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ISSN 0017-8748
doi: 10.1111/head.13479
Published by Wiley Periodicals, Inc.

Review Article

Transcranial Magnetic and Direct Current Stimulation (TMS/tDCS) for the Treatment of Headache: A Systematic Review

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Background.—Headache is among the most prevalent causes of disability worldwide. Non-pharmacologic interventions, including neuromodulation therapies, have been proposed in patients who are treatment resistant or intolerant to medications.

Objective.—To perform a systematic review on the use of transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) for the treatment of specific headache disorders (ie, migraine, tension, cluster, posttraumatic).

Methods.—*Data sources:* Ovid MEDLINE, Cochrane Central Register of Clinical Trials, Embase, Scopus, PsycINFO. *Data extraction:* All references were reviewed by 2 independent researchers (3039 abstracts, duplicates removed). Records were selected by inclusion criteria for participants (adults 18-65 with primary or secondary headaches), interventions (TMS and tDCS applied as headache treatment), comparators (sham or alternative standard of care), and study type (cohort, case-control, and randomized controlled trials [RCT]). Studies were assessed using the Cochrane Risk of Bias Tool and overall quality determined through the GRADE Tool. A structured synthesis was performed due to heterogeneity of participants and methods.

Results.—Thirty-four studies were included: 16 rTMS, 6 TMS (excluding rTMS), and 12 tDCS. The majority investigated treatment for migraine (19/22 TMS, 8/12 tDCS). Quality of evidence ranged from very low to high.

Conclusion.—Of all TMS and tDCS modalities, rTMS is most promising with moderate evidence that it contributes to reductions in headache frequency, duration, intensity, abortive medication use, depression, and functional impairment. However, only few studies reported changes greater than sham treatment. Further high-quality RCTs with standardized protocols are required for each specific headache disorder to validate a treatment effect.

Registration Number: PROSPERO 2017 CRD42017076232.

Key words: transcranial magnetic stimulation, transcranial direct current stimulation, migraine, headache

(*Headache* 2019;0:1-19)

INTRODUCTION

Rationale.—Headache disorders are within the top 10 most prevalent medical disorders world-wide and are a significant global contributor to years lived with disability (YLD).[1] In particular, migraine has recently been listed by the Global Burden of Disease Study's 2016 systematic analysis as the second leading cause, next to back pain, of YLD. Tension-type headaches were found to have the fourth and sixth highest worldwide prevalence and incidence, respectively.[1] In addition to the major burden of headache, there is a significant need for non-pharmacologic treatments, particularly in individuals who experience side effects, are treatment resistant, or have medical conditions

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Accepted for publication December 15, 2018.

Conflict of Interest: Drs. Joan Stilling, Chantel Debert, Farnaz Amoozegar, and Oury Monchi have nothing to disclose relevant to this manuscript.

Funding: This systematic review did not receive any funding from any public, private, or nonprofit organizations.

that preclude pharmacologic management. Recent promise in headache treatment has been demonstrated using noninvasive neurostimulation methods; however the number of techniques and treatments vary widely. Specific systematic review of promising neurostimulation methods, including transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), is therefore warranted.

Background.—There are a number of non-pharmacologic, noninvasive neurostimulation techniques currently being researched, which include but are not limited to, TMS, transcranial electric stimulation such as tDCS and transcranial alternating current stimulation (tACS), functional electrical stimulation (FES), transcutaneous electrical nerve stimulation (TENS), peripheral nerve stimulation (vagus, trigeminal, supraorbital, occipital nerves), pulsed radiofrequency, transcranial near-infrared stimulation (NIRS), and electroacupuncture. This is in contrast to invasive electrode neurostimulation techniques, such as sphenopalatine ganglion stimulation (SPG), vagus nerve stimulation (VNS), cortical, and deep brain stimulation (DBS).

The present report will concentrate on 2 promising noninvasive technologies, TMS and tDCS, for the treatment of headache.

Transcranial Magnetic Stimulation (TMS).—TMS is a noninvasive technique that applies Faraday's law of electromagnetic induction, whereby a rapidly alternating magnetic field can induce an electric current in a nearby conductor. During TMS, a brief electric current runs through a wire coil, which induces a magnetic field of up to 2 Tesla.[2] When applied in a rapidly alternating manner, an electric current in the brain is induced parallel to the plane of the coil, which may cause neuronal depolarization and either excitation or inhibition, depending on the type of neuron stimulated.[2,3] TMS is postulated to activate interneurons in the second and third layers of the cortex, which ultimately synapse to pyramidal neurons of the fifth layer.[4] For a comprehensive review of TMS technology, refer to Hallet et al.[2]

There are various protocols of TMS that can be used for different purposes, including single-pulse (sTMS), paired-pulse TMS, and repetitive (rTMS) stimulation. Of the repetitive stimulation modes, there is opportunity to stimulate at low frequency (1 Hz), high frequency (5-20 Hz), or extremely high frequency (50 Hz), defined as theta burst (TBS). TBS can be delivered in an intermittent (iTBS) or continuous (cTBS) manner. Deep TMS (dTMS) is yet another method of stimulation that utilizes a special coil shape to penetrate deeper into the cortex than traditional TMS.

Single-pulse TMS can help determine neuronal thresholds, or the amount of intensity required to elicit a chain of action potentials in a specific region of the cortex. For example, when TMS is applied over the visual cortex, a phosphene can be produced. In patients with migraine, phosphene thresholds have been used to determine cortical excitability. Migraineurs tend to have a lower phosphene threshold than control participants.[5,6] Motor thresholds are an analogous phenomenon to phosphene production. When TMS is applied over the motor cortex, motor-evoked potentials (MEPs) can be recorded through electromyography (EMG) of muscles in the contralateral extremity. A motor threshold is defined as the lowest TMS intensity required to cause a MEP in the target muscle following a single TMS pulse. When 5/10 single pulses (at least 50% of successive trails) of more than 50 μV (peak to peak amplitude) are elicited, motor threshold is attained.[7]

In rTMS, a train of TMS pulses, similar to those delivered in sTMS, are applied at frequencies of 1-50 Hz. Low frequency rTMS (1 Hz) has been demonstrated to inhibit cortical excitability, whereas high-frequency stimulation (5-20 Hz) may lead to an increase in excitability.[8] Theta burst stimulation (TBS) is a form of rTMS that has a 50 Hz frequency and can be applied in the continuous or intermittent mode, which are thought to have inhibitory and facilitative effects, respectively.[2] In addition, rTMS may have long-lasting effects that extend beyond the treatment session,[9] and as a result, has been used as a tool for numerous neurologic and psychiatric diseases, with significant benefit demonstrated in the depression literature.[10-13] Studies investigating its use in stroke,[14] cerebral palsy,[15] neurodegenerative disease,[16] chronic pain,[17] addictions,[18] and anxiety[19] have also shown much promise. TMS was FDA cleared for prevention and acute treatment in migraine with aura (sTMS)[20] in 2014 through use of a handheld, patient administered device, and for treatment-resistant depression (rTMS) in 2011.[21-28]

Common side effects from TMS include headache, dysesthesias/scalp discomfort, facial twitching, mood changes, tinnitus, and fatigue.[29] Serious adverse, however, rare effects include seizures.[8] TMS is available in most urban treatment centers, but is quite costly and inconsistently covered through insurance.[30,31]

Transcranial Direct Current Stimulation (tDCS).—tDCS is another form of noninvasive neurostimulation that applies a low voltage, direct current to the scalp through battery-powered electrodes. In its classical version, 2 electrodes about 25-35 cm^2 in size, are placed in a moistened saline sponge or in contact with conductive gel, and applied to separate areas of the head using EEG International 10-20 coordinates.[25] Current literature suggests that tDCS modulates spontaneous neuronal firing rate through polarization of the resting membrane potential and modification of the synaptic GABAergic activity or NMDA receptor strength.[32,33] This is in contrast to TMS, which is thought to act through suprathreshold depolarization of the neuronal membrane.[33] In general, it is thought that anodal (positive) stimulation results in increased cortical excitability, while cathodal (negative) stimulation contributes to hyperpolarization and decreased excitability.[33] Unlike TMS, tDCS has few adverse events, is very portable, and low in cost.[31,34] Common side effects include mild tingling or light itching under the electrodes, burning sensation, headache, and discomfort.[35] Adverse, rare effects include skin burns and mania or hypomania in patients with major depressive disorder.[36]

tDCS has been used in a number of neuropsychiatric conditions including depression,[32] chronic pain,[17] cognitive enhancement,[37] and motor neurorehabilitation.[17,32] Various studies have been performed using tDCS for both episodic and chronic migraine, tension-type headache, and mixed headache.[10,38-47] Anodal tDCS is the most commonly employed technique with the anode over M1 and the cathode over the contralateral supraorbital area using 1-2 mA current intensity for 15-20 minutes. See included studies section below for further description.

Objectives.—To perform a systematic review on the use of TMS and transcranial direct current stimulation (tDCS) for the treatment of the following headache disorders: migraine, tension, cluster, and posttraumatic headache.

METHODS

Protocol and Registration.—A registered review protocol (PROSPERO 2017 CRD42017076232) can be accessed at: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=76232.

Information Sources.—Ovid MEDLINE (1946-2017 June 28), Cochrane Central Register of Clinical Trails (June 2017), Embase (1974-2017 June 28), Scopus (1823-2017 June 28), PsycINFO (1806 to June Week 3, 2017). We did not impose any date or human restrictions. The search was limited to the English language. The search strategy was repeated on September 1, 2018 to include studies published during the year our review was being performed. Study authors were not contacted to identify additional investigations.

Search.—The search strategy was developed with assistance of a university health sciences librarian (Supplementary Materials 1 – Database Search Strategies). An example search strategy for Embase is listed in Table 1.

Eligibility Criteria.—Inclusion and exclusion criteria for participants, interventions, comparators/controls, outcomes, and study types are displayed in Table 2.

Study Selection.—All references found through database searching were reviewed by 2 independent researchers, after duplicates had been removed. Records were screened and excluded based on eligibility criteria. Any discrepancies between included/excluded studies were reviewed and when a general consensus was not achieved by the 2 reviewers, a third independent reviewer was called upon to resolve conflicts.

Data Collection and Data Items.—Data were collected by an independent researcher and included the following: Study Design (Type, randomization, blinding), Duration, Age (mean), Sex, Headache type, Number in each group, Stimulation Modality, Stimulation Parameters (*TMS:* Intensity [I], Frequency [f], Number of pulses [#], Inter-train interval [ITI], Coil Type, Number of sessions; *tDCS:* Electrode size [E], Intensity [I], Duration [D]), Stimulation Location, Outcome Measures (time points recorded), and Results. Disclosures for each study were reviewed through the publication bias assessment.

Table 1.—Example Search Strategy

Embase Search Strategy
1. exp cough headache/or exp thunderclap headache/or exp primary headache/or exp cluster headache/or exp posttraumatic headache/or exp vascular headache/or exp chronic tension headache/or exp postural headache/or exp chronic daily headache/ or exp episodic tension headache/or exp new daily persistent headache/or exp postdural puncture headache/or exp drug-induced headache/or exp tension headache/or exp episodic cluster headache/or exp exertional headache/or exp stabbing headache/or exp hypnic headache/or exp secondary headache/or exp headache/or exp chronic cluster headache/or exp sinus headache/or exp "headache and facial pain"/
2. exp basilar-type migraine/or exp migraine aura/or exp migraine with aura/or exp complicated migraine/or exp menstrual migraine/or exp migraine without aura/or exp migraine/or exp retinal migraine/or exp vestibular migraine/or exp episodic migraine/or exp sporadic hemiplegic migraine/or exp hemiplegic migraine/or exp familial hemiplegic migraine/or exp "MIDAS (migraine)"/ or exp ophthalmoplegic migraine/or exp transformed migraine/
3. (((headache* or cephalgia* or cephalea* or cephalodynia* or hemicrania* or "head ache*" or (cranial* or head* or cephal* or cerebral*)) adj2 pain*) or migrain*).mp.
4. exp transcranial magnetic stimulation/
5. exp transcranial direct current stimulation/or exp electrostimulation/
6. ("transcranial magnetic stimulation*" or tms or rtms or "tanscranial direct current stimulation*" or tdcs or (transcranial adj3 stimulation)).mp.
7. 1 or 2 or 3
8. 4 or 5 or 6
9. 7 and 8
10. limit 9 to English language

Table 2.—Eligibility Criteria

Eligibility Criteria	Inclusion	Exclusion
Participants	Adults 18-65 with primary or secondary headaches. Primary headaches included both episodic and chronic migraine, tension and cluster headache Secondary headaches, which are caused by an alternative medical condition, included sinus, medication overuse, spinal, infectious (meningitis), brain tumor, aneurysm, cervicogenic, or posttraumatic headache	Pediatric patients (<18 yrs old) and studies with the primary focus including animals, psychiatric disorders (depression, anxiety, obsessive compulsive disease, bipolar, schizophrenia, ADHD, bulimia/ anorexia nervosa, addictions), cognition (memory, neurodegenerative disease), neurologic conditions (seizure, movement disorder, Tourette's, spinal cord injury, multiple sclerosis, Bechet's, restless leg syndrome, spasticity, dystonia, tinnitus, vertigo), and pain (phantom limb pain, fibromyalgia, idiopathic facial pain)
Interventions	Transcranial magnetic stimulation (single or double coiled, for any intensity, frequency, or duration; ie, repetitive transcranial magnetic stimulation (rTMS), single-pulse TMS (sTMS), paired-pulse TMS, theta burst magnetic stimulation (TBS), deep TMS (dTMS), and transcranial direct current stimulation (tDCS) applied as a prophylactic or abortive headache treatment method	Deep brain stimulation (DBS), direct electrical stimulation through surgery, functional electrical stimulation (FES), transcutaneous electrical nerve stimulation (TENS), peripheral nerve stimulation (trigeminal, supraorbital, occipital nerves), electroacupuncture, sphenopalatine ganglion stimulation (SPG), vagus nerve stimulation (VNS), pulsed radiofrequency, transcranial near-infrared stimulation (NIRS), cortical stimulation with invasive electrodes
Comparators/Controls	Sham/placebo or alternative standard of care (ie, botulinum toxin, headache drug)	
Outcomes	Headache frequency, duration, intensity, use of abortive medications, depression, anxiety, and quality of life	
Study Types	Randomized controlled (single, double, or unblinded), cohort, and case-control trials	Expert opinion, case reports/case series

Primary Outcomes: Headache frequency (days/month) and response rate.

Secondary Outcomes: Headache duration, pain intensity, use of abortive medications, depression, anxiety, functional impairment, and quality of life.

Risk of Bias Assessment.—Risk of bias for each individual study was assessed by 2 independent researchers with the Cochrane Collaboration's tool for assessing risk of bias.[48] Discrepancies were resolved by a third researcher. Risk of bias across studies looking at publication bias and selective reporting was also completed by 2 independent researchers. The information obtained was used in the GRADE working group certainty of evidence classification system.[49]

Data Synthesis.—Strong heterogeneity was present with regard to study methods, patient demographics, headache types, intervention characteristics, and outcome measures, which inhibited the pooling of data for a meta-analysis. As a result, aggregate data were obtained and a structured synthesis was performed. Quality of evidence for each primary and secondary outcome was assessed through use of the GRADE working group certainty of evidence classification system.[49,50] All studies reporting on a specific outcome were considered with regard to phase of investigation, risk of bias, and potential publication bias, inconsistency, indirectness, or imprecision across all studies. Phase of investigation was graded based on the Cochrane Handbook's Guidelines for Factor 1 in a GRADE Assessment recommendations.[51] Conflict of interest statements and disclosures were reviewed at the end of each article to assess publication bias. Based on the above disclosures, we downgraded if a study's author was financially invested in the technology. Downgrading for inconsistency occurred when the outcome in question had varying results following use of either TMS or tDCS (ie, headache frequency decreased following rTMS in some studies but increased in others). Indirectness was rated based on the scope of the included sample's population. The overall GRADE score was downgraded for imprecision if only a small number of participants and/or few studies contributed to results for each outcome.

RESULTS

Study Selection.—A total of 6064 studies were discovered and after duplicates removed, 3012 abstracts were screened. Of those, 2878 were excluded based on lack of fulfilment of inclusion and exclusion criteria. The most common reason for exclusion was not utilizing TMS or tDCS as a technology (1310). Ultimately, 134 full text articles were assessed for eligibility, of which 103 were excluded, leaving 31 articles which were included in the qualitative synthesis. A re-search completed on September 1, 2018 added 3 more studies to the analysis. Please refer to the Prisma Flowchart (Fig. 1) for full details and exclusion reasons.

Study Characteristics.—There were a total of 34 studies included in the descriptive synthesis. Of those, 22 were TMS[52-73] (16 rTMS[52-66,72]) and 12 were tDCS[10,38-47,74] articles (Supplementary Materials 2 – Study Characteristics Tables). A comparison of defining study parameters is outlined below.

TMS.—*TMS Methods.*—Twelve TMS studies (9 rTMS,[52,53,56,58,59,62-64,66] 2 sTMS,[69,70] and 1 dTMS[67]) were randomized trials. The remaining 10 were either non-randomized controlled or prospective cohort/open label trials.[54,55,57,60,61,65,68,71-73] Baseline duration among studies ranged from 1 day to 4 weeks, treatment duration varied from 1 day to 3 months, with 4 weeks being most common. The most frequent follow-up duration was from 4 to 8 weeks following completion of treatment, with a few studies collecting data up to 3 months.

TMS Demographics.—The number of people in each study varied from 9 to 100 with a 43.5 median number of participants across all studies. With regard to sex, females significantly outnumbered male participants with an average 3:1 female to male ratio across all subjects. Age range across all studies was 18-65 with an average age of 38.4 (SD 5.7) years.

Headache Type.—Thirteen TMS studies investigated treatment for chronic migraine,[52,53,55,56,61,62,64,65,67,68,71-73] 12 looked at episodic migraine[55,60,61,63,65,66,68-73] and only 5 investigated alternate headache types. These include: chronic tension-type headache,[56] medication overuse headache,[55,72] posttraumatic headache,[57,58] cluster headache,[54] atypical pain,[54] and trigeminal neuropathic pain.[54]

TMS Intervention Characteristics.—Four types of TMS were observed through the review, which include repetitive (rTMS), single-pulse (sTMS), deep (dTMS), and continuous theta burst (cTBS) TMS.

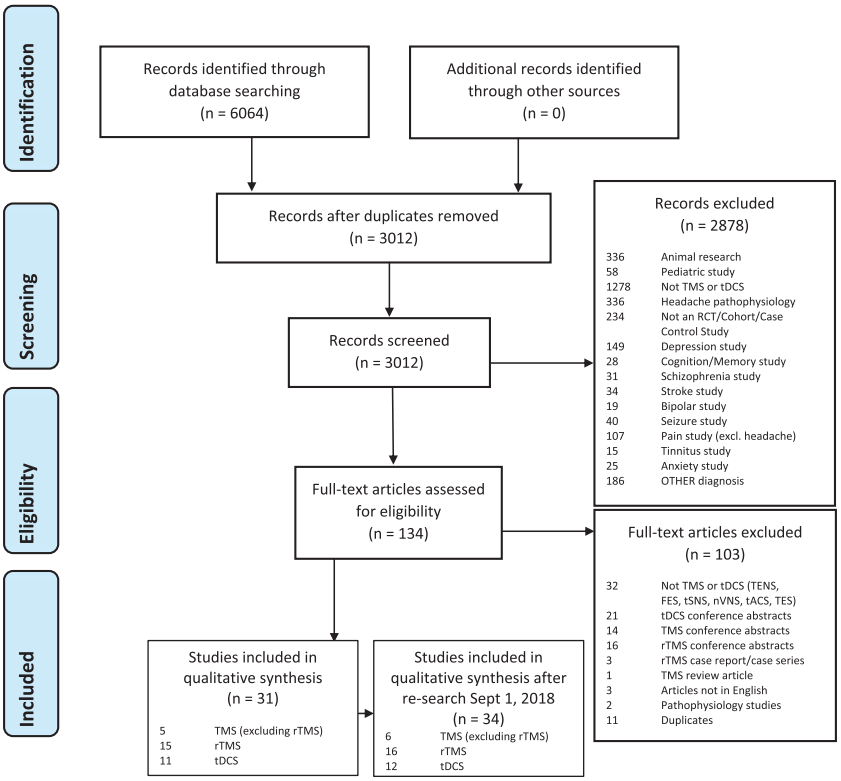

Fig. 1.—Prisma 2009 flow diagram. Abbreviations: transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), randomized controlled trial (RCT), transcutaneous electrical nerve stimulation (TENS), functional electrical stimulation (FES), transcutaneous supraorbital neurostimulation (tSNS), noninvasive vagus nerve stimulation (nVNS), transcranial alternating current stimulation (tACS), transcranial electrical stimulation (TES).

rTMS Parameters.—Most studies stimulated at sub-resting motor threshold intensities (70-90%). Out of the 16 rTMS studies, only Conforto et al[53] and Koski et al[57] stimulated at 110% RMT for 23 and 20 sessions, respectively. The number of rTMS sessions varied from 1 to 23 total treatments. Stimulation location varied between the left dorsolateral prefrontal cortex (DLPFC), bilateral DLPFC, left motor cortex (M1), right motor cortex, occipital cortex, and area of perceived pain.

sTMS.—Four studies investigated the use of single-pulse TMS (sTMS) in the treatment of migraine. Two of the studies (Lipton et al[69] and Clarke et al[70]) looked solely at treatment of episodic migraine, while Bhola et al[71] and Starling et al[73] included both episodic and chronic migraine participants. In general, 1 to 2 pulses of 0.9-1.1 T were delivered 5-30 seconds apart over either the occipital region or the area of perceived pain or region of aura generation.

cTBS.—One study by Chen et al in 2016[68] used continuous theta burst stimulation (cTBS) for the treatment of both episodic and chronic migraine. Theta burst stimulation was directed over the motor cortex at 50 Hz, with 200 ms intervals for 40 seconds, at an intensity of 80% resting motor threshold (RMT) of the abductor pollicis brevis muscle. Sessions were completed every weekday for 4 weeks (20 sessions).

dTMS.—Only 1 study by Rapinesi et al[67] investigated dTMS as a treatment for chronic migraine. Stimulation was completed over bilateral DLPFC at 100% MT (APB), at 10Hz, with 360 total pulses using an H1 coil. Treatment was delivered for 3 sessions on alternate days, for a total of 12 sessions over 1 month.

tDCS.—*tDCS Methods.*—Eight tDCS investigations were randomized trials.[39-42,44,45,47,75] The remaining 4 were either retrospective[43] or prospective[38,46,74] cohort studies. Baseline duration among studies ranged from 1 day to 3 months, treatment length varied from 1 to 12 weeks (4 weeks

most common), and follow-up duration ranged from 4 to 20 weeks.

tDCS Demographics.—The number of people in each study varied from 9 to 112 with a median number of 21 participants across all studies. Average age across all studies was 36.2 (SD 7.6) years. The female to male ratio was 1.8:1 among all subjects.

Headache type.—Treatment duration ranged from 1-12 weeks. The majority of studies were done on patients with migraine (7 episodic,[40,41,43,44,46,47,75] 3 chronic[38,39,42]), with 3 additional studies looking at chronic tension-type headache,[38,43,44] 2 at episodic tension headache,[43,45] 1 at mixed headache (tension and migraine),[45] 1 at chronic daily headache[38] and 1 at refractory chronic cluster headache.[74]

tDCS Intervention Characteristics.—Most studies performed anodal tDCS stimulation, while 3 completed cathodal tDCS stimulation.[40,47,75] Electrode size ranged from 25-42 cm^2, with a 1-2 mA stimulation intensity over a 15-20 minute duration. The number of sessions varied between studies, with some having daily treatment to others delivering therapy 3x/week for a total of 5-20 sessions. Cathode position varied between primary visual cortex (Oz), contralateral supraorbital area (Fp2), ipsilateral mastoid process, temple of side with greatest pain, spinous process of C7 and the chin. Anode position was located at the vertex (Cz), L-M1 (C3), L-DLPFC (F3), midline (Fz), to the temple on the opposite side of greatest pain.

Risk of bias in individual studies.—The risk of bias in the included TMS studies demonstrated 11 high, 7 unclear, and 4 low risk investigations. In contrast, the tDCS articles had 6 high, 5 unclear, and 1 low risk studies (Tables 3–6: Risk of bias).

Results of Individual Studies.—Study characteristics with results of each individual study are presented in the Supplementary Materials 2 – Study Characteristics Tables. Below are descriptions of the individual studies that were included in our systematic review. None of the high-quality studies reported effect size measures. As such, we calculated odds ratios (OR) and Cohen's d where data were available.[76]

rTMS and Headache.—Sixteen rTMS and headache studies were discovered through the systematic review. Three were graded as high quality with a low overall risk of bias.[52,53,66] Five studies were moderate (uncertain risk of bias),[56,58,59,62,63] 6 low (high risk of bias),[55,57,60,61,64,65] and 2 very low quality (high/uncertain risk of bias).[54,72]

The 3 high-quality rTMS studies were different with regard to type of headache investigated, treatment duration, stimulation intensity and frequency, number of pulses, location, and outcome measures.

The first of these high-quality studies was done by Brighina et al who performed a parallel-group, randomized, double-blind, clinical trial looking at patients with a diagnosis of chronic migraine in 2004.[52] After a 4-week baseline period, 11 participants were exposed to 12 sessions of rTMS therapy on alternate days of the week. Their stimulation intensity was at 90% of resting motor threshold (RMT), at a frequency of 20 Hz, with a total of 400 pulses delivered each session (40 pulses of 10 trains with 30s inter-train interval [ITI]). Their target stimulation location was the left DLPFC which was localized anatomically by proceeding 5 cm anterior to the FDI motor hotspot. They measured headache attack frequency, headache index (frequency × intensity), and number of abortive medications. Findings included a significant Treatment × Time interaction for attack frequency ($F(2,18) = 13.86$, $P < .0002$), number of abortive pills ($F(2,18) = 16.83$, $P < .0001$), and headache index ($F(2,18) = 28.78$, $P < .0001$). There was a change between baseline and 2 months of −13 (6.8) attacks/month for the TMS group and −1.8 (2.8) attacks/month for the placebo (mean (SD); Cohen's d = 2.15, very large effect size). The number of abortive pills decreased by 20 (10.3) pills/month in the TMS group and 1.4 (9.9) in the placebo (Cohen's d = 1.84, very large effect size), while headache index decreased by 36 (19.2) for the TMS and 4.8 (9.0) for the placebo (Cohen's d = 2.09, very large effect size) when comparing baseline to 2 months. Furthermore, there was no significant difference in the sham group when compared to baseline.

In contrast, Misra et al completed a single-center, randomized, sham-controlled, double-blind trial in 2013 investigating the treatment of episodic migraine with rTMS.[66] In this study, 100 participants underwent 3 sessions on alternate days. Stimulation intensity set to 70% RMT of the abductor digiti minimi muscle was delivered at 10 Hz for a total of 600 pulses (60 × 10 trains with 45 s ITI). The location of stimulation in this study varied from the above in that

Table 3.—Risk of Bias assessment for use of repetitive transcranial magnetic stimulation (rTMS) as a treatment for headache.

1st Author, Year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Incomplete outcome data addressed (attrition bias) (Short-term outcomes (2-6 weeks))	Incomplete outcome data addressed (attrition bias) (Long-term outcomes (>6 weeks))	Selective reporting (reporting bias)	OVERAL Risk of Bias	GRADE Quality
Brighina, F. 2004	+	?	+	+	+	+	+	+	High
Conforto, AB. 2014	+	+	+	+	+	+	+	+	High
Hodaj, H. 2015	-	-	-	-	-	-	-	-	Very Low
Kalita, J. 2016(Cephalalgia)	-	-	-	?	+	?	+	-	Low
Kalita, J. 2016(J neuro)	-	?	?	-	+	+	+	?	Moderate
Koski, L. 2015	-	-	-	-	+	+	-	-	Low
Leung, A. 2017	+	+	+	?	?	?	+	?	Moderate
Leung, A. 2016(Neuromodulation)	+	?	+	?	+	?	+	?	Moderate
Misra, U. K. 2012	-	-	-	-	+	?	+	-	Low
Misra, U. K. 2013	+	+	+	+	+	?	+	+	High
Shehata, H.S. 2016	+	+	-	-	+	+	+	?	Moderate
Teepker, M. 2010	?	?	+	-	+	+	+	?	Moderate
Teo, W. P. 2014	?	?	+	?	-	-	+	-	Low
Misra, U. K. 2017	-	-	+	-	?	?	?	-	Low
Misra, U. K. 2013	-	-	-	-	?	?	?	-	Low
Kalita, J. 2017	-	?	?	-	?	?	?	?	Very Low

+ = low risk; ? = uncertain risk; - = high risk.

Table 4.—Risk of Bias assessment for use of transcranial magnetic stimulation (TMS) as a treatment for headache, excluding repetitive TMS.

1st Author, Year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Incomplete outcome data addressed (attrition bias) (Short-term outcomes (2-6 weeks))	Incomplete outcome data addressed (attrition bias) (Long-term outcomes (>6 weeks))	Selective reporting (reporting bias)	OVERALL Risk of Bias	GRADE Quality
Rapinesi, C. 2016	?	?	-	-	+	?	+	-	Low
Chen, P. R. 2016	-	-	-	-	+	+	+	-	Low
Lipton, R. 2010	+	+	+	+	+	+	+	+	High
Clarke, B.M. 2006	?	?	+	+	?	?	+	?	Moderate
Bhola, R. 2015	-	-	-	-	-	-	+	-	Low
Starling, A. 2018	-	-	-	-	+	+	+	-	Low

+ = low risk; ? = uncertain risk; - = high risk.

the left motor cortex was the target. Their primary outcomes included a headache frequency and intensity reduction of 50% on visual analog scale (VAS), with secondary outcomes of headache severity (0-3 scale), functional disability, rescue medication, and adverse events. They found a significant, >50% reduction in headache frequency and VAS score in the experimental group compared to sham at 1 month [frequency (78.7 vs 33.3%, $P = .0001$; OR 7.4 [95% CI: 2.95-18.59], large effect size) and VAS score (76.6 vs 27.1%, $P = .0001$; OR 8.81 [95% CI: 3.48-22.29], large effect size). In addition, headache severity, rescue medication, and functional disability improved significantly in both groups compared to baseline, with a significant difference between the experimental group and sham at 1 month for functional impairment (Mean (SD); 1.19 (0.75) vs 2.06 (0.70), $P = .0001$; Cohen's d = 1.20, large effect size).

Finally, Conforto et al performed a parallel-group, randomized, double-blind, single-center, proof-of-principle clinical trial involving 14 participants with chronic migraine in 2014.[53] They too obtained a 4-week baseline period, after which 23 rTMS sessions were delivered over 8 weeks. Stimulation intensity was higher in this study, at 100% of RMT, and a greater number of pulses were delivered each session (1600 total pulses; 32 pulses with 30s ITI) at a lower frequency of 10 Hz. Stimulation was also applied to the left DLPFC using each patient MRI and a frameless stereotaxic system. Investigators looked at the number of headache days/month, compliance, and adverse events as primary outcomes and pain intensity, depression, anxiety, and disability (MIDAS) as secondary outcome measures. There was a significant headache frequency Group × Time interaction ($\chi^2(2) = 19.9$; $P < .001$). They found that headache frequency (days) decreased by >50% in the sham group (14.7 ± 9.0 day decrease in number of days with pain), however found no significant change in rTMS group (3.6 ± 4.5 day decrease) suggesting a large effect size (Cohen's d = 1.59). Headache intensity reduced in both sham and rTMS groups at 8 weeks (significant Time effect ($\chi^2(2) = 6.79$; $P = .034$). Anxiety and disability index scores decreased significantly in sham and rTMS group at 8 weeks (Migraine disability assessment, median (range); sham = 16 (1-39) to 2 (0-10) and active = 7 (4-38) to 4 (0-19); Cohen's d = 1.13, large effect size), while only sham demonstrated

Table 5.—Risk of Bias assessment for use of transcranial direct current stimulation (tDCS) as a treatment for headache.

1st Author, Year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Incomplete outcome data addressed (attrition bias) (Short-term outcomes (2-6 weeks))	Incomplete outcome data addressed (attrition bias) (Long-term outcomes (>6 weeks))	Selective reporting (reporting bias)	OVERALL Risk of Bias	GRADE Quality
Rocha, S. 2014	+	+	+	?	-	-	+	?	Moderate
Andrade, S. 2017	+	+	+	+	+	?	+	+	High
Antal, A. 2011	?	?	?	?	+	+	?	?	Moderate
Auvichayapat, P. 2012	?	?	+	+	+	+	?	?	Moderate
DaSilva, A. 2012	?	?	+	+	+	+	?	?	Low
Pinchuk, D. 2013	-	-	-	-	?	?	-	-	Very Low
Przeklasa-Muszynska, A. 2017	?	?	-	-	?	?	?	-	Very Low
Solomon, S. 1989	?	?	+	?	+	+	?	?	Moderate
Wickmann, F. 2015	-	-	+	?	+	+	?	-	Low
Vigano, A. 2013	-	-	-	-	?	?	?	-	Very Low
Alhassani, G. 2017	-	-	-	-	?	?	?	-	Very Low
Magis, D. 2018	-	-	-	-	+	?	+	-	Very Low

+ = low risk; ? = uncertain risk; - = high risk.

Table 6.—Summary of Findings (SoF) for Use of Repetitive Transcranial Magnetic Stimulation (rTMS) as a Treatment for Headache

rTMS for the Treatment of Headache

People: Adults aged 18-65 with primary or secondary headaches
Intervention: rTMS
Comparison: Sham/placebo or alternative standard of care

Outcomes	Findings	Number of Studies/ Number of Participants	Certainty of the Evidence (GRADE)[†]
Headache Frequency	Nine studies reported a decrease following rTMS. Of those, 3 had a decrease that was not statistically different from sham treatment. One reported an increase in frequency, and 1 found a decrease in sham with no change in the real treatment	11/565	⊕⊕⊕⊖ Moderate
Response Rate	Of the 7 studies reporting response rates, 4 had a greater than 50% reduction in headache frequency between 1-4 weeks following rTMS and 1 had a 75% decrease. One study described a >50% decrease in the sham but not the real group. Two studies reported a >50% decrease in headache severity	7/426	⊕⊕⊕⊖ Moderate
Headache Duration	Headache duration decreased in 2 studies, with no statistical difference between sham and real in 1 report	2/125	⊕⊕⊖⊖ Low
Headache Intensity	Eleven studies demonstrated a decrease in intensity after rTMS. Decreases in intensity were also seen with sham stimulation in 6 studies, however to a lesser degree than real stimulation in 5/6 reports. One study reported no change in intensity	12/631	⊕⊕⊕⊖ Moderate
Abortive Medication Use	Six reports described a decrease in medication use, while 1 reported no change	6/261	⊕⊕⊕⊖ Moderate
Depression	One study showed a decrease in both real and sham stimulation, another reported a real>sham decrease, and there was no change in the last	3/72	⊕⊕⊕⊖ Moderate
Anxiety	A decrease was seen in both real and sham stimulation	1/14	⊕⊕⊕⊖ Moderate
Quality of Life	None of the 15 rTMS studies looked at quality of life as an outcome	0	—
Function	All 4 studies reported a decrease in functional disability	4/140	⊕⊕⊖⊖ Low

High = This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different[‡] is low.
Moderate = This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different[‡] is moderate.
Low = This research provides some indication of the likely effect. However, the likelihood that it will be substantially different[‡] is high.
Very low = This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different[‡] is very high.
[†]GRADE Working Group grades of evidence.
[‡]Substantially different = a large enough difference that it might affect a decision.

Table 7.—Summary of Findings (SoF) for Use of Transcranial Magnetic Stimulation (TMS) as a Treatment for Headache; Single-Pulse TMS (sTMS), Deep TMS (dTMS), Continuous Theta Burst Stimulation (cTBS)

TMS (excluding rTMS) for the Treatment of Headache			
People: Adults aged 18-65 with primary or secondary headaches Intervention: sTMS, dTMS, cTBS Comparison: Sham/placebo or alternative standard of care			
Outcomes	Findings	Number of studies/ Number of Participants	Certainty of the Evidence (GRADE)[†]
Headache Frequency	Four studies (2 sTMS, dTMS, cTBS) showed a decrease in headache frequency, with 2 being statistically greater than sham	4/345	⊕⊖⊖⊖ Very low
Response Rate	One sTMS study reported 50% reduction in headache days in 46% of participants	1/132	⊕⊖⊖⊖ Very low
Headache Duration	One sTMS study investigated duration and did not find a difference with sham treatment	1/42	⊕⊕⊖⊖ Low
Headache Intensity	All 3 studies (dTMS, 2 sTMS) found a decrease in intensity with 2 papers reporting a greater decrease than sham or control	3/368	⊕⊕⊕⊖ Moderate
Abortive Medication Use	Three reports described a decrease in medication use, with 1 showing a greater decrease than control (dTMS) and the other 2 showing no difference with sham (sTMS)	3/310	⊕⊕⊖⊖ Low
Depression	Both dTMS and cTBS studies showed a decrease with real stimulation; the dTMS study found a significant difference compared to control	2/23	⊕⊖⊖⊖ Very low
Anxiety	No reports discussed anxiety as an outcome	0	_
Quality of Life	None of the 5 TMS studies looked at quality of life as an outcome	0	_
Function	One sTMS study reported an improvement in function	1/132	⊕⊖⊖⊖ Very low

High = This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different[‡] is low.
Moderate = This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different[‡] is moderate.
Low = This research provides some indication of the likely effect. However, the likelihood that it will be substantially different[‡] is high.
Very low = This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different[‡] is very high.
[†]GRADE Working Group grades of evidence
[‡]Substantially different = a large enough difference that it might affect a decision

reduction in depression scores at 8 weeks (Beck depression inventory; 5 (1-20) at baseline and 4 (0-10) at 8 weeks), suggesting a small effect of real over sham (Cohen's d = 0.25).

The remainder of the reviewed studies were of moderate, low, or very low quality. These studies demonstrated many biases, including selection (not using random sequence generation or concealed allocation), performance (lack of blinding of the participants or the personnel), detection (improper blinding of outcomes), attrition (short follow-up period <6 weeks), and reporting bias (Table 4). Despite this, results were promising in terms of decreases seen in headache frequency, duration, and intensity, use of abortive medications, depression, anxiety, and functional impairment. The only study with an increase in headache frequency was performed by Teo et al,[64] where stimulation over the right M1 at 10 Hz and 80% RMT for 1000 total pulses was stopped prematurely as 3 of the 9 subjects reported exacerbation of headache. It should also be noted that decreases in headache characteristics were not always significantly different than sham treatment.

Other TMS and Headache protocols.—The other TMS studies included 4 single-pulse TMS (sTMS), 1 deep TMS (dTMS), and 1 continuous theta burst

Table 8.—Summary of Findings (SoF) for Use of Transcranial Direct Current Stimulation (tDCS) as a Treatment for Headache

tDCS for the Treatment of Headache			
People: Adults aged 18-65 with primary or secondary headaches Intervention: tDCS Comparison: Sham/placebo or alternative standard of care			
Outcomes	Findings	Number of studies/ Number of Participants	Certainty of the Evidence (GRADE)[†]
Headache Frequency	Seven of 8 studies found a decrease in headache frequency, with only 1 showing a greater difference in real than sham. One study found no change in frequency	8/230	⊕⊕⊖⊖ Low
Response Rate	One study reported a 50% reduction in cluster headache attack frequency	1/23	⊕⊖⊖⊖ Very low
Headache Duration	Five papers reported a decrease in duration of which 1 showed a greater difference than sham. Two studies found no change in duration	7/190	⊕⊕⊖⊖ Low
Headache Intensity	Seven studies found a decrease in intensity with 2 papers reporting a greater decrease than sham and 1 showing no difference between real and sham. Two papers found no change in intensity	10/413	⊕⊕⊕⊖ Moderate
Abortive Medication Use	Four reports described a decrease in medication use, with 1 showing a greater decrease than sham. One study reported no change in medication use	5/165	⊕⊕⊖⊖ Low
Depression	One study reported no change in depression	1/23	⊕⊖⊖⊖ Very low
Anxiety	No reports discussed anxiety as an outcome	0	_
Quality of Life	Two studies looked at QoL with 1 reporting an increase with tDCS and the other showing a greater improvement with sham stimulation than real	2/29	⊕⊕⊖⊖ Low
Function	Both studies reporting on functional disability found a decrease following the intervention	2/26	⊕⊕⊖⊖ Low

High = This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different[‡] is low.
Moderate = This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different[‡] is moderate.
Low = This research provides some indication of the likely effect. However, the likelihood that it will be substantially different[‡] is high.
Very low = This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different[‡] is very high.
[†]GRADE Working Group grades of evidence.
[‡]Substantially different = a large enough difference that it might affect a decision.

stimulation (cTBS). Of those, 1 was high quality (low risk of bias),[69] 1 moderate quality (uncertain risk of bias),[70] and 4 low quality (high risk of bias).[67,68,71,73]

The single high-quality study with low risk of bias was completed by Lipton et al in 2010.[69] A multicentre, parallel-group, two-phase, randomised, double-blind, sham-controlled study using single-pulse TMS (sTMS) as a treatment for 164 episodic migraine with aura patients. A 1-month baseline period was obtained prior to a 3-month treatment phase whereby participants were advised to deliver two 0.9 T single magnetic field pulses, 30 seconds apart (rise time 180 μs, total pulse length ≤1 ms), as soon as possible after their headache aura began. Stimulation was delivered to the occipital cortex. The primary outcome measure was a pain-free response 2 hours (h) after the first attack and non-inferiority at 2 hour for nausea, photo/phono-phobia. Secondary outcomes included proportion of participants with: mild/no pain after 2 hours, 24 hours and 48 hours, number of

rescue medications used, patient global assessment (PGA), emesis, and migraine disability assessment score (MIDAS). They found that pain-free response rates after 2 hour were significantly higher with sTMS (39%; 32/82 participants) than with sham stimulation (22%; 18/82), for a therapeutic gain of 17% [95% CI: 3-31%], $P = .0179$; OR 2.28 [95% CI: 1.15-4.51]. Non-inferiority was also shown for nausea and photo/phono-phobia. Among secondary outcomes, there was a significant difference between sTMS and sham in pain-free response at 24 hours (24/82 [29%] vs 13/82 [16%], $P = .0405$; OR 2.20 [95% CI: 1.03-4.70]) and 48 hours (22/82 [27%] vs 11/82 [13%], $P = .0327$; OR 2.37 [95% CI: 1.06-5.27]). However, there was no significant difference between groups for the number of participants who achieved no or mild pain at 2 hours after treatment (67% vs 72%, $P = .50$; OR 0.79 [95% CI: 0.41-1.55]), use of rescue drugs (46% vs 48% at 48 hours, $P = .88$; OR 0.95 [95% CI: 0.52-1.76]), consistency of pain relief response (PGA, $P = .68$), MIDAS (−4.7 (21.3) vs −4.6 (21.8) change from screening, $P = .98$; Cohen's d = 0.004), or total disability time (452.2 (530.3) vs 510.6 (656.6) minutes, $P = .58$; Cohen's d = 0.098).

The lower quality studies demonstrated evidence of selection, performance, detection, and attrition bias (Table 5). Despite this, there were reported decreases in headache frequency[67,68,71,73] and intensity[67,71] using sTMS,[70,73] cTBS,[67] and dTMS[67] technologies.

tDCS and Headache.—There was only 1 out of the 12 tDCS studies graded as high quality with low risk of bias.[39] Four were moderate (uncertain risk of bias),[40,41,45,75] 2 low (uncertain/high risk of bias),[42,47] and 5 very low quality (high risk of bias).[38,43,44,46,74]

The only high-quality study with low risk of bias reviewed was done by Andrade et al in 2017.[40] A pilot, randomized, double-blind, sham-controlled, concealed allocation trial of using anodal tDCS as a treatment for 13 medically refractory chronic migraine patients was completed. Intervention protocol involved a 1-day baseline, followed by 12 sessions over a period of 30 days (20 minutes, 3x/week). Anodal tDCS with a 5 × 5 cm (25 cm^2) electrode operating at 2 mA (0.08 A/m^2) was applied to 3 different groups of participants. The first group received sham current over L-M1 (C3), while group 2 experienced active anodal current on L-M1 (C3) with the cathode at the R-supraorbital (Fp2) location. Finally, group 3 underwent active anodal current on L-DLPFC (F3) and cathode at R-supraorbital (Fp2). The primary outcome measure was a reduction on the Headache Impact Test-6 (HIT-6) questionnaire, a measure of impact on participant function. Secondary outcomes included pain intensity on the visual analog scale and the quality of life measure, SF-36. The authors found that anodal stimulation to left DLPFC showed more improvements in headache impact, pain intensity, and quality of life compared to M1 stimulation. There was no significant change identified in the sham group. Specific findings included: HIT-6, headache impact difference between baseline and endpoint [M1 z = 2.59 ($P = .01$), DLPFC z = 2.78 ($P = .02$), sham z = 0.06 ($P = 0.219$)], pain intensity (median difference between baseline and endpoint on VAS [M1: 3.1 (95% CI:2.0-8.9), DLPFC: 6.2 (95% CI: 1.7-9.2), Sham: 0.5 (95% CI: 6.0-7.2)], SF-36 (median difference between baseline and endpoint [M1:12 (95% CI: 60.4-79.1), DLPFC: 23.7 (95% CI: 60.7-89.1), Sham: 2.4 (95% CI: 60.5–66.8)].

The remainder lower quality studies demonstrated many biases, including selection, performance, detection, attrition, and reporting bias (Table 6). In regard to outcomes, most of the studies reported decreases in headache frequency and abortive medication use, excluding the Antal et al[41] study which reported no change for frequency and Alhassani et al[39] that showed no change for abortive medication use. Studies reporting on headache duration and intensity either decreased or had no reported change.

Synthesis of Results.—Summary of findings tables were constructed based on predefined primary and secondary outcome measures including headache frequency, response rate, duration, and intensity. Abortive medication use, depression, anxiety, quality of life, and functional outcomes were also identified. GRADE certainty of evidence ranged from very low to moderate[50] (Tables 6–8: Summary of Findings).

Moderate Certainty of Evidence.—There is moderate evidence for rTMS in the treatment of headache with regard to reduction in headache frequency, intensity, abortive medication use, depression, and anxiety. sTMS for the acute treatment of migraine demonstrated a decrease in headache intensity. Finally, tDCS demonstrated a reduction in headache intensity.

Low Certainty of Evidence.—There is low certainty of evidence that rTMS contributes to reduced headache duration and function. Headache duration (1 sTMS study), and abortive medication use were reduced (2 sTMS, dTMS), with low certainty. tDCS demonstrated reductions in headache frequency, duration, abortive medication use, quality of life, and functional impairment.

Very Low Certainty of Evidence.—Headache frequency was reduced, with very low certainty of evidence, in sTMS, dTMS, and cTBS, while depression was improved in dTMS and cTBS studies. One sTMS study reported a 50% frequency response rate and improvement in function. In the tDCS studies, there is very low certainty of evidence that depression is not influenced by the intervention. However, response rate, characterized by a 50% reduction in headache attack frequency, may result from tDCS treatment.

Insufficient Evidence.—There is insufficient evidence for rTMS's effect on quality of life, as well as sTMS/dTMS/cTBS's effect on anxiety and quality of life. tDCS's influence on anxiety cannot be determined.

DISCUSSION

Summary of Evidence.—GRADE certainty of evidence ranged from very low to moderate for outcome measures including headache frequency, response rate, duration, and intensity, abortive medication use, depression, anxiety, quality of life, and functional impairment[50] (Tables 6–8). Looking specifically at our primary outcome measure, headache frequency was reduced in 9/11 rTMS studies (Moderate GRADE) and frequency response rate was lowered by >50% in 5/6 reports (Moderate GRADE). Two sTMS, the dTMS, and cTBS studies reported a decrease in headache frequency (Very Low GRADE), while one sTMS reported a 50% response rate. Finally, 7/8 tDCS studies reported a headache frequency decrease (Low GRADE) with one study reporting a 50% headache frequency response rate.

Limitations.—A quantitative synthesis couldn't be performed based on significant differences in headache type studied, protocol stimulation parameters, location and duration of treatment, and outcome measures. In addition, many of the studies lacked random sequence generation or concealed allocation. There was strong evidence of insufficient blinding of either outcome assessor or participants with short follow-up periods (<6 weeks), and occasional reporting bias. Many studies did not have appropriate control groups and in general, sample sizes were small. Finally, many mixed headache populations were studied.

Comparison With Other Reviews.—Two recent meta-analyses have been published on noninvasive brain stimulation in migraine. Lan et al[78] investigated the efficacy of rTMS for the treatment of migraine; however, this study did not include tDCS treatment. In addition, Shirahige et al[78] study from 2016 was looking specifically at migraine (episodic with and/or without aura and chronic), as opposed to any headache disorder which is assessed in this review. They also investigated alternative outcome measures than those used in our analysis. As a result, to the best of our knowledge, the current systematic review is unique in its findings.

Future Directions.—There is significant opportunity to investigate noninvasive neurostimulation treatment for non-migrainous headache disorders such as tension-type, posttraumatic, and cervicogenic headaches. For rTMS studies, there is promise in stimulation over the left DLPFC or motor cortex. Subthreshold rTMS (<100% RMT) stimulation seems effective and tolerable, without significant, long-lasting exacerbations in headache characteristics. There is evidence that persistent effects may endure after only a few treatments,[57] which would increase accessibility and decrease costs associated with using the technology. Further cTBS, dTMS, and sTMS studies would be beneficial to replicate current findings.

In regards to tDCS, common stimulation parameters included anodal stimulation using a 1-2 mA stimulation intensity over a 15-20 minute duration (25-35 cm^2 electrode). Average treatment duration was for 4 weeks with daily to 3x/week sessions. Anode position was most commonly located at L-M1 (C3) or L-DLPFC with the cathode over the contralateral supraorbital area (Fp2). Further high-quality studies utilizing the above parameters, controlling for biases, and with more lengthy follow-up (>6 weeks) would be beneficial in determining the utility of tDCS, a promising cost-effective and accessible treatment.

CONCLUSIONS

Neuromodulation therapies, including TMS and tDCS, may provide a non-pharmacologic treatment alternative for prevention and acute management of numerous headache disorders. In addition to their mild side effect profile, these technologies could be beneficial in patients who are treatment resistant to conventional therapies or those with contraindications to oral pharmacologic management. In this systematic review, 34 studies were included: 16 rTMS, 4 sTMS, 1 dTMS, 1 cTBS, and 12 tDCS. The majority investigated treatment for migraine (19/22 TMS, 8/12 tDCS). Only 3 rTMS, 1 sTMS, and 1 tDCS articles had low overall risk of bias and quality of evidence ranged from very low to high in these studies. The majority of rTMS studies reported reductions in headache frequency, duration, intensity, abortive medication use, depression, and functional impairment. A promising sTMS study demonstrating reduction in acute migraine intensity has led to FDA clearance of the technology.[70] In contrast, tDCS may decrease headache intensity. However, only few studies in the entire review reported changes greater than sham treatment. Despite this, further high-quality RCTs with standardized protocols are required for each specific headache disorder to validate a treatment effect. rTMS studies with investigation into high frequency (>5 Hz), sub-resting motor threshold stimulation (<100%) over the left motor cortex or left DLPFC are warranted. A small number of studies have been performed using dTMS, cTBS, and sTMS technologies, and as a result repeated studies may help to increase the level of evidence for these devices. tDCS studies with 1-2 mA anodal stimulation over the left DLPFC or motor cortex for a 15-20 minute duration may help further elucidate the influence of treatment. Overall, the evidence for noninvasive neuromodulation treatment in headache is promising, but our findings suggest that larger, well-designed clinical trials are necessary before widespread use of TMS and tDCS can be suggested for mainstream clinical care.

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