procedure but increases with a high-frequency one. Furthermore, it seems that the application's site is significant. Several studies have noted its potential use in motivational-affective zones, cortical areas involved in voluntary movement, as well as pathways pertaining to descending pain inhibition. But the M1 receptor has been one of the centers of attention in attempts to alleviate pain (5).

One non-invasive neuromodulation approach that has been utilized to alter maladaptive brain pathways associated with pain chronification is known as transcranial direct current stimulation (tDCS). Electrodes inserted on the scalp produce a low-intensity electrical current (0.5-2.0 mA) during tDCS. Primarily, the method has alleviated pain in FM patients after being administered to the primary motor cortex (M1). It was suggested that tDCS of the neuron M1 may alter inhibitory networks between the neuron and the thalamus, as well as the projections of the neuron M1 to the nociceptive areas of the brain, both in the cortex and inside it. Improvements in cognitive and emotional symptoms of FM patients have been seen after applying this approach across the dorsolateral prefrontal cortex (DLPFC). Since the DLPFC is connected to the anterior cingulate cortex, insula, as well as subcortical regions, stimulating it may reduce fronto-thalamic connectivity and impact processes of nociceptive descending regulation (2).

Methods

The registration for this systematic review is recorded in the PROSPERO review database (Reference: CRD42024514000). The study followed the guidelines outlined in PRISMA (PRISMA 2014), which offers a systematic approach to conducting and reporting data in systematic reviews and meta-analyses (PRISMA Statement) (6).

Search strategy and study selection

The identification of records involved searches across several literature databases, including the Cochrane Controlled Trials Register, PubMed, and PEDro, from 2012 to 2024. The search strategy utilized a comprehensive approach encompassing search terms associated explicitly with rTMS, tDCS on Pain, Fatigue and QOL for individuals diagnosed with Fibromyalgia. These key terms were utilized to search the electronic databases: “fibromyalgia” was added to (“transcranial” and “stimulation”) or “TMS” or “tDCS” or “transcranial magnetic stimulation” or “transcranial direct current stimulation” or clinical trial or “chronic pain” or “neuromodulation”. The search yielded a total of 498 articles. Screening, initially based on titles and abstracts, followed by subsequent independent full-text screening, was done by two authors (Sara Zakaria and Hossam El Sayed).

Inclusion and exclusion criteria

Studies were included according to the following criteria: (1) Randomized control trials (RCTs) of studies from 2012 to 2024. (2) The intervention in the studies was the rTMS and tDCS in patients suffering from fibromyalgia. (3) Studies must be in the English language. Studies that were excluded from the review: (1) A participant's medical history includes conditions like, severe psychological disorders, neurological disorder, developmental disability, pregnancy, drug abuse, cardiac device (pacemaker or defibrillator), inflammatory or autoimmune diseases. (2) Any study was other than RCTs (e.g., cross-sectional, cohort studies, case-control, case series, case reports, and review articles). (3) Articles published in non- English language.

Data extraction and quality assessment

This systematic review employed a structured process to include studies, as depicted in **Figure 1**. Two research team members independently screened articles according to the inclusion criteria at each step, aiming to minimize bias. The title/abstract and full-text screenings were conducted by two reviewers. In cases of discrepancy between the two initial reviewers, a 3rd reviewer was consulted to decide on the inclusion or exclusion of the study.

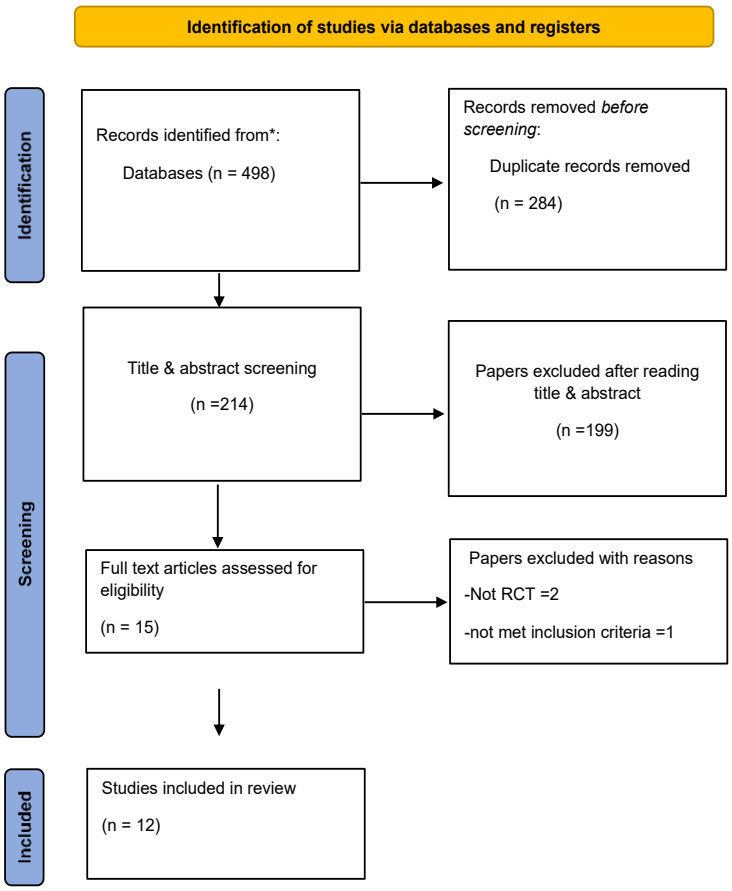


Figure 1. The PRISMA flow chart of the reviewed studies

Two independent reviewers scored all the included studies on their methodological. Using the PEDro scale is more specific to rating RCT quality **(Table 1).** The PEDro scale examines 11 criteria of the quality of methodology. Each satisfied item (except the first item, which is related to external validity) Adds 1 point to the total PEDro score within a range of 0 to 10 topics. The study is considered high- quality RCTs when PEDro Scale scores ≥ 6. The methodological quality was graded using the following system: a scoring of 4 on the PEDro scale denoted poor quality, a scoring of 4-5 characterized fair rates, a scoring of 6-8 denoted good quality, and a scoring of 9–10 denoted excellent quality (7).

Table 1: PEDro scale scores of the studies reviewed

Study	Items											Total	Study Quality
	1	2	3	4	5	6	7	8	9	10	11		
Fagerlund et al. (2015) [8]	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	9/10	Excellent
To et al. (2017) [9]	Y	Y	Y	Y	Y	N	N	N	N	Y	Y	6/10	Good
Khedr et al. (2017) [10]	Y	Y	Y	Y	Y	N	Y	Y	N	Y	N	7/10	Good
Yoo et al. (2018) [11]	Y	Y	Y	N	Y	N	Y	Y	Y	Y	Y	8/10	Good
Veiga et al. (2022) [2]	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	9/10	Excellent
Maestú et al. (2013) [12]	Y	Y	Y	Y	Y	Y	Y	N	N	Y	N	7/10	Good
Tekin et al. (2014) [13]	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	8/10	Good
YAĞCI et al. (2014) [14]	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	8/10	Good
Boyer et al. (2014) [15]	Y	Y	Y	Y	Y	N	Y	N	Y	Y	N	7/10	Good
Fitzgibbon et al. (2018) [16]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	9/10	Excellent
Altas et al. (2019) [4]	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	8/10	Good
Tanwar et al. (2020) [3]	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	8/10	Good

1. Eligibility criteria were specified.
Not counted in the final score.
Out of 10: N: criterion is not met; Y: criterion is met
2. Subjects were randomly allocated to groups.
3. Allocation was concealed.
4. The groups were similar at baseline regarding the most important prognostic indicators.
5. There was blinding of all subjects.
6. There was blinding of all therapists who administered the therapy.
7. There was blinding of all assessors who measured at least one key outcome
8. Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups.
9. All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by ‘‘intention to treat.’’
10. The results of between-group statistical comparisons are reported for at least one key outcome.
11. The study provides both point measures and measures of variability for at least one key outcome

Level of evidence

The level of evidence was measured qualitatively utilizing the modified Sackett’s scale (Sackett et al., 2000). This assessment aimed to make systematic and explicit judgments about the quality of the evidence as well as the strength of the recommendations. The quality of the evidence was then modified based on how well the studies performed across these five domains. Levels of evidence were described as follows:

- 1a (Strong): Three or more randomized controlled trials (RCTs) with similar outcomes or two or more RCTs of excellent quality (PEDro Scale scores ≥6).
- 1b (Moderate): One randomized controlled trial of high quality (PEDro Scale score ≥6)
- 2a (limited): One randomized controlled trial of fair quality (PEDro Scale score=4-5)
- 2b (Limited): A minimum of one properly designed non-experimental study: randomized controlled trials, research without a random assignment of subjects, studies using cohorts with different baselines, and studies using single-subject series with different baselines
- (Consensus): there must be agreement from a panel of experts, a body of field specialists, or many pre-post design studies that have shown similar results for this to be considered a consensus.
- (Conflicting): Data from two or more studies with similar designs that contradict each other
- 5. NO Evidence: No research that were well-designed Research trials of low quality (RCTs) with PEDro ratings of 3 or below, excluding case studies, cohort studies, and single-subject series without various baselines.

Results:

Selection of studies

An overall of 498 studies were found from all electronic and manual search. After excluding all duplicate studies, a total of 214 studies have been screened. Then, 199 studies have been excluded by title and abstract, and 3 studies were excluded after full-text reading. Resulting in 12 studies met the inclusion criteria, as shown in (Figure 1). Descriptions of studies and characteristics of the populations can be found in **(Table 2).**

Study characteristics

Total 12 RCTs were reviewed in this systematic review of both tDCS (5 RCTs) and rTMS (7 RCTs), with a total of 635 patients. Other studies were excluded for not fulfilling the eligibility criteria set for this systematic review.

Level of evidence and quality assessment

The PEDro scale was utilized for the risk of bias assessment, yielding the following results: one study scored 6/10 To et al. [9], three scored 7/10 Boyer et al. [15]; Maestú et al. [12]; Khedr et al. [10] and five scored 8/10 Yoo et al. [11]; Tekin et al. [13]; YAĞCI et al. [14]; Altas et al. [4]; Tanwar et al. [3] and three 9/10 Fagerlund et al. [8]; Veiga et al. [2]; Fitzgibbon et al. [16]. **Table 1** presents comprehensive information on the PEDro scores for all included studies. There was complete consensus between authors for all PEDro scale items. The reviewers considered all chosen trials clinically homogeneous, and a meta-analysis was conducted.

	Table 2: Results of the articles included in the review.							
	Author	**Sample (N) /Age**	**Gender information & Characteristics**	**Inclusion & Exclusion Criteria**	**Intervention**	**Study Variables**	**Results**	**Follow up**
tDCS = 5 articles	**Fagerlund et al. (2015)**	**G1:** n= 24 49.04 ± 8.63 **G2:** n= 24 48.17 ± 10.56	**G1:** 24 Females – 0 males **G2:** 21 Females – 3 males	**Inclusion:** All patients had a positive FIM diagnostic status **Exclusion:** severe psychiatric conditions, neurological conditions, developmental disorders, pregnancy, and drug abuse.	**G1:** tDCS over M1, intensity of 2 mA, 5 consecutive days / 20 min session **G2:** sham tDCs, intensity of 2 mA, 5 consecutive days / only 30 seconds active tDCS	**NRSs** (pain), **FIQ** (FIM symptoms), **HADS** (anxiety & depression), **SF-36** (general physical and mental health), **SCL- 90 R** (psychiatric symptoms and distress)	**Pain intensity:** Active tDCS reported 13.6% reduction in pain compared with sham. **FIQ, HADS, SF-36, SCL-90R:** no primary significant effect of condition was observed.	Not reported
	To et al. (2017)	**G1:** n= 15 47.13 (10.01) **G2:** n= 11 47.81 (10.17) **G3:** n = 16 46.19 (49)	**G1**: M: 3/F: 12 **G2:** M: 1/F: 10 **G3:** M: 2/F: 14 All patients were intractable to tricyclic antidepressants (amitriptyline), pain medication, magnesium supplements, physical therapy and psychological support	**Inclusion**: Patients suffering from fibromyalgia **Exclusion:** patients harboring pathologies mimicking the symptoms of fibromyalgia, having a history of epileptic insults, severe organic comorbidity, a pacemaker or defibrillator, current pregnancy, neurological disorders such as brain tumors, and patients suffering from severe organic or psychiatric co-morbidity	(The site for stimulation was determined by the International 10/20 Electroencephalogram System) **All groups:** 8 sessions, two times a week for 4 weeks **G1:** left and right C2 area tDCS (occipital nerve), intensity of 1.5 mA, ramp up 5 sec until it reached 1.5 mA. tDCS	**NRS** (pain) **PCS** (pain) **MFIS** (fatigue)	**G1:** improve pain only (NRS and PCS) **G2:** improve pain and fatigue (NRS, PCS and MFIS)	Not reported

					stimulation was maintained for a total of 20 min and then ramped down over 5 sec. (total 20 min and 10 sec) **G2:** bifrontal DLPFC tDCS, intensity of 1.5 mA, ramp up 5 sec until it reached 1.5 mA. tDCS stimulation was maintained for a total of 20 min and then ramped down over 5 sec. (total 20 min and 10 sec) **G3:** sham (8 patients C2 – 8 patients DLPFC), intensity of 1.5 mA, ramp up 5 s until reach 1.5 mA then ramp down 5 s, followed by 20 min no active stimulation to blind the procedure (total 10 sec)			
	Khedr et al. (2017)	**G1:** n= 18 31.3 ± 10.9 **G2:** n= 18 33.9 ± 11.2	**G1:** 17 F/ 1 M **G2:** 17 F/ 1 M	**Inclusion:** We included FM patients who reported a mean pain score ≥ 4 on a 10-point visual analog scale (VAS) **Exclusion:** patients with autoimmune or chronic inflammatory disease or	**G1:** tDCS over the left motor cortex (M1) electrode was placed over C3, according to the international 10–20 EEG system, 2 mA, daily for 10 days,	**WPI** (pain) **SS** (pain) **VAS** (pain) **HAM-D** (depression) **HAM-A** (anxiety)	Higher improvement in G1 > G2 (P = 0.001 for WPI, SS, VAS, pain threshold, and 0.002, 0.03 for	at the post 5th session, post 10th session, 2 weeks after the end of sessions and

				inflammatory bowel disease), history of, neuropsychiatric disorders, (major depression and schizophrenia), pregnant and lactating women.	20 minutes on 5 consecutive days/week for 2 weeks **G2:** sham tDCS, 2 mA, daily for 10 days, current applied only 30 seconds		HAM-A, HAM-D respectively).	one month later
	Yoo et al. (2018)	**G1:** n=21 47.81 ± 8.23 **G2:** n=21 45.76 ± 10.80 **G3:** n=16 47.19 ± 8.14	**G1:** 20 F /1 M **G2:** 20 F /1 M **G3:** 15 F /1 M	**Inclusion:** fibromyalgia for at least three months **Exclusion:** major depressive disorders and other psychiatric disorders that are associated with fibromyalgia symptoms. Postmenopausal women were excluded, note that changes in female hormones are associated with the pathogenesis and symptoms of fibromyalgia	**G1:** on the occipital nerve only (ON – tDCS), 1.5 mA, 20 min duration. **G2:** bilateral DLPFC before occipital stimulation (prefrontal added) DLPFC tDCS and ON-tDCS, 2 mA, 40-minute session. consecutively, 20 minutes for both DLPFC tDCS and ON-tDCS on the same day **G3:** Sham, 1.5 mA, 20 min duration (only 10 sec active stimulation) **All groups** had 8 sessions for 4 weeks (tDCS twice weekly – 3 days apart)	**FIQ:** (general disabilities caused by FM) **BDI:** (depression) **NPRS:** (pain)	NPRS and FIQ improved in G1 compared to G3 ($P < .05$). No differences between G2 and G3. BDI improved in G1 and G2 compared to G3 ($P < .05$).	Not reported
	Veiga et al. (2022)	**G1:** n= 32 49.38±8.83 **G2:** n= 33	All participants are females	**Inclusion:** women diagnosed with FM.	**On the left hemisphere** **G1:** M1, 2 mA	**SF-36:** (QoL) **FIQ-R:** (symptoms	All groups improved (active sham)	After treatment

		51.00±9.15 **G3:** n= 33 50.21±8.20 **G4:** n= 29 50.67±8.88		**Exclusion:** immune system pathology substance abuse; psychiatric diseases (except depression and anxiety); brain damage or neurodegenerative disease;	**G2:** DLPFC, 2 mA **G3:** OIC, 2 mA **G4:** Sham, 15 seconds ramp up / down but no current in between **All groups** 15 sessions/ 3 weeks (Monday to Friday) 20 min/session 15 seconds ramp up / down	impact on daily life) **FSQ: include** **-** ***WPI:*** number of body areas pain **-** ***SSS:*** tiredness/fatigue, non-restorative sleep, and cognitive problems, depression, and headache	**with no difference between groups** and maintained for 6 months. For most variables a significant difference np^2>0.14. For general health a small effect between post treatment and follow up 6 months np^2>0.01	and at 6 months
rTMS = 7 articles	**Maestú et al. (2013)**	**G1:** n= 34 **G2:** n= 33 The selected patient group had a mean (± SD) age of 40.7±6.7 years	All participants are females	**Inclusion:** Female patients with fibromyalgia aged between 20 and 60 years. **Exclusion:** Pregnancy, Pacemaker or any other metal implant and patients diagnosed of any other medical condition other than FMS	**G1:** low-intensity TMS across entire cortex, number of series and pulses not specified, 8 Hz pulsed (low frequency **G2:** sham TMS, no stimulation **All groups:** Once per week for eight consecutive weekly sessions 20 min	**PPT:** (pain threshold on 18 tender points **VAS**: (pain) **FIQ:** (ADLs, pain intensity, fatigue, anxiety, depression, sleep quality and severity of headaches).	G1 showed improvements in VAS for daily activities, sleep quality, and perceived pain, compared to G2 (P < .05). No differences were observed in the remaining domains (P > .05)	Not Reported
	Tekin et al. (2014)	**G1**: n = 27 42.4 ± 7.63 **G2**: n = 25	**G1:** 24 F / 3 M **G2:** 23 F / 1 M	**Inclusion:** FMS patients, Right-handed between 18 and 65 years, who could	**G1:** M1, 30 sequential series for 5	**WHOQOL-BREF:** (physical,	Compared to G2, G1 showed	Not Reported

		46.5 ± 8.36		read and write, had no analgesic use at least for 1 month. **Exclusion:** inflammatory or rheumatologic diseases, active psychiatric disorders other than depression, or drug abuse, epilepsy, those with metal implants in the head or facial region, or those with a history of head trauma	seconds/ interval 12 seconds. High frequency (10 Hz) A total 1500 pulse/day **G2:** sham (produce sound only similar to the real TMS) **All groups:** 10 consecutive sessions	psychological, social, environmental, quality of life and general health items) **VAS:** (pain) **MADRS:** (intensity of depressive symptoms)	improvements in VAS and in the physical health domain of the WHOQOL-BREF (P < .05). No differences were observed in the remaining variables (P > .05).	
	YAĞCI et al. (2014)	G1: n= 12 45.25±9.33 G2: n= 13 43±7.63	All participants are females	**Inclusion:** 18-60 years of age, and no improvement in cases of using medical treatment for FM for at least 3 months **Exclusion:** The patients who had inflammatory rheumatic disease, current primary psychiatric disease, previous surgical treatment to the cranial area, pregnancy, or history of substance abuse	**G1:** low rTMS of left M1, Frequency 1 Hz 1200 pulse / session 60 seconds with 45 seconds interval Number of series not reported **G2:** coil placed 90 angles to the motor cortex **All groups:**10 sessions daily for 2 weeks	**VAS:** (pain) **FIQ:** (effects of the treatment on the health domains **BDI:** (Depression and mood)	G1 improved > G2 in FIQ scores and BDI post treatment but not in long term follow up No statistical improvement in other parameters	1st and 3rd months
	Boyer et al. (2014)	**G1:** n= 19 49.1 ± 10.6 **G2:** n= 19 47.7 ± 10.4	All participants are females	**Inclusion:** age > 18 years; right-handed; diagnosis of fibromyalgia, persistent pain for > 6 months and stable treatment > 1 month before enrollment **Exclusion:** inflammatory rheumatic disease, autoimmune disease, major	**G1:** High frequency rTMS on left M1, 20 series of 10 Hz; 2000 pulse. **G2:** sham coil of identical size, color, and shape, emitting a sound similar to that	**FIQ:** (QoL) **SF-36:** (mental and physical QoL component **BDI** (depression) **NPRS** (pain) **PPT:** (pain)	**No differences between groups were observed after treatment (P > .05).**	At week 11: **FIQ** G1>G2 (p = 0.032) **mental component of the SF-36** G1>G2 (p = 0.019)

				depression, substance abuse; neurologic disorders; and contraindications for rTMS including (seizures, brain trauma, brain surgery, intracranial hypertension, a pacemaker or metallic implants, pregnancy & breastfeeding.	emitted by the active coil. **All groups:** 14 sessions/ 10 weeks: **an "induction phase"** of 10 sessions over 2 weeks followed by a **"maintenance phase"** of 4 sessions (1 session at weeks 4, 6, 8, and 10).	**HADS:** (anxiety & depression)		No significant impact was found for other clinical outcomes
	Fitzgibbon et al. (2018)	**G1:** n= 14 45.07 ± 11.02 **G2:** n= 12 46.25 ± 15.04	**G1:** 13 F /1 M **G2:** 11 F/1 M	**Inclusion:** diagnosis of fibromyalgia and had symptoms > 6 months **Exclusion:** TMS contraindications (including epilepsy, seizure, pacemakers, serious head injury, and pregnancy), neurological and/or psychiatric illness, infection, neoplasm, metastasis, osteoporosis, or fracture.	**G1:** TMS over left DLPFC, 75 series of 10 Hz; 3000 pulses **G2:** sham TMS (coil producing a similar sound to the active coil, placed 45 degrees away from the head) **All groups:** 5 sessions, 30-min/session were performed per week for 4 weeks. Total of 20 sessions	**SF-MPQ:** (Pain) **BPI:** (Pain) **NPRS:** (Pain) **SF-36: (**quality of life and current health status) **FIQ: (**quality of life and current health status) **MFI-20:** (fatigue, sleep, cognitive and somatic) **PCS: (**exploring how people think and feel when they are in pain) **BDI:** (Depression) **BAI**: (Anxiety)	G1 improved in the MFI-20, compared to G2 ($P < .05$). No differences between groups were observed in the remaining variables ($P > .05$)	The improvement persists at one month follow –up ($P < .05$)

	Altas et al. (2019)	**G1:** n=10 46.3 ± 9.01 **G2:** n= 10 47.9 ± 7.89 **G3:** n=10 48.2 ± 9.38	All participants are females	**Inclusion:** FMS patients, age > 18 years, right handed, VAS score > 4, pain persist > 3 months and stable treatment > 4 weeks. **Exclusion:** inflammatory rheumatological diseases, autoimmune diseases major depression, substance abuse, neurologic disorders, pregnancy/breastfeeding and contraindications to brain stimulation (seizures, medication-resistant epilepsy, cardiac pacemaker, implanted metal devices in the head).	**G1:** left M1, 10 Hz; 60 series, 1200 pulses, 15 sessions/3 weeks (2 seconds of 10 Hz trains followed by 28 seconds inter-train intervals at 90% resting motor threshold for 30 minutes) **G2:** left DLPFC, 10 Hz; 60 series, 1200 pulses, 15 sessions/3 weeks (2 seconds of 10 Hz trains followed by 28 seconds inter-train intervals at 90% resting motor threshold for 30 minutes) **G3:** Sham, reverse positioned coil over vertex; 0.1 Hz. 1% RMT in order to ensure the clicking sound without actual stimulation of the brain, 15 sessions in 3 weeks (5 session/week)	**VAS:** (Pain) **FIQ:** (QoL) **FSS:** (Fatigue) **SF-36:** Physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role, social role functioning, and mental health **BDI:** (Depression)	Significant improvement in depression, pain and QoL. **- G1>G2** at depression, physical function, physical role and general health. - Emotional role improves in **G1** only. **- G1>G3** in VAS score. (P < .05) **- G2>G1** in physical role function. - No differences between groups were observed in the FIQ or FSS (P > .05).	Not reported
	Tanwar et al. (2020)	**G1:** n=45 41.54 ± 8.58 **G2:** n= 41 39.05 ± 7.12	All participants are females	**Inclusion:** Female patients with FMS (age, 18–50 years) having regular	**G1:** low rTMS right DLPFC, 1 Hz/ 1200 pulses/8 trains (150 pulses/train at inter	**NPRS:** (pain) **MPQ:** (Pain related depression,	G1 shows significant improvement compared to	This improvement maintained in the 3

				menstrual cycle were recruited **Exclusion:** i) unable to give written informed consent form ii) History of seizures iii) History of seizures in first-degree relatives iv) History of any illness involving the brain v) Consumption of medications (like tramadol) vi) History of tinnitus vii) History of bipolar disorder viii) having implants ix) pregnant or lactating x) having chronic systemic disease, and/or any psychiatric disorder xii) currently undergoing psychotherapy	train interval of 1 min). **G2:** (inactive rTMS coil placed over the same area as the active coil. The sham coil produced similar sound as the real coil but without active stimulation of the brain). **All groups:** 5 sessions/ week over 4 consecutive weeks (20 sessions) for 27 min/session.	anxiety, impact of pain and quality of life) **WHOQOL-BREF:** (Pain related depression, anxiety, impact of pain and quality of life).	G2 in NPRS, MPQ, WHOQOL-BREF (physical component only) $P<0.05$ No change in other WHOQOL-BREF components (psychological, social and environmental) or in sham group $P>0.05$	points follow up (15 days Post-rTMS, 3-months and 6-months after the therapy)

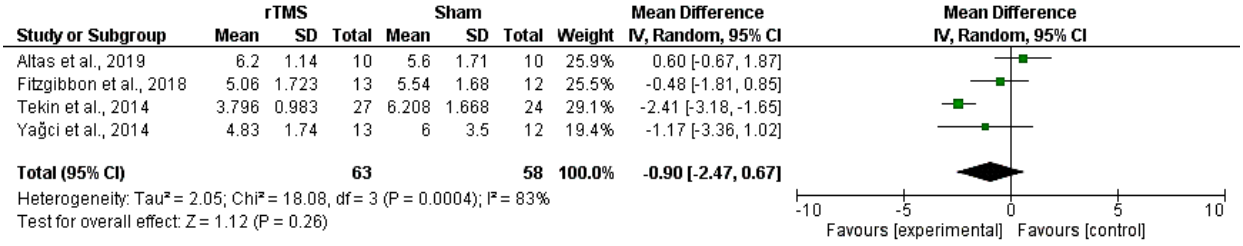
ADLs: Activity Daily Living; BAI: Beck Anxiety Inventory; BDI: The Beck Depression Inventory; BPI: Brief Pain Inventory; DLPFC: Dorsolateral Prefrontal Cortex; F: Female; FIM: Fibromyalgia; FIQ: Fibromyalgia Impact Questionnaire; FSQ: Fibromyalgia Survey Questionnaire; FSS: Fatigue Severity Scale; G: Group; HADS: Hospital Anxiety and Depression Scale; HAM-D & HAM-A: Hamilton Depression and Anxiety Scale; M: Male; M1: Primary Motor Area; mA: milliampere; MADRS: Montgomery-Asberg Rating Scale; MFI-20: Multidimensional Fatigue Inventory; MFIS: Modified Fatigue Impact Scale; MPQ: McGill Pain Questionnaire; N: number; NRS/NPRS: Numeric Pain Rating Scale; OIC: Operculo-insular Cortex; ON: Occipital Nerve; PCS: Pain Catastrophizing Scale; PPT: Pressure Pain Threshold; QoL: Quality of Life; RMT: Resting Motor Threshold; SCL- 90 R: Self Report Instrument containing 90 items; SF-36: 36-item Short Form Health Survey; SF-MPQ: Short-Form McGill Pain Questionnaire; SS: Symptom Severity of Fibromyalgia; SSS: Symptoms Severity Scale; tDCS: Transcranial Direct Current Stimulation; TMS/rTMS: Repetitive Transcranial Magnetic Stimulation; VAS: Visual Analogue Scale; WHOQOL-BREF: World Health Quality of Life-BREF; WPI: Widespread Pain Index.

Meta - analysis

This meta-analysis combined information from individual studies to draw conclusions about the effectiveness of rTMS and tDCS in decreasing pain, fatigue and improving quality of life. Review Manager (RevMan – version 5.4.1, The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark, 2021), as well as Microsoft Excel 2019 (Microsoft Corp., Redmond, WA, USA) were used in the analysis. For results for which data were available, a formal meta-analysis was carried out, with pooled continuous effect measures expressed as the mean difference (MD) with a 95% confidence interval (CI). The I2 test was utilized to investigate and quantify statistical heterogeneity among research. In the studies that had a statistically significant amount of heterogeneity ($p < 0.05$) and the inter-class correlation (I2) was greater than 50%, the random-effects model recommended by (Der Simonian and Laird, 1986) was used. The statistical analysis was two-sided, with the α-error level set at 0.05.

Pain intensity (rTMS):

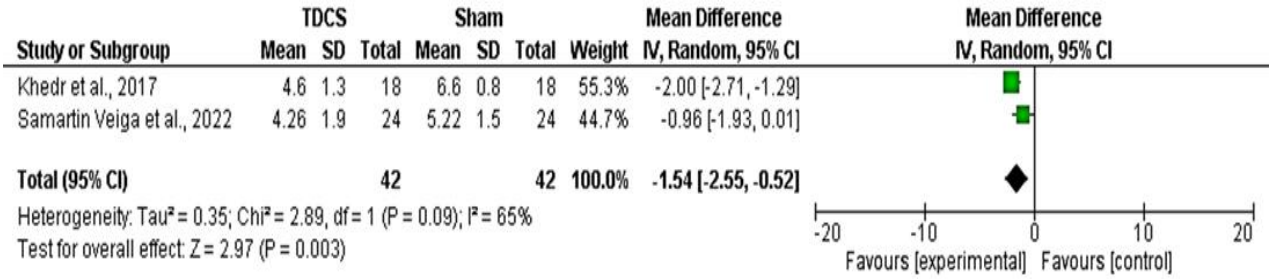
Four studies assessed pain intensity between study group and sham group **(Forest plot 1).** There was significant heterogeneity in pain intensity among four studies (n= 4 studies, n= 121 participants, P=0.0004; I2= 83%). No significant difference was found (P=0.26; P>0.05) in pain intensity (MD= -0.90; 83% CI, -2.47 to 0.67) between study group and sham group **(Figure 2).**



Pain intensity rTMS (Figure 2) Forest plot (1): Comparison between rTMS and Sham TMS groups, outcome: Pain intensity

Pain intensity (tDCS):

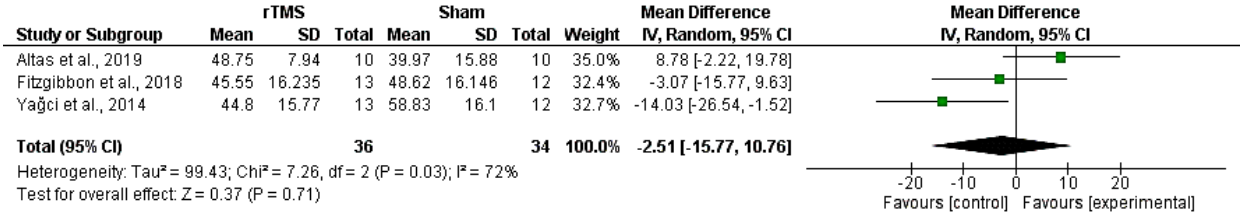
Two studies assessed pain intensity between study group and sham group (Forest plot 5). There was no heterogeneity in pain intensity among two studies (n= 2 studies, n= 84 participants, P=0.09; I2= 65%). There was significant difference (P=0.003; P>0.05) in pain intensity (MD= -1.54; 65% CI, -2.55 to -0,52) between study group and sham group **(Figure 3).**



Pain inte nsity tDCS (Figure 3) Forest plot (2): Comparison between tDCS and Sham tDCS groups, outcome: Pain intensity.

Fatigue Impact Questionnaire (rTMS):

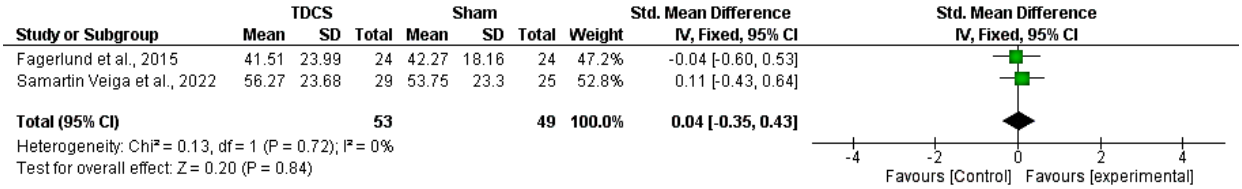
Three studies assessed fatigue impact questionnaire between study group and sham group (Forest plot 2). There was significant heterogeneity in fatigue impact questionnaire among three studies (n= 3 studies, n= 70 participants, P=0.03; I2= 72%). No significant difference was found (P=0.71; P>0.05) in pain intensity (MD= -2.51; 72% CI, -15.77 to 10.76) between study group and sham group **(Figure 4).**



Fatigue Impact Questionnaire (rTMS) (Figure 4) Forest plot (3): Comparison between rTMS and Sham TMS groups, outcome: Fatigue impact questionnaire

Fatigue Impact Questionnaire (tDCS):

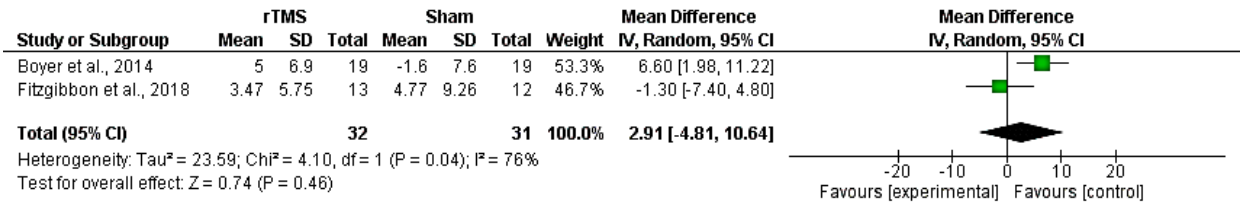
Two studies assessed fatigue impact questionnaire between study group and sham group (Forest plot 6). There was no heterogeneity in fatigue impact questionnaire among two studies (n= 2 studies, n= 102 participants, P=0.72; I2= 0%). No significant difference was found (P=0.84; P<0.05) in fatigue impact questionnaire (MD= 0.04; 0% CI, -0.35 to 0.43) between study group and sham group **(Figure 5).**



Fatigue Impact Questionnaire (tDCS) (Figure 5) Forest plot (4): Comparison between tDCS and Sham tDCS groups, outcome: Fatigue impact questionnaire.

Quality of Life (SF-36) Mental Component (rTMS):

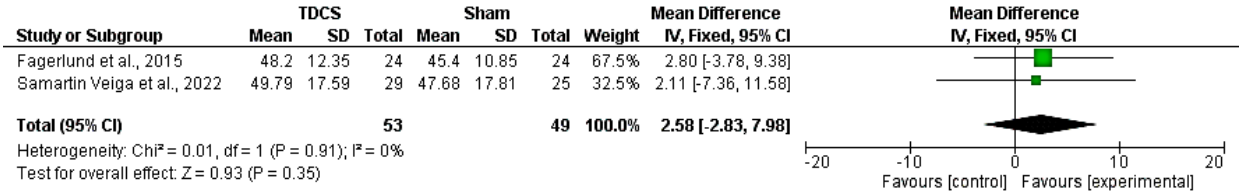
Two studies assessed quality of life (SF-36) mental component between study group and sham group (Forest plot 3). Ther e was considerable heterogeneity in quality of life mental component among two studies (n= 2 studies, n= 63 participants, P=0.04; I2= 76%). No significant difference was found (P=0.48; P>0.05) in quality of life (SF-36) mental component (MD= 2.91; 76% CI, -4.81 to 10.64) between study group and sham group **(Figure 6).**



Quality of Life (SF-36) Mental Component (rTMS) (Figure 6) Forest plot (5): Comparison between rTMS and Sham TMS groups, outcome: Quality of Life (SF-36) Mental component

Quality of Life (SF-36) Mental Component (tDCS):

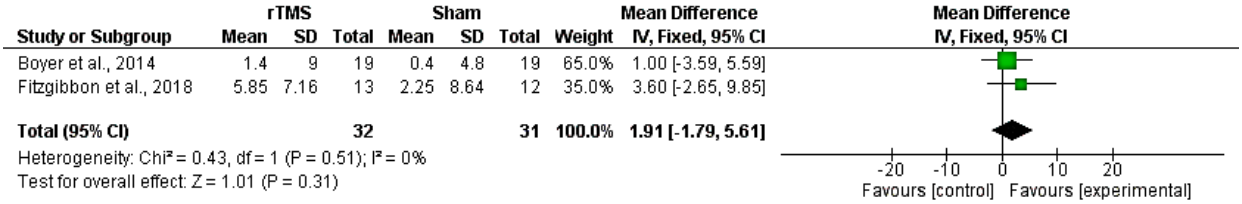
Two studies assessed quality of life (SF-36) mental component between study group and sham group (Forest plot 7). There was no heterogeneity in quality of life mental component among two studies (n= 2 studies, n= 102 participants, P=0.91; I2= 0%). No significant difference was found (P=0.35; P>0.05) in quality of life (SF-36) mental component (MD= 2.58; 0% CI, -2.83 to 7.98) between study group and sham group **(Figure 7).**



Quality of Life (SF-36) Mental Component (tDCS) (Figure 7) Forest plot (6): Comparison between tDCS and Sham tDCS groups, outcome: Quality of Life (SF-36) Mental component

Quality of Life (SF-36) Physical Component (tDCS):

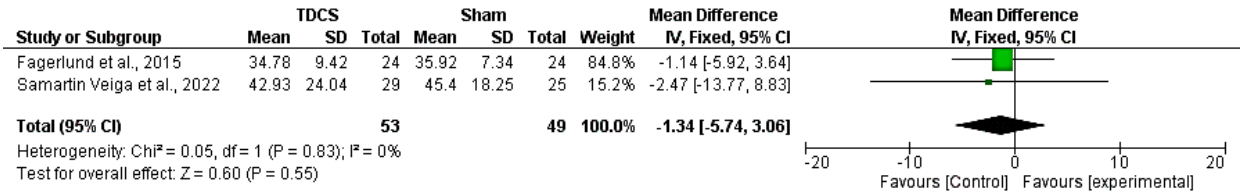
Two studies assessed quality of life (SF-36) physical component between study group and sham group (Forest plot 4). There was no heterogeneity in quality of life physical component among two studies (n= 2 studies, n= 63 participants, P=0.51; I2= 0%). No significant difference was found (P=0.31; P>0.05) in quality of life (SF-36) physical component (MD= 1.91; 0% CI, -1.79 to 5.61) between study group and sham group **(Figure 8).**



Quality of Life (SF-36) Physical Component (rTMS) (Figure 8) Forest plot (7): Comparison between rTMS and Sham TMS groups, outcome: Quality of Life (SF-36) Physical component

Quality of Life (SF-36) Physical Component (tDCS):

Two studies assessed quality of life (SF-36) physical component between study group and sham group (Forest plot 8). There was no heterogeneity in quality of life physical component among two studies (n= 2 studies, n= 102 participants, P=0.83; I2= 0%). No significant difference was found (P=0.55; P>0.05) in quality of life (SF-36) physical component (MD= -1.34; 0% CI, --5.74 to 3.06) between study group and sham group **(Figure 9).**



Quality of Life (SF-36) Physical Component (tDCS) (Figure 9) Forest plot (8): Comparison between tDCS and Sham tDCS groups, outcome: Quality of Life (SF-36) Physical component

Discussion:

This systematic review aimed to find the evidence supporting the effectiveness of tDCS and rTMS in patients with fibromyalgia pain, fatigue and quality of life.

Searching and evaluation of the available relevant studies were done using systematic methods that were reported according to PRISMA flowchart **(Figure 1).** Systematic approaches were followed to find, critically appraise relevant studies, extract and analyze data from the included studies.

Methodological quality assessment in systematic reviews is essential, as variations in study quality can impact conclusions about existing evidence (17). This review utilized the PEDro scale **(Table 1),** to evaluate the quality of the included RCTs. The PEDro scale is a well-validated tool that comprehensively measures the methodological quality of RCTs in physiotherapy interventions (18).

Previous published (19) systematically reviewed nine studies (five rTMS and four tDCS) on non-invasive brain stimulation for fibromyalgia pain, finding that all tDCS studies and most rTMS studies reported significant pain reductions when targeting M1 or DLPFC. Though methodological variability (e.g., stimulation parameters, session numbers and follow-up intervals) prevented quantitative meta-analysis despite available outcome data.

Our systematic review has according to PEDro score three included studies of excellent quality (2,8,16) and the other included studies were of good methodological quality.

Meta-analysis was done to investigate if there was significant difference in the effectiveness between using tDCS / rTMS and using Sham tDCS/ Sham rTMS alone regarding pain, fatigue as well as QOL in patients suffering from fibromyalgia.

Total 12 RCTs were reviewed in this systematic review of both tDCS (5 RCTs) and rTMS (7 RCTs), with a total of 635 patients. Other studies were not included in this systematic review because they failed to fulfill the criteria for inclusion. At rTMS studies, five RCTs (4,13,14,15,16) of the “7" included RCTs in this review were homogenous regarding the outcome measure. Meta-analysis was done in subgroups of the homogenous studies and their data were quantitatively analyzed regarding pain, fatigue and quality of life.

At tDCS studies, three RCTs (2,8,10) of the “5” included RCTs in this review were homogenous regarding the outcome measure and the intensity of the intervention. Meta-analysis was done in subgroups of homogenous studies and their data were quantitatively analyzed regarding pain, fatigue and quality of life.

The meta-analysis of tDCS homogenous RCTs showed significant difference among the two groups (tDCS and sham tDCS) relating to pain in patients with fibromyalgia. No significant difference was noted between the two groups relating to fatigue and QOL. While the meta-analysis of rTMS homogenous RCTs showed no significant difference between the two groups (rTMS and sham rTMS) relating to pain and fatigue and QOL in patients with fibromyalgia.

Heterogeneity was found between the other included studies regarding the outcome measures, the intensity of the intervention and the area of stimulation. So, a qualitative analysis was used to present their data.

All of the rTMS studies are of good quality according to PEDro scale scores table (1) except (16) which of e xcellent quality. Also, they are all double-blind RCT except (3) which was a single blinded trial. All

of the rTMS studies applied stimulation om M1 except two studies applied on DLPFC (3,16) and one study applied on both M1 and DLPFC (Altas et al. 2019). The rTMS studies undergo a meta-analysis in our study except two studies (3,12) which result that there is no significant difference between real and sham rTMS groups regarding pain, fatigue and quality of life.

All of the tDCS included studies are double blind studies except (9,11) are single blind studies. Also, they are all of good quality according to PEDro scale scores **Table (1)** except (2,8) which of excellent quality.

All of the tDCS included studies undergo a meta-analysis in our study except two studies (9,11) which result that there is significant difference among the two groups (tDCS and sham tDCS) relating to pain in patients with fibromyalgia. While no significant difference was observed among the two groups relating to fatigue and QOL.

Several strength points present in this systematic review which included: specificity of the PICO model and collecting all the studies that strictly adhere to the items of the PICO model, RCT studies only were included. The pain, fatigue and quality of life outcomes were mainly reviewed. The PEDro score of the included studies lied between 6 and 9 indicating good quality. It included both descriptive analysis and meta-analysis.

This systematic review encountered several important limitations that should be acknowledged. The heterogeneity between studies prevented meaningful meta-analysis of all outcomes, while the relatively small number of included randomized controlled trials limited the strength of conclusions that could be drawn. Significant variability was observed in both the outcome measures used across studies and the specific stimulation parameters (including type and dose of either tDCS or rTMS), which could not be adequately analyzed due to insufficient data. Despite these constraints, the review's findings - particularly regarding tDCS interventions - demonstrate encouraging potential for pain management in fibromyalgia patients. However, these positive findings must be interpreted with appropriate caution given the methodological limitations.

To establish more definitive evidence, future research efforts should prioritize conducting larger-scale, rigorously designed randomized controlled trials with standardized protocols. Such studies would not only help verify the effectiveness of these neuromodulation techniques but could also investigate additional clinically relevant outcomes beyond those examined in the current literature. The development of such an evidence base would significantly enhance both the reliability and generalizability of findings in this promising therapeutic area.

Study Strengths and Limitations

The strength of this review is that the focused approach provides valuable insights for clinicians considering rTMS & tDCS in managing FMS.

It includes only studies with a randomized controlled trial (RCT) design. The included studies in this syst ematic review exhibit a mean PEDro score of 7.83, indicating good quality. Furthermore, the review employs both descriptive analysis and meta-analysis techniques.

However, the study has certain limitations. The sample size of participants and the number of involved studies are slightly small, which may affect the generalizability of the findings.

Conclusion

In conclusion, this systematic review indicates strong evidence supporting the effectiveness of tDCS for patients with fibromyalgia in decreasing pain intensity with no effect on the secondary outcomes fatigue and QoL. On the other hand, current evidence does not support rTMS efficacy either on the primary outcome (pain) or the secondary outcomes (fatigue & QoL).

However, additional clinical trials are necessary to clinically support this intervention's impact on other outcomes. Confirmation of this evidence require more high quality and large scale randomized clinical trial.

Implication for Physiotherapy Practice

The findings of this systematic review suggest that tDCS may be a beneficial adjunct therapy for reducing pain in patients with fibromyalgia. As such, physiotherapists could consider incorporating tDCS into multimodal treatment plans, particularly for pain management. However, since tDCS did not demonstrate significant effects on fatigue or quality of life, clinicians should complement its use with other evidence-based interventions (e.g., exercise therapy, cognitive-behavioral strategies) to address these secondary outcomes.

Conversely, rTMS did not show consistent benefits across pain, fatigue, or quality of life in fibromyalgia patients. Therefore, physiotherapists should prioritize alternative neuromodulatory or rehabilitation approaches with stronger supporting evidence. Further high-quality research is needed to clarify optimal stimulation protocols before rTMS can be recommended in clinical practice.

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Conflict of Interest

The authors affirm that they have no conflicts of interest.

Author Contributions

All people named as authors meet all four criteria of the ICMJE.

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