REVIEW ARTICLE

Efficacy of Transcranial Direct Current Stimulation and Repetitive Transcranial Magnetic Stimulation for Treating Fibromyalgia Syndrome: A Systematic Review

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■ **Abstract**

Objective: To systematically review the literature to date applying repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS) for patients with fibromyalgia syndrome (FMS).

Method: Electronic bibliography databases screened included PubMed, Ovid MEDLINE, PsychINFO, CINAHL, and Cochrane Library. The keyword ''fibromyalgia'' was combined with (''transcranial'' and ''stimulation'') or ''TMS'' or ''tDCS'' or ''transcranial magnetic stimulation'' or ''transcranial direct current stimulation''.

Results: Nine of 23 studies were included; brain stimulation sites comprised either the primary motor cortex (M1) or the dorsolateral prefrontal cortex (DLPFC). Five studies used rTMS (high-frequency-M1: 2, low-frequency-DLPFC: 2, high-frequency-DLPFC: 1), while 4 applied tDCS (anodal-M1: 1, anodal-M1/DLPFC: 3). Eight were double-blinded, randomized controlled trials. Most (80%) rTMS studies that measured pain reported significant decreases, while all (100%) tDCS studies with pain measures reported significant decreases. Greater longevity of significant pain reductions was observed for excitatory M1 rTMS/tDCS.

Conclusion: Studies involving excitatory rTMS/tDCS at M1 showed analogous pain reductions as well as considerably fewer side effects compared to FDA approved FMS pharmaceuticals. The most commonly reported side effects were mild, including transient headaches and scalp discomforts at the stimulation site. Yearly use of rTMS/tDCS regimens appears costly ($11,740 to 14,507/year); however, analyses to appropriately weigh these costs against clinical and quality of life benefits for patients with FMS are lacking. Consequently, rTMS/tDCS should be considered when treating patients with FMS, particularly those who are unable to find adequate symptom relief with other therapies. Further

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work into optimal stimulation parameters and standardized outcome measures is needed to clarify associated efficacy and effectiveness. ■

Key Words: fibromyalgia, transcranial direct current stimulation, transcranial magnetic stimulation, clinical trials, systematic review

INTRODUCTION

The recent Institute of Medicine report—*Relieving Pain in American: A Blueprint for Transforming Prevention, Care Education, and Research*—describes pain as a ''national challenge'' for the United States.[1] It calls for a ''cultural transformation'' in order ''to better prevent, assess, treat, and understand pain of all types''.[1] Fibromyalgia syndrome (FMS) is a chronic widespread pain disorder that affects 4 to 10 million Americans.[2–14] It is the second most common condition seen by rheumatologists[15,16] and is much more common in women than in men (75% to 90% of cases).[3–6,17] The 1990 American College of Rheumatology (ACR) diagnostic criteria include chronic widespread pain and a painful response to 11 of 18 standardized tender points.[18] Other symptoms include nonrestorative sleep, extreme fatigue, cognitive and mood disturbances, and decreased physical function.[17,18] These patients endure functional limitations (potentially disability), a decreased quality of life, and reduced social and occupational productivity.[19–34] Reports have also shown considerably increased FMS-related direct (by 3-fold[25,35,36]) and indirect (more than 2-fold[25,35,36]) costs when compared to those without FMS.

A multidisciplinary treatment strategy has been recommended for FMS,[19,37–46] including pharmaceuticals (the first-line and most commonly used modality[37,38,40]), behavioral interventions,[37,38] physical therapy,[37,38,45] exercise,[37,38,44] and complementary and alternative medicine;[38,39] notably, no single treatment has proven effective for relieving the full range of FMS symptoms. Further, randomized controlled trials of FDA approved FMS pharmaceuticals have reported considerably high proportions of patient drop-outs and/or adverse events (pregabalin: 21% to 35%, duloxetine: 29%, and milnacipran: 34% to 35%).[47–50]

Recent neuroimaging studies indicate centrally augmented pain processing for individuals with FMS,[51,52] suggesting that therapeutic regimens which target the central nervous system may be effective. Thus, a viable therapeutic option may be noninvasive brain stimulation, including transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). Stimulation of the primary motor cortex (M1) produces antinociceptive effects, while targeting the dorsolateral prefrontal cortex (DLPFC) has antidepressant effects.[53–55] Theoretically, repetitive stimulation of the prefrontal cortex sends information to the connected limbic areas and mood-regulating regions of the cingulate gyrus, orbitofrontal cortex, insula, and hippocampus; also, it may initiate a release of dopamine in the caudate nucleus.[56–58] Additionally, changes in brain activity after repetitive stimulation of the motor cortex are not limited to the motor system; rather, several cortical (cingulate, orbitofrontal and prefrontal cortices, thalamus, and striatum) and subcortical (periaqueductal gray matter) areas are involved.[59–61]

The application of TMS involves an electrical current, which passes through a magnetic coil and produces a brief, intense, and localized magnetic field in the vicinity of the coil. When the coil is held over a subject's head, this magnetic field penetrates their skull to generate an electrical field in their brain.[62] Parameters of each TMS session include brain site, frequency (high/fast ≥5 Hz, low/slow ≤1 Hz), intensity (percentage of the individual's motor threshold), intertrain interval, total trains, and duration.[62] High-frequency (HF) stimulation increases brain excitability, while low-frequency (LF) stimulation has an inhibitory effect;[63] results have been hypothesized to be similar to long-term potentiation and long-term depression.[64] Therefore, TMS can directly target cortical structures of the CNS involved in pain processing[55–61,65,66] and may modulate the inhibited intracortical circuitry of pain perception.[53–55,65]

The tDCS procedure applies a weak current (1 to 2 mA) to the scalp with anodal and cathodal electrodes for typically 20 minutes per session. The suggested mechanisms are electrode dependent and involve either (1) membrane depolarization (increased spontaneous firing and excitability of cortical neurons for anodal stimulation) or (2) membrane hyperpolarization (decreased neuronal firing and excitability for cathodal stimulation).[62] In the most common methodology, one electrode is placed over a specific site, and the other reference electrode(s), placed in another location(s), completes the circuit. The electrode positioning is critical in determining direction and spatial distribution of the current flow and, ultimately, the effectiveness of the treatment.[67] These neuromodulatory

mechanisms may also affect superficial remote structures, in contrast to repetitive transcranial magnetic stimulation (rTMS) (which produces strong, focal effects), and involve various neural circuits of chronic pain.[55]

While exact pathways involved in their analgesic effects are not fully understood,[53] these noninvasive brain stimulation techniques have been increasingly studied regarding their potential as clinically significant treatments for chronic pain conditions.[53–55] A number of recent studies have investigated the use of repetitive TMS (rTMS) and tDCS specifically among patients with FMS, the first being published in 2006.[68] Our objective was to summarize these studies in a systematic review, including specific modalities of rTMS/tDCS (including brain site, frequency, intensity, duration, total sessions), FMS symptom outcomes, and the level of evidence for each study. Results of this report, comparing and analyzing emergent literature in this area, may be used as a patient advocacy resource to integrate rTMS/tDCS into multidisciplinary care for FMS.

METHODS

Systematic Review of the Literature Search Criteria

Electronic bibliography databases screened included PubMed, Ovid MEDLINE, PsychINFO, CINAHL, and the Cochrane Library. The keyword ''fibromyalgia'' was used with (''transcranial'' and ''stimulation'') or ''TMS'' or ''rTMS'' or ''tDCS''. Reference sections of studies that met our inclusion criteria were also manually screened for relevant publications.

Inclusion Criteria

Studies had to meet the following criteria: (1) published in English, (2) involve human subjects only, (3) report original research, (4) used rTMS/tDCS for treatment purposes, (5) consisted only of patients with FMS, and (6) have outcome measures regarding changes in FMS symptoms.

Data Extraction

Full-text records of each retrieved article were reviewed to determine which studies would be included. Extracted study characteristics were adopted from the Cochrane Handbook of Systematic Reviews for Intervention Studies;[69] these comprised country of origin, FMS diagnostic criteria, level of evidence and study design, study population inclusion and exclusion criteria, concomitant treatment use, intervention (including type [rTMS/tDCS], session description, total sessions, and follow-up time), totals per group (active/sham, including proportions completing study), study quality (Jadad score[70]), FMS symptom measures, significant results, adverse events, and side effects.

RESULTS

Study Selection

Electronic bibliography database searches identified 23 citations. Full-text articles were reviewed for our criteria, with 9 of these included in this review.[68,71–78] Excluded studies[53,62–65,67,79–86] are described in Figure 1. Manual screens of reference sections of these 9 studies did not identify any additional citations.

Level of Evidence, Study Design, and FMS Diagnostic Criteria

Four of the 5 rTMS studies were double-blinded randomized clinical trials (RCTs), while all tDCS studies were double-blinded RCTs (Table 1). The fifth rTMS study was a case series extracted from a double-blind RCT of rTMS for treatment-resistant depression and borderline personality disorder, and thus, all FMS subjects were blinded. Also of note, the double-blinded status of the RCTs for rTMS/tDCS only applies to

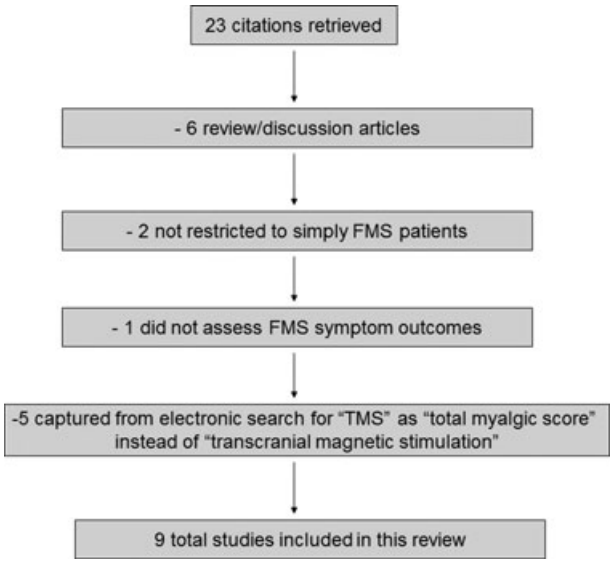

Figure 1. Systematic review study exclusion criteria.

Table 1. Level of Evidence, Study Population, and Interventions

Author, Year, Country, Fibromyalgia Diagnostic Criteria	Level of Evidence and Study Design	Study Sample	Exclusion Criteria	Concomitant Treatments	Intervention(s)	Active Group Total *N*/ Completing (%)	Sham Group Total *N*/ Completing (%)
rTMS studies							
Short,[78] 2011, U.S.A., ACR: 1990	Double-blinded, randomized clinical trial	*N* = 20, naïve to TMS, with or without history of major depression (by DSM-IV [83] criteria), pain solely due to FMS	Medication use known to increase the risk of TMS-related seizures, any medication changes within 4 weeks of the trial or during the trial, or for having pacemakers, epilepsy, recent head trauma, stroke, bipolar disorder, or schizophrenia	Allowed for concomitant FMS medications provided stable use 4 weeks before and during the trial	rTMS of left-DLPFC using ''solid focal'' coil, 2 sets of 5 consecutive daily sessions (10 total), follow-up visits at weeks 3 and 4 (1 and 2 weeks after intervention), 80 trains at 120% of resting motor threshold for 5 seconds at 10 Hz and an interval of 10 seconds between trains (20,000 pulses/session)	10/10 (100%)	10/10 (100%)
Mhalla,[74] 2011, France, ACR: 1990	Double-blinded, randomized clinical trial	*N* = 40, all females, ≥4 of 10 using BPI at baseline	<18 Years of age; inflammatory rheumatic diseases, autoimmune disease, or other painful disorders; a current psychiatric condition; history of substance abuse; pregnancy or no use of contraceptives; history of seizures, brain trauma, brain surgery, or intracranial hypertension; pacemaker or other metallic implants; neurological disorders	Allowed for concomitant medications for pain and sleep, provided the dose was stable for at least 1 month prior to enrollment	rTMS of left-M1 using ''figure-8'' coil; 5 consecutive days, 1/week for 3 weeks, 1/2 weeks for 6 weeks, 1/month for 3 months (14 total over 21 weeks), follow-up visit at week 25; 15 trains at 80% of resting motor threshold for 10 seconds at 10 Hz and an interval of 50 seconds between trains (1,500 pulses/ session)	20/16 (80%)	20/14 (70%)
Carretero,[77] 2009, Spain, ACR: 1990	Double-blinded, randomized clinical trial	*N* = 26, patients with major depression (by DSM-IV [83] criteria) and FMS	<18 Years of age	Allowed for antidepressants up to the maximum tolerated dose ≥6 weeks prior	rTMS of right-DLPFC using ''figure-8'' coil, 4 sets of 5 consecutive daily sessions (20 total), 8 weeks of follow-up, 20 trains at 110% of motor threshold for 60 seconds at 1 Hz and a 45-seconds interval between trains (1,200 pulses/ session)	14/14 (100%)	12/12 (100%)
Passard,[76] 2007, France, ACR: 1990	Double-blinded, randomized clinical trial	*N* = 30, 1 male and 29 females, 18+ years of age, right-handed, ≥4 of 10 pain level of BPI at baseline	Inflammatory rheumatic diseases, autoimmune disease, other painful disease; history of seizures, brain trauma, or brain surgery; intracranial hypertension; pacemaker or other metallic device; current primary psychiatric disorders; pregnancy or no use of contraceptives	Allowed for concomitant pain and sleep medications if ≥1 month pre-enrollment dose stability	Unilateral rTMS of left-M1, 2 sets of 5 consecutive daily sessions (10 total); follow-up at 15, 30, & 60 days after 1st session; 25 series of 8-seconds pulses with 52-seconds interval between series; 10 Hz; 80% resting motor threshold intensity (2,000 pulses/session)	15/13 (86.67%)	15/13 (86.67%)

Table 1. Continued

Author, Year, Country, Fibromyalgia Diagnostic Criteria	Level of Evidence and Study Design	Study Sample	Exclusion Criteria	Concomitant Treatments	Intervention(s)	Active Group Total *N*/ Completing (%)	Sham Group Total *N*/ Completing (%)
Sampson,[75] 2006, U.S.A., not listed	Case series, with subjects blinded to treatment	*N* = 4, subjects with FMS extracted from a trial for TMS in subjects with treatment-resistant major depression and BPD (by DSM-IV [83]), all females	Diagnosis of schizophrenia or schizoaffective disorder, substance abuse within 1 year (except nicotine), unprovoked seizure history or family history of treatment-resistant epilepsy, pregnancy, history of failure to respond to ECT, metal in the head (except dental fillings), any implanted devices, prior brain surgery, any significant change in psychotropic medication within 4 weeks, or any significant change in treators within 6 weeks, suicide attempt within 3 months	Allowed for concomitant and stable use of psychotropic medications	rTMS of right-DLPFC using ''figure-8'' coil, 4 sets of 5 consecutive daily sessions (20 total), 2 trains at 110% of resting motor threshold for 800 seconds at 1 Hz and an interval of 60 seconds between trains (1,600 pulses/ session), 1 subject had sham TMS before receiving active, 1 subject had an additional 12 sessions over 6 weeks as part of a taper protocol for those who had remission of depression	4/4 (100%)	n/a
tDCS studies							
Antal,[73] 2010, Germany, not listed	Double-blinded, randomized clinical trial, with partial cross-over design	*N* = 23, all with therapy-resistant chronic pain (trigeminal neuralgia, poststroke pain syndrome, back pain, FMS), 3 with FMS, all with pain score ≥3 at baseline	Any clinically significant or unstable medical or psychiatric disorder, history of substance abuse, neuropsychiatric comorbidity, patients with metallic or electric implants, use of carbamazepine (which can decrease the effects of tDCS)	Allowed use of other treatments provided use ≥4 weeks prior to enrollment and ability to consistently use during the study	Anodal tDCS of left-M1 with reference cathode over the contralateral supra-orbital area, 5 consecutive daily sessions with 4 weeks of follow-up, constant current of 1 mA intensity applied for 20 minutes	6/5 (83.3%)* active, 13/13 (100%)* with cross-over (active and sham)	4/3 (75%)*
Valle,[72] 2009, Brazil, ACR: 1990	Double-blinded, randomized clinical trial	Women with medically refractory FMS, *N* = 41, ≥4 of 10 level mean pain score over 2 weeks prior to enrollment	Any clinically significant or unstable medical, neuropsychiatric, or other chronic pain disorder, pregnancy, lactation, alcohol/ substance abuse, use of central nervous system affecting medications in the past month, and history of brain surgery, tumor, or intracranial metal implantation	NR	Anodal tDCS of left-M1 at C3 or left-DLPFC at F3 with reference cathode at contralateral supra-orbital area, 2 sets of 5 consecutive daily sessions (10 total) with follow-up at the 10th session and at 30 and 60 days after treatment, constant current of 2 mA intensity applied for 20 minutes	Left-M1 = 14/14 (100%), left-DLPFC = 13/13 (100%)	14/14 (100%)

Table 1. Continued

Author, Year, Country, Fibromyalgia Diagnostic Criteria	Level of Evidence and Study Design	Study Sample	Exclusion Criteria	Concomitant Treatments	Intervention(s)	Active Group Total *N*/ Completing (%)	Sham Group Total *N*/ Completing (%)
Roizenblatt,[71] 2007, Brazil, ACR: 1990	Double-blinded, randomized clinical trial	Females, *N* = 32, ≥4 of 10 level pain score	Any uncontrolled clinical disease, alcohol/ substance abuse, pregnancy, lactation, and current neuropsychiatric disorders	Allowed use of pain medications if stable dose for ≥2 months pre-enrollment	Anodal tDCS of left-M1 at C3 or left-DLPFC at F3 with reference cathode at contralateral supra-orbital area, 5 consecutive daily sessions with follow-up at 21 days, constant current of 2 mA intensity applied for 20 minutes	M1 = 11/11 (100%), left-DLPFC = 11/11 (100%)	10/10 (100%)
Fregni,[68] 2006, Brazil, ACR: 1990	Double-blinded, randomized clinical trial	Females, *N* = 32, ≥4 of 10 level pain and tender point score ≥20 of 72 during 2 weeks pre-enrollment	Any uncontrolled clinical disease, alcohol/ substance abuse, pregnancy, lactation, neuropsychiatric disorders	Allowed use of pain medications if stable dose for ≥2 months pre-enrollment	Anodal tDCS of left-M1 at C3 or left-DLPFC at F3 with reference cathode at contralateral supra-orbital area, 5 consecutive daily sessions with follow-up at 21 days, constant current of 2 mA intensity for 20 minutes	M1 = 11/10 (90.91%), left-DLPFC = 11/11 (100%)	10/10 (100%)

*The study does not give specific enough information for us to extract which members completed/dropped out (ie, according to chronic pain group).
ACR, American College of Rheumatology; BPD, borderline personality disorder; BPI, Brief Pain Inventory; DLPFC, dorsolateral prefrontal cortex; FMS, fibromyalgia syndrome; M1, primary motor cortex; NR, not reported; rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation.

subjects and investigators recording outcomes, not to individuals involved in performing rTMS/tDCS (ie, single-blinded treatment, double-blinded outcomes). Only 2 of 9 total extracted studies were conducted in the United States, with others based in France, Spain, Germany, and Brazil. For 7 of 9 studies, the 1990 ACR criteria[18] were applied for subject FMS diagnosis, while this information was not listed for one each of the rTMS and tDCS studies.[73,75]

Study Sample

Fibromyalgia syndrome samples (N = 228) included 4, 20, 26, 30, and 40 subjects for rTMS and 3, 32, and 41 subjects for tDCS studies (Table 1). The majority of these studies had subject populations that were either all or predominately females. Concomitant medication and/or other treatment uses were reported for 8 studies; dosing/use was stable before enrollment, and continued use during follow-up was planned. Additional study inclusion and exclusion criteria are detailed in Table 1.

Study Quality

Jadad scores were 1 (25%), 3 (25%), and 5 (50%) for rTMS studies and 5 for all of tDCS studies (Table 2). Power estimates were reported for only one study (11.1%),[74] which was also the only study to report intent-to-treat analysis. Seven (77.8%) studies reported appropriate use of either repeated-measures or mixed-effect models for statistical methodology. Of the other 2 studies, one used paired sample t-tests,[77] while the other did not describe their statistical methods.[75] Bonferroni corrections for multiple comparisons were applied in 5 (55.6%) studies.[68,71–73,76] Quantitative data useful for meta-analysis were reported and available for each study, yet meta-analysis methods are not appropriate for this systematic review because of the high degree of variability in interventions reported, particularly regarding brain site, stimulation frequency/intensity, total number of sessions, and follow-up intervals.

Interventions and Follow-up

Specifics of the stimulation modality for each study are described in Table 1. Sites stimulated included left-M1 (40%),[74,76] left-DLPFC (20%),[78] or right-DLPFC (40%)[75,77] for the rTMS studies, and left-M1 (25%)[73]

Table 2. Study Quality and Outcomes

Author, Year, Country, Fibromyalgia Diagnostic Criteria, Intervention	Quality: 1) Jadad Score, 2) Power Reported, 3) Intent-to-treat Analysis, 4) Statistical Method, 5) Multiple Comparisons Adjustment, 6) Data Suitable for Meta-analysis	Analyzed Measures of FMS Symptoms	Significant Results	Adverse Events
Short,[78] 2011, U.S.A., ACR: 1990, HF rTMS of left-DLPFC	1) 5, 2) no, 3) n/a – 100% completed, 4) mixed-effects models and paired t-tests 5) no, 6) yes	9-Item daily pain diary at bedtime to track pain, mood, activity, and sleep; HRSD; BPI; FIQ; tender point assessments	rTMS vs. sham: ND in daily pain, FIQ, or BPI but SL tender points for rTMS at week 2; rTMS: SL pain (29% mean reduction) and depressive symptoms vs. baseline (on average, pain reduction preceded depression improvement by 1 day); sham: ND in pain (4% mean reduction) vs. baseline	2 Complained of a headache after the first treatment
Mhalla,[74] 2011, France, ACR: 1990, HF rTMS of left-M1	1) 5, 2) yes, 3) yes, 4) mixed-effects model, 5) no, 6) yes	Self-reported pain in the past 24 hours using BPI, McGill Pain Sensory and Affective domains, BPI pain interference, FIQ, 21-item Hospital Anxiety and Depression Scale, 13-item short form of BDI, Pain Catastrophizing Scale	rTMS vs. sham, SL: 24-hour recall pain intensity day 5 – week 25; McGill Affective, BPI Interference, and PCS Catastrophizing scores day 5 – week 25; FIQ day 5 – week 9	2 Per group discontinued treatment for headache; 9 others (5 active, 4 sham) with transient mild headache during or just after 1 session, 1 with transient dizziness after 1 session during the induction phase
Carretero,[77] 2009, Spain, ACR: 1990, LF rTMS of right-DLPFC	1) 3, 2) no, 3) n/a – 100% completed, 4) independent and paired sample t-tests, 5) no, 6) yes	17-Item HRSD, self-administered Likert Pain Scale (0 to 10), CGI, Zachrisson FibroFatigue Scale	rTMS vs. sham: ND; within rTMS and sham groups: SL (vs. baseline) CGI at 4 and 8 weeks as well as FibroFatigue Scale at 8 weeks (but changes not clinically meaningful)	TMS group: 6 with neck pain with headache, 1 with worsening of depressive symptoms; sham group: 2 with neck pain with headache, 4 with nausea and increased tiredness
Passard,[76] 2007, France, ACR: 1990, Unilateral HF rTMS of left-M1	1) 5, 2) no, 3) not described, 4) repeated-measures ANOVA & Pearson's correlations, 5) Bonferroni corrections for ANOVA, 6) yes	24-Hour recall pain intensity, McGill sensory, McGill pain, BPI, FIQ, HRSD, BDI, Hospital Depression Scale, pressure pain threshold at tender points	rTMS vs. sham: SL pain VAS at day 15; McGill total and sensory scores at day 15; McGill affective scores on days 15 and 30; BPI general activity, walking and sleep activity scores at days 15 and 30; FIQ total on day 15 and FIQ rest and fatigue on days 15 and 30. SG % of past week pain relief at days 15 and 30; day 15 contralateral epicondyle and trochanter pain thresholds	9 Active and 1 sham with mild and transient headache after 1 of 10 sessions, 1 patient with nausea after 5th visit, 2 with transient tinnitus, and 1 with mild dizziness after sham visit
Sampson,[75] 2006, U.S.A., not listed, LF rTMS of right-DLPFC	1) 1, 2) no, 3) n/a – 100% completed, 4) not described, 5) no, 6) yes	28-Item HRSD, Montgomery Asberg Depression Rating Scale, CGI, GAF, subject pain reports (0 to 10 scale)	All subjects (no sham group) had SL pain vs. baseline; 2 had remission of pain; duration of pain improvement ranged 15 to 27 weeks (when pain ratings increased by ≥1.5 points)	None reported
Antal,[73] 2010, Germany, not listed, anodal tDCS of left-M1	1) 5, 2) no, 3) no, 4) repeated-measures ANOVA, 5) Bonferroni corrections, 6) yes, but only for all pain conditions combined	VAS for pain (rated 3 times/day and computed to daily average) at 30 days before, during, and 30 days after stimulation	tDCS vs. sham in patients with FMS (1 with cross-over, 1 with sham, and 1 with tDCS): ND in pain	tDCS related: headache, difficulty concentrating, acute mood changes, visual perceptual changes, fatigue, and discomforts at the stimulation site (pain, tingling, itching, or burning during and after tDCS)

Table 2. Continued

Author, Year, Country, Fibromyalgia Diagnostic Criteria, Intervention	Quality: 1) Jadad Score, 2) Power Reported, 3) Intent-to-treat Analysis, 4) Statistical Method, 5) Multiple Comparisons Adjustment, 6) Data Suitable for Meta-analysis	Analyzed Measures of FMS Symptoms	Significant Results	Adverse Events
Valle,[72] 2009, Brazil, ACR: 1990, anodal tDCS of left-M1 or left-DLPFC	1) 5, 2) no, 3) n/a – 100% completed, 4) mixed ANOVA model, 5) Bonferroni corrections, 6) yes	VAS for pain, tender point scores, FIQ, BDI, IDATE State-Trait Anxiety Inventory, Geriatric Depression Scale, MMSE for Cognition and Safety	tDCS vs. sham: ND; Pain: ND for sham; SL at the end of treatment, at 30 days, and at 60 days for M1 active; SL at the end of treatment (but not at 30 or 60 days) for DLPFC active; FIQ: SL for M1 and DLPFC active at the end of treatment (only time point measured for FIQ), ND for sham	Minor and uncommon (eg, skin redness and tingling at stimulation site) with equal distribution across the 3 treatment groups
Roizenblatt,[71] 2007, Brazil, ACR: 1990, anodal tDCS of left-M1 or left-DLPFC	1) 5, 2) no, 3) n/a – 100% completed, 4) repeated-measures ANOVA and Spearman's rank correlations, 5) Bonferroni corrections for ANOVA, 6) yes	VAS for pain, tiredness, and anxiety; BDI; FIQ; MMSE for Cognitive and Safety Evaluation; all night polysomnography in a sleep laboratory setting to collect sleep efficiency (%), sleep latency (min), REM latency (min), total sleep time (min), Stage 1 (%), Stage 2 (%), Stages 3 & 4 (%), REM sleep (min), arousals (events/hr), IAH (events/hr), alpha frequencies during non-REM sleep, delta frequencies during non-REM sleep, and the alpha/delta index	M1 and DLPFC tDCS had opposite effects on sleep; M1: SG sleep efficiency, SG arousals, SL delta frequency, and SG alpha/delta index as well as SP correlations for REM latency with FIQ and sleep latency with pain; DLPFC: SL sleep efficiency, SG REM latency, SG sleep latency, SI alpha frequency, SL delta frequency, and SL alpha/delta index as well as SP correlations of sleep latency with pain.	Minor and uncommon with equal distribution across the 3 treatment groups
Fregni,[68] 2006, Brazil, ACR: 1990, anodal tDCS of left-M1 or left-DLPFC	1) 5, 2) no, 3) not described, 4) mixed linear model for pain outcomes, repeated-measures ANOVA for others, & Pearson's correlations, 5) Bonferroni corrections for models, 6) yes	VAS for pain, anxiety, and analgesic use; CGI; PGA; number of tender points; FIQ; SF-36; BDI; MMSE for Cognition and Safety; Stoop Test; digit span forward and backward; simple reaction time	SL pain among M1 active vs. sham, SL CGI among M1 vs. both sham and DLPFC and among DLPFC vs. sham, SL change (%) of tender point assessment in sham vs. both M1 and DLPFC, SG decrease (%) in FIQ among M1 vs. both sham and DLPFC, higher SF-36 physical functioning scores among M1 vs. both sham and DLPFC (ANOVA $P = 0.02$), higher SF-36 pain scores among sham vs. both M1 and DLPFC (ANOVA $P = 0.05$), improved performance of right-hand reaction time among M1 and among DLPFC vs. sham (ANOVA $P = 0.02$), SN correlation between BMI and pain improvement, SN correlation between number of tender points and pain improvement	1 Patient withdrew from study (M1 group) after the 2nd session because of mild and transient redness and itching at the stimulation site

ACR, American College of Rheumatology; BDI, Beck Depression Inventory; BPI, Brief Pain Inventory; CGI, Clinical Global Impression; DLPFC, dorsolateral prefrontal cortex; FIQ, Fibromyalgia Impact Questionnaire; FMS, fibromyalgia syndrome; GAF, Global Assessment of Functioning; HF, high frequency; HRSD, Hamilton Rating Scale for Depression; LF, low frequency; M1, primary motor cortex; MMSE, Mini-Mental State Examination; ND, nonsignificant difference; PGA, Patient Global Assessment; REM, rapid eye movement; rTMS, repetitive transcranial magnetic stimulation; SF-36, Short Form 36 Health Survey; SG, standard gamble SI, significant improvement; SL, significantly lower; SN, significant and negative; SP, significant and positive; tDCS, transcranial direct current stimulation; VAS, visual analog scale.

or a randomized selection of either left-M1 or left-DLPFC (75%)[68,71,72] for tDCS studies. Total treatment sessions were as follows: 10 (40%),[76,78] 14 (20%),[74] and 20 (40%)[75,77] for rTMS studies and 5 (75%)[68,71,73] and 10 (25%)[72] for tDCS studies. Frequencies for rTMS comprised either 1 Hz (LF, 40%)[75,77] or 10 Hz (HF, 60%),[74,76,78] while tDCS sessions were all anodal (100%) with intensities of either 1 mA (25%)[73] or 2 mA (75%)[68,71,72] for 20 minutes. The last follow-up visits for rTMS studies ranged 4 to 25 weeks after the first treatment session. For tDCS studies, the final follow-up visits ranged 21 days to 5 weeks (Table 1).

FMS Symptom Outcome Measures

All (100%) studies assessed pain levels (0- to 10-point scale) and relative changes (Table 2). The Sensory and Affective Domains of the McGill Pain Questionnaire[87] were additionally included for 2 (22.2%).[74,76] One (11.1%)[78] also included a 9-item daily symptom diary (recorded at bedtime to track pain, mood, activity, and sleep), while another (11.1%)[74] also included the Pain Catastrophizing Scale.[88] Three (33.3%)[74,76,78] included the Brief Pain Inventory pain interference assessment.[89] Tender point assessments were recorded for 4 (44.4%).[68,72,76,78] Six (66.7%)[68,71,72,74,76,78] assessed the quality of life outcomes using the Fibromyalgia Impact Questionnaire (FIQ),[90] and one (11.1%)[68] additionally used the SF-36 Health Survey.[91]

Depression assessments included the Beck Depression Inventory (BDI) for depressive outcomes[92] for 55.6%,[68,71,72,74,76] the Hamilton Depression Rating Scale[93] for 44.4%,[75–78] Hospital Depression Scale[94] for 22.2%,[74,76] Montgomery Asberg Depression Rating Scale[95] for 11.1%,[75] and Geriatric Depression Scale[96] for 11.1%.[72] Anxiety assessments included self-reported visual analog scale (VAS) measurements for 22.2%, Hospital Anxiety Scale[94] for 11.1%, and IDATE State-Trait Anxiety Inventory[97] for 11.1%. The Mini-Mental State Examination (MMSE) for Cognition and Safety[98] was conducted for 33.3%.[68,71,72] Fatigue-specific measures were applied in 2 (22.2%). One[77] used the Zachrisson FibroFatigue Scale,[99] while the other[71] used a self-reported VAS measurement.

Other reported measures were the Clinical Global Impression scales[100] for 3 studies (33.3%),[68,75,77] Global Assessment of Functioning scale[101] for one (11.1%),[75] and Patient Global Assessment[100] for another (11.1%).[68] One (11.1%)[68] reported outcomes for analgesic use on a VAS, the Stroop test, simple reaction time, and digit span forward and backward. Another (11.1%)[71] focused primarily on all night polysomnography outcome measurements from a sleep laboratory setting; see Table 2 for details.

Symptom Improvements

Detailed study results are listed in Table 2. Descriptions of more commonly reported outcome measures (ie, used in at least 3 studies) follow.

- *Pain*:
  The majority (80%) of rTMS studies that assessed changes in pain outcomes reported significant decreases.[74–76,78] Significantly decreased pain for active compared to sham groups was reported by Mhalla et al.[74] (HF to left-M1) at day 5 through week 25 and by Passard et al. (HF to left-M1) at day 15 but not for day 30 or 60.[76] Three of the 4 total tDCS studies assessed the changes in pain outcomes;[68,72,73] 2 of these 3 (66.7%)[68,72] reported significant decreases. Fregni et al. (anodal) reported significantly decreased pain for the left-M1 active compared to sham groups at days 1 to 5 and week 3.[68]
- *FIQ*:
  All studies with FIQ assessments (3 for rTMS, 2 for tDCS) reported significant improvements.[68,72,74,76,78] Significantly lower total FIQ scores for the active compared to sham groups were reported by Mhalla et al.[74] (HF rTMS at left-M1) at day 5 through week 9, Passard et al. (HF rTMS at left-M1) at day 15 (as well as rest- and fatigue-specific scores at days 15 and 30),[76] and Fregni et al.[68] (anodal tDCS to left-M1) at day 5.
- *BDI*:
  Of the 5 studies (2 rTMS and 3 tDCS) that assessed BDI, none found significant changes.[68,72,74,76]
- *Tender points*:
  Results of the 4 studies (2 rTMS and 2 tDCS) that evaluated tender point outcomes varied. Among the active compared to sham groups, Passard et al.[76] (HF rTMS at left-M1) found significantly greater pain thresholds for contralateral epicondyles and trochanters at day 15; Short et al.[78] (HF rTMS at left-DLPFC)

reported significantly fewer responsive tender points; Fregni et al.[68] (anodal tDCS, both left-M1 and left-DLPFC groups) found a significantly greater percent decrease in responsive tender points at day 5, while Valle et al.[72] (anodal tDCS, neither left-M1 nor left-DLPFC groups) found no significant differences in responsive tender points.

Drop-outs and Side Effects

The most common side effects for rTMS included transient headache for active groups, while for tDCS the most common side effects were discomforts at the stimulation site, with equal distribution across sham and active stimulation groups (Table 2). Discontinuations because of adverse events were quite rare overall (Table 2). Proportions of subjects completing each study were 70% (1 HF rTMS at M1),[74] 75% (1 of 1 with anodal tDCS to M1 and crossover design—the all sham group),[73] 86.67% (1 HF rTMS to M1),[76] and 100% (1 LF rTMS at DLPFC, 1 HF rTMS at DLPFC, 3 tDCS at M1/DLPFC)[68,71,72,77,78] for the sham stimulation groups and 80% (1 HF rTMS at M1),[74] 83.33% (1 of 1 with anodal tDCS to M1 and crossover design—the all active group),[73] 86.67% (1 HF rTMS to M1),[76] 90.91% (1 of 3 with anodal tDCS to M1),[68] and 100% (3 rTMS, 2 of 3 with anodal tDCS to M1, 3 of 3 with anodal tDCS to DLPFC, 1 of 1 with tDCS to M1 and crossover design—the active + sham group)[68,71–73,75,77,78] for the active stimulation groups (Table 1).

DISCUSSION

Pain Outcomes

The results of this evidence-based systematic review showed that excitatory rTMS/tDCS at left-M1 has an effective and lasting impact on significant pain reduction beyond the duration of the stimulation session (ie, anodal tDCS, HF rTMS).[68,74,76] Also, despite right-DLPFC having a theoretical justification as a stimulation site in patients with FMS, current studies are mixed regarding this site region as an option for LF rTMS.[75,77] Further, the results concerning the use of HF left-DLPFC rTMS[78] as well as anodal left-DLPFC tDCS[68,71] are inconclusive.

Regarding schedules for these noninvasive neurostimulation techniques, Mhalla et al.[74] (published in 2011) applied HF rTMS treatments at left-M1 in 14 total sessions over 21 weeks, while Passard et al.[76] (published in 2007) administered similar treatments in 10 total sessions over 2 weeks. Fregni et al.[68] (published in 2006) used anodal tDCS in 5 consecutive daily sessions. Results from these studies indicate that a combination of ''induction'' with ''maintenance'' phases, as derived from studies on depression,[102] could be both feasible and acceptable to patients with FMS.[74] However, further randomized controlled trials are needed to determine the optimal modality.

FIQ, Depression, & Sleep Assessment Outcomes

Four of the 5 studies that assessed FIQ scores (2 rTMS and 2 tDCS) showed significant improvements among excitatory left-M1 stimulation compared to sham groups.[68,72,74,76] However, these results were only noted earlier during the study follow-up, suggesting a more transient effect of noninvasive neurostimulation on quality of life compared to analgesic relief. Further, no significant differences were noted in the 5 studies (2 HF left-M1 rTMS and 3 anodal tDCS randomized to either left-M1 or left-DLPFC) for BDI outcomes.[68,72,74,76]

Roizenblatt et al.[71] used anodal tDCS randomized to either left-M1 or left-DLPFC and compared polysomnography results (a unique assessment among the studies of this report) prior to and after stimulation. Complaints of nonrestorative sleep are one of the hallmark symptoms of FMS, yet the impact of alpha sleep pattern changes in FMS is unknown.[81,103,104] Slow-wave sleep fragmentation by alpha rhythm or extrinsic stimuli[105–108] is, however, connected to nonrestorative sleep and musculoskeletal pain.[81] Their results showed that excitatory left-M1 stimulation had differing effects on sleep outcomes compared to excitatory left-DLPFC stimulation.[71] Also, the positive impact of excitatory left-M1 stimulation on the sleep variables assessed (specifically, decreased rapid eye movement (REM) latency as well as sleep latency) seemed to have a related positive impact on FIQ score and pain symptoms (with significant correlations observed).

Practical Considerations

In comparison with rTMS, tDCS is less costly and easier to apply in daily practice.[53] Zaghi et al.[109] examined costs of these neuromodulatory approaches for treating chronic pain disorders from a healthcare system perspective, including room utilization, equipment leasing and maintenance, supplies, technician

time, neurologist coverage for each session and/or consultation, and administrative fees. Their cost estimates per treatment session (U.S.$) comprised $167.72 for tDCS and $207.24 for rTMS, with $1.68 and $32.60 for equipment maintenance/leasing, respectively.[109] They also reported costs for one year (10 sessions during the first 2 weeks, followed by once/week as well as 2 sets of booster treatments, totaling 70/year) and for 5 years (with 3% annual discounting) of treatment sessions. Year one costs were $11,740 for tDCS and $14,507 for rTMS, while costs over 5 years were $55,284 and $68,311, respectively.[109] They performed a preliminary cost-effectiveness analysis by summarizing studies in the literature that used these techniques for treating chronic pain. Mean reductions in VAS of pain for each stimulation method were converted to Standard Gamble (SG) utility score summary measures for quality-adjust life years. Their estimates for increases in Standard Gamble utility scores included 0.25 for rTMS and 0.30 for tDCS; this larger response coupled with lower costs suggests that tDCS is always more cost-effective than rTMS for treating chronic pain.[109]

tDCS also has fewer risks than rTMS, which has to apply special safety measures because of threats of induced seizures in certain individuals (now considered very low with use of precautions). However, even though it is relatively safe, more practical for frequent use, and similar in its induced aftereffects, tDCS does not produce the strongly localized effects of rTMS. The most commonly reported side effects of rTMS include headaches, scalp pain, nausea, and temporary hearing problems (requiring the use of ear plugs for prevention). Rare side effects from rTMS include syncope and transient cognitive changes. The most common side effect of tDCS is the tingling sensation felt under the electrodes; nausea, headache, and/or dizziness are also, but rarely, experienced at the start of stimulation. Studies that included a neuropsychological test battery have indicated no adverse cognitive side effects associated with tDCS;[67] notably, the considerably low incidence of adverse effects and treatment discontinuation for rTMS and tDCS among the studies included in this systematic review compare quite favorably to those observed in randomized trials of the FDA approved FMS pharmaceuticals.[47–50]

Limitations

The process of this systematic review of the literature to date has elucidated the need for more research into the optimal parameters for applying rTMS/tDCS to treat FMS, including the site of stimulation, frequency/intensity, and scheduling of sessions. This review has also provided insight into the need for standardized outcome measures for both clinical applications and use in future FMS trials of rTMS/tDCS. Standardized outcome measures are necessary to achieve objective evaluations of these techniques across multiple sites and studies for their therapeutic potential among patients with FMS. Such standardized measures and treatments would also allow an appropriate meta-analysis of future studies in this field. With indications of positive cognitive effects related to enduring rTMS,[67] future studies should also incorporate a neuropsychological battery during follow-up. Further, the literature consistently failed to report proportions of patients per stimulation group with clinically meaningful changes in FMS symptoms, such as patients with ≥30% decrease in pain reported by the clinical trial literature for FDA approved FMS pharmaceuticals. These results are of critical importance for this emerging field in order to compare the results of rTMS to tDCS as well as rTMS/tDCS to prescription medications using cost-effectiveness methodologies.

CONCLUSIONS

Our systematic review provides an evidence-based and educational account for patients with FMS, clinicians, health policy stake-holders, and researchers. rTMS devices have been recently approved for mildly treatment-resistant major depression in Canada, Australia, New Zealand, the European Union, Israel, and the United States.[110] A recent meta-analysis report showed an effect size of 0.55 ($P < 0.001$) for the use of rTMS compared to sham treatment for psychiatric disorders, better than those of pharmaceuticals for depression (0.17 to 0.46). While discussion remains regarding precise mechanisms of action, our systematic review demonstrates that HF rTMS or anodal tDCS at left-M1 significantly improves the main complaints of patients with FMS. The most commonly reported side effects were mild, including transient headaches and scalp discomforts at the stimulation site. Yearly use of rTMS/tDCS regimens appears costly; however, analyses to appropriately weigh these costs against the clinical and quality of life benefits for patients are lacking. Further, as noted by Zaghi et al.,[109] tDCS devices could potentially be designed for patient home use, allowing extended treatment durations for little or no extra

costs. Consequently, excitatory rTMS/tDCS should be considered when treating patients with FMS, particularly for those with pain symptoms resistant to other therapies or who are unable to continue the use of such therapies because of their adverse side effects (as commonly experienced with the FDA approved pharmaceuticals).

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