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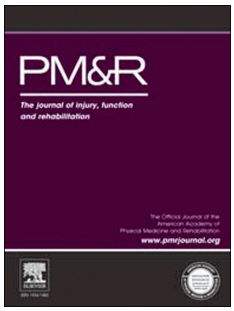

"rTMS Therapy in Parkinson Disease: A Meta-analysis"

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"rTMS Therapy in Parkinson Disease: A Meta-analysis".

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Abstract

Objective: Several studies have reported rTMS therapy as an effective treatment for control of motor symptoms in Parkinson's disease. The objective of the study is to quantify the overall efficacy of this treatment.

Types: Systematic review and Metaanalysis

Literature survey: We reviewed the literature on clinical rTMS trials in Parkinson's disease since the technique was introduced in 1980. We used the following databases: MEDLINE, Web of Science, Cochrane, and CINAHL

Methodology: Patients and setting: Parkinson's disease patients participating in prospective clinical trials that included an active arm and a control arm and change in motor scores on Unified Parkinson's Disease Rating Scale as the primary outcome. We pooled data from 21 studies which met these criteria. We then separately analyzed the effects of low and high frequency rTMS on clinical motor improvements.

Synthesis: The overall pooled mean difference between treatment and control groups in the Unified Parkinson's Disease Rating Scale motor score was significant (4.0 points, 95% confidence interval, 1.5, 6.7; p= .005). rTMS therapy was effective when low frequency stimulation (≤ 1Hz) was used with a pooled mean difference of 3.3 points (95% confidence interval 1.6, 5.0; p=.005). There was a trend for significance when high frequency stimulation (≥5 Hz) studies were evaluated with a pooled mean difference of 3.9 points (95% confidence interval, -0.7, 8.5; p=.08). rTMS therapy demonstrated benefits at short term follow-up (immediately after a treatment protocol) with a pooled mean difference of 3.4 points (95% confidence interval, 0.3, 6.6; p= 0.03) as well as at long term follow-up (average follow-up 6 weeks) with mean difference of 4.1 points (95% confidence interval, -0.15, 8.4; p=.05). There were insufficient data to statistically analyze the effects of rTMS when specifically examining bradykinesia, gait, and levodopa induced dyskinesia using quantitative methods

Conclusion: rTMS therapy in Parkinson's disease results in mild to moderate motor improvements. The therapy has a potential to be utilized as an adjunct therapy for treatment of Parkinson's disease. Future large sample studies should be designed to isolate the specific clinical features of Parkinson's disease that respond well to rTMS therapy.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease manifesting with tremors, rigidity, bradykinesia and postural instability [1]. Pharmacological therapies such as dopaminergic medications form the mainstay treatment for the control of motor symptoms [2]. Additionally, deep brain stimulation (DBS) surgery is approved by FDA for select indications such as medication refractory tremors and motor complications arising from chronic dopaminergic treatments [3], does not necessarily improve gait and balance disturbances in many patients with PD [4]. Alternate treatments like repetitive transcranial magnetic stimulation are increasingly used in research settings but their exact therapeutic potential is not clearly established

Transcranial magnetic stimulation (TMS) is a painless, non-invasive, well tolerated technique of brain stimulation based on the theory of electromagnetic induction [5]. rTMS is the repetitious application of TMS pulses over a predefined target with ability to modulate the excitability of the brain and therefore serve a therapeutic role in control of PD symptoms. rTMS therapy is offered at low and at high frequency of stimulation with distinct mechanisms of action. rTMS at frequencies of 5 Hz and higher enhances motor cortex excitability [6], whereas rTMS at frequencies of 1 Hz and lower depresses the cortical excitability [7]. Several controlled and uncontrolled studies have tested the therapeutic application of rTMS in PD and have found beneficial effects [8]. However, most studies have involved small sample sizes and varied greatly in terms of rTMS dosing regimens, outcome measures, inclusion/exclusion criteria, use of sham-TMS, brain sites for stimulation, and the rigor in monitoring safety and tolerability. A meta-analysis of pooled results from 10 controlled trials found that there was an effect size of -0.58 on the Unified Parkinson's Disease Rating Scale (UPDRS) for the use of high-frequency rTMS whereas there were no significant effects seen for low-frequency rTMS studies [9]. Recently, many more studies, mostly using high frequency stimulation parameters, have been published [10,11]. Here we present a systematic review and analysis of rTMS studies that investigated the motor benefits in PD.

Methods

We searched the literature for articles on the use of rTMS in PD published between the period 1980 and 2013. We used the following databases: MEDLINE, Web of Science, Cochrane, and CINAHL using the following key search terms; ‘‘Parkinson’s disease’’, ‘‘transcranial magnetic stimulation’’, ‘‘brain stimulation’’, ‘‘repetitive transcranial magnetic stimulation’’ and ‘‘noninvasive brain stimulation’’. We retrieved 130 articles. We then searched the reference lists in systematic reviews; searched conference abstracts and searched clinical trials.gov for any ongoing trials in this field. As a first step we reviewed the abstracts to screen articles deemed relevant and subsequently read the full articles for extraction of outcome measures. We removed all the duplicate articles based on the abstract. Articles were excluded if the score information was missing [12-15], the method of TMS stimulation was not clear [16] or reflected duplication of results [17].

Selection criteria for meta-analysis:

We used the following inclusion criteria: (a) prospective studies that evaluated the effects of rTMS on motor function in PD; (b) studies that used the UPDRS motor section to measure the motor symptoms (c) manuscripts or findings reported in English language; (d) findings that were published in a peer reviewed journal, book, proceedings; and (e) findings for the motor section were reported as a continuous variable with mean and standard deviation (SD) before and after treatment, or provided other parameters that could be used to derive these values; (f) we also included studies that reported objective motor measurements such as finger tapping speed, Pegboard test, gait speed and studies that recorded control of levodopa induced dyskinesia.

We used a semi-structured form to extract data and plot the final findings on a master work sheet. We then created separate work sheets for studies that included UPDRS score as a motor outcome measure, reported rTMS effects on dyskinesia and those that reported objective measurements for bradykinesia and

gait assessments. For each study, the data were extracted and checked independently by two authors. If there were disagreements, these were resolved with the help of oral discussions and consensus. Data were analyzed with the help of a biostatistician. The following variables were extracted: (i) demographic and clinical characteristics (for example, number of patients, age, disease duration, medication status); (ii) study design; (iii) baseline Hoehn and Yahr stage; (iv) TMS parameters (frequency, intensity, number of pulses, number of sessions, coil type used, evaluation time after TMS); (v) mean and SD of the motor section (part III) of the UPDRS for baseline and after treatment for the active and placebo group (some studies used sham stimulation as control); (vi) mean and SD for the follow up period evaluations (if these data were available); and (vii) mean and SD of the outcome measures used for evaluation of dyskinesia and bradykinesia. Our primary analyses examined the effects of low (≤1 Hz) and high (≥5 Hz) frequency rTMS studies separately. We then conducted additional analysis for studies that had a control group, studies that included a specific sham coil in the control group, and finally we analyzed the short and long duration benefits of rTMS.

Statistical Methods.

The primary analysis was based on all controlled studies with baseline and final results for both the control group and treatment group. The endpoint (metric) was the difference in changes: baseline minus final for the treated group less that for the control group. Other analyses were done, to confirm qualitatively that the point and interval estimates were consistent with the main analysis. These included analyzing subsets of studies and analyzing the post-test results only (second metric), whether there was a baseline value reported or not.

Since we lacked patient level data, and since some studies either lacked Cohen D data [18] for either metric or lacked standard error information for either metric, we were restricted from using either Cohen's D or inverse variance weighted random effects methods. In addition, without these patient level data, it was not possible to construct tests for heterogeneity, forest plats, or funnel plots.

We therefore adopted a minor modification (explained below) of the patient weighted random effects method of Shuster [19], Section 3. Conceptually, we have presumed that we have a large urn of studies, from which we extracted a sample of studies. Our inference is aimed to be applied to the entire urn, not to the actual sample. The target parameter was the following: Pick a study at random from the urn with probability proportional to its "effective sample size" defined below. What is the average difference in the metric if the subject was assigned to treatment vs. assigned to control? If there were no repeated evaluations and no three- arm studies, this would be straight forward, but the reality is that both issues exist. For studies with three treatment arms (including one control arm), we defined the effective sample size as the number of controls plus the average number of treated subjects for the two active treatment groups. For example if there were 10 controls, 12 on A and 13 on B, the effective sample size would be 10+12.5=22.5. The metric would be defined as the difference between the arithmetic mean for the two active treatments less the mean for the controls. [19] For repeated time points, the effective sample size would be the average sample size for controls (the same controls were used, but some may lack the later endpoint) plus the average sample size for treatment. If both issues exist, we first calculated the metric at each time point, and then combined them as above. The metric within studies in all of these cases would represent the arithmetic mean of the treatment values less the arithmetic mean for the control values (equally weighted to timing and treatment groups). Although somewhat complex, we do have a clean population interpretation of the effect size, in TRS units, along with a random effects interpretation. Each study contributes one and only one result to the meta-analysis. This approach was followed by a similar metaanalysis. [20].

Criteria for Classifying Study Quality and Strength of Evidence

We applied three standardized methods to grade the quality of studies and strength of evidence. Although all three scales are designed for grading the quality of clinical trial, there are differences when one considers users and their specialty for each of these scales, and the approach each scale takes while

assigning points to the quality of study. As there are no guidelines currently available to unify these scales, we will list them individually in Table 3B. First we used the Oxford Centre for Evidence-Based Medicine levels [21]. According to this grading scale, evidence for quality is rated from level 1 (best quality) to level 5 (lowest quality) based on criteria listed in table. These criteria examine the quality of evidence based on design of the study. We then used the Physiotherapy Evidence Database (PEDro) scale. This scale is commonly used in physical therapy-based systematic reviews [22]. The scale includes 11 questions and is based on a scale of 0 to 10 to assess the overall quality of the randomized controlled trial. The first question is used to determine external validity and is not graded in the scale. The PEDro scale is described in the table. Finally we followed the guidelines recommended by American Academy of Neurology(AAN) for evaluation of quality of evidence (see table). These guidelines use the following quality-of-evidence indicators: use of a comparison (control) group, method of treatment allocation (randomized versus other), method of allocation concealment, proportion of patients with complete follow-up, use of intent-to-treat methodologies, use of masking throughout the study (single-blind, double-blind, independent assessment). Details of these guidelines are available at the website www.aan.com/Guidelines/.

Results

We found 21 studies that satisfied the above inclusion criteria. There were 10 randomized controlled studies [10,11,23, 25-30] and four studies with uncontrolled design [31-34]. There were 10 studies(table 1) that tested the effects of low frequency (≤1 Hz) rTMS [11,23,25,27,29,31-33,35,36] and 13 studies (table 2) used high frequency(≥5 Hz) for stimulation [10,11,24-26,28-30,34,38-40]

We conducted a separate analysis, for studies that evaluated the rTMS effects at two different time points after the intervention (short term and long term). These studies included: Dragasevic et al 2002[31] (two

hours and 20 days), Okabe et al 2003 (one month and two months)[23], Khedr et al 2003 (immediate and at one month)[24], Pal et al 2010 (one day and at 30 days)[28], Fregni et al 2004 (immediate and at 6 weeks),[38] Lomarev et al 2006 (one day and at one month)[26], Aria et al 2010 (immediate and at one week)[29], Benninger et al 2011(1 day and at one month)[10], Shirota et al 2013 (one week and at twelve weeks)[11]. For those studies that had more than one active group, for example when two different doses of TMS were administered, we considered each arm as one study in the quantitative analysis. This approach was used for the following two studies: Khedr et al 2006[41] and Shirota et al 2013[11]. Then some studies used objective instruments for assessment of bradykinesia along with UPDRS [24,2526,34] whereas[10,30,32,36] included objective gait measures in their analysis. Finally rTMS studies that investigated therapeutic effects on levodopa induced dyskinesia included: Koch et al 2005[42], Brusa et al 2006[43], Wagle Shukla et al 2007[44] and Filipovic et al 2009[45].

Pooled weighted effects of rTMS therapy (see Figures)

The overall pooled mean difference between treatment and control groups for controlled studies was significant (4.0 points, 95% confidence interval, 1.5, 6.7, p= .005). Figure 1 includes analysis was studies where the baseline pretreatment UPDRS scores were available. As seen in Figure 1, the point estimates were similar regardless of whether one considered sub-groups with low or high frequency stimulation, short or long term follow-up and use of sham coil as the control arm. rTMS therapy was effective in low frequency stimulation group, the pooled mean difference was significant (3.3 points,CI,1.6,5.0, p= .005) and it showed a trend for significance in the high frequency stimulation group (3.9 points, CI, -0.7, 8.5, p= .08). rTMS therapy showed definite short term benefits with a pooled mean difference of 3.4 points (CI, 0.3, 6.6, p= .04) and the mean difference of 4.1 points, approached significance at long-term follow-up (CI, -0.15,8.4, p= .05). In studies that specifically used a sham coil in their control arm, we found the pooled mean difference showed a significant trend (4.1 points, CI -0.08, 8.4, p= .05).

Figure 2 reflects our post-test analysis in which the baseline values of the treatment and control arms were ignored. The results of this analysis were qualitatively consistent with previous analysis; the overall pooled mean difference of 4 points achieved significance (CI, 0.5, 7.3, p= .02). However in individual subgroup analysis of stimulation frequency, time to follow-up and presence of sham coil, we found the mean difference was significant only for high frequency stimulation group (4.6 points, CI, 1.2, 8.0, p= .01) and the sham coil group (4.8 points, CI, 1.3, 8.2, p= .01).

Objective assessment of bradykinesia and gait

Few studies were found to include objective assessment of bradykinesia as an outcome measure. However they all used variable stimulation protocols. Dragasevic et al 2002[31] delivered low frequency (0.5 HZ) rTMS for a period of 10 days to the bilateral dorsolateral prefrontal cortex (DLPFC). Although the study was open labeled, rTMS was seen to improve the finger tapping performance in seven patients on day 10 (2.2 ± 0.6 and 3.0 ± 1.5 on day 1 vs. 3.0 ± 1.1 and 3.7 ± 1.3 for the right and left hand, respectively). Similar improvements in finger tapping performance were seen by Sommer et al[46] where 900 pulses at low frequency were delivered in a single session of 15 minutes to the left primary motor cortex (M1) in 11 subjects. Although the use of low frequency was promising for finger tapping performance, the effect on gait was highly variable. Ikeguchi et al[36] stimulated the frontal region at a frequency of 0.2 Hz for a period of 2 weeks where 30 stimuli were delivered every day for 10 minutes with the help of coil placed over the vertex. At the end of therapy, the gait speed recorded over a 10 minute walking distance revealed no significant improvements. In contrast, Lefaucheur et al [25] delivered rTMS to the M1 at frequency of 0.5 Hz and found improvements in both gait speed and arm rigidity.

Many studies employed high frequency for stimulation, for example, Pascual-Leone et al found positive improvements on the pegboard test when 5 Hz rTMS was delivered to the M1[47] and Khedr and his colleagues[24] noted improvement in walking when suprathreshold 5-Hz rTMS was applied to the leg areas of the M1. Subsequently Lomarev and colleagues [26], published their experience with a higher

frequency (25 Hz) of rTMS when delivered to the bilateral M1 and DLPFC once a week for a period of eight weeks. They found a cumulative improvement in gait and upper extremity bradykinesia which they postulated were a result of repeated episodes of long-term potentiation and remodeling of circuits. These results were replicated by Khedr et al [41] who tested both 10 Hz and 25 Hz rTMS with the latter demonstrating greater benefits, thus suggesting benefits of rTMS to be more potent with higher frequency of stimulation. However, a recent study that used intermittent theta burst stimulation (50 Hz), a pattern of stimulation known to induce long term potentiation effects, to the M1 and DLPFC surprisingly did not show any improvements in gait and timed motor tests.

Clinical outcomes in patients with levodopa induced dyskinesias.

Similar to bradykinesia and gait, rTMS benefits for levodopa induced dyskinesias have been evaluated in only few small sample studies with variable stimulation protocols. Koch and coworkers found alleviation of dyskinesias that lasted for only about 30 minutes when they delivered a low frequency rTMS (1Hz frequency, 900 stimuli over 15 minutes) over the supplementary motor cortex [42]. In their subsequent study, they delivered stimulation for five consecutive days (daily sessions for 15 minutes). However, to their surprise, no cumulative benefits developed at the end of therapy [43]. In another similar study, Wagle Shukla et al used the same parameters (900 stimuli at 1Hz over 15 minutes) for a period of two weeks but targeted the M1 instead of the supplementary motor cortex. Although the study was open labeled, patients were evaluated with blinded video assessments at three time points of one day, two weeks and at four weeks after therapy. They found significant improvements at one day and two weeks assessment in the dyskinesia rating scale and the scores based off a diary maintained by patients. However, the benefits were seen to be lost at the four weeks follow-up[44]. Subsequently, Filipovic et al conducted a randomized controlled study on 10 patients with severe levodopa induced dyskinesias using real and sham rTMS (1800 pulses; 1Hz rate over 4 days). Although the real and sham groups responded in same proportions, only the real group demonstrated significant improvements at the end of therapy.

The investigators felt the stimulation parameters and the overall dose used in the study were probably too low to establish significant differences between the real and sham group.[45]

Quality of evidence

We graded the quality of studies using three different scales as reported in Table 3A. When considering the Oxford Centre for Evidence-Based Medicine scale, we found the average score ranged from 2 to 4, with nine out of 21 studies scoring 2. None of the studies had a score of 1, which corresponds with the highest level of evidence. According to the PEDro scale, a randomized controlled trial is assigned high quality if its total score is 6 out of 10 or better. In our study we did not include the first question on the PEDro scale that describes the source of the participants and eligibility criteria used. With this scale, we found the grading of articles revealed a wide inter-article variability with total scores ranging from 3 to 9 on a scale of 0 to 10. We had nine controlled studies which scored 6 or greater, only one of the articles could be scored 10. We then used the AAN criteria according to which, there were two randomized controlled studies meeting criteria for a Class I evidence (Benninger et al, Shirota et al), and five other studies meeting criteria for Class II evidence (Khedr et al, Okabe et al, Fregni et al, Lomarev et al, Pal et al). In summary, there were nine studies that could be assigned a high quality status using one or the other grading scheme and in general studies that received the highest score on the PEDro scale appeared to also receive the highest scores on other classification scales.

DISCUSSION

Several studies have shown the therapeutic benefits of rTMS therapy for control of motor symptoms in PD [9,48]. Since rTMS therapy is offered at low and high frequency stimulation we analyzed the results separately. In contrast to a previous meta-analysis [9], we found rTMS therapy as a beneficial treatment with the use of low frequency stimulation while there was only a trend for significance in the high

frequency group. In the low frequency group, there were two large sample studies by Okabe et al [23] (n=85, results were negative) and Shirota et al [11] (n=106, results were positive). A contrast between their findings was possibly related to the dose of stimulation used. Shirota et al employed a higher dose of stimulation of 1000 stimuli per session in their protocol. Recently, several publications have reported the effects of high frequency stimulation including the use of theta burst stimulation in which multiple stimuli are delivered either as a continuous or an intermittent train. The enthusiasm for high frequency stimulation primarily developed from the rationale that under-activation of the M1, supplementary motor area and the DLPFC can potentially be corrected by increases in excitability induced by high frequency stimulation [49]. The high frequency group of studies also consisted of two large sample Class I studies, and interestingly their findings were conflicting too. Benninger et al (n=26, results negative) employed high frequency theta burst stimulation whereas Shirota et al (n= 106, results positive) had positive findings with 10 Hz stimulation. A variation in stimulation pattern might have accounted for the difference in outcome.

In spite of these conflicting results, the net analysis supported rTMS therapy as beneficial. It should be noted based on prior work showing a difference of 2.7 points in the UPDRS scale as minimal and 6.7 points as moderate [50], our pooled mean estimate difference between the treatment and the control group of 4 points was consistent with only mild beneficial changes. An important consideration is the heterogeneity of stimulation parameters that were used in these studies including the: sites of stimulation, coil type, number of pulses delivered, pattern of stimulation used (theta burst) and the number of sessions employed. Most of the high frequency studies, unlike the low frequency stimulation group, seemed to employ a focal figure-of-eight coil to achieve a greater precision in targeted stimulation. Nearly 50% of high frequency stimulation studies chose M1 as the target for rTMS therapy with DLPFC noted to be the second preferred choice. Studies in the low frequency stimulation group chose the supplementary motor cortex, dorsal premotor cortex, DLPFC and M1 in nearly equal proportions. Interestingly, stimulation of a nonmotor target such as the DLPFC, a target that is approved by FDA for treatment of depression, was

noted to demonstrate motor improvements which were likely related to the spread of stimulation effects along specific neural connections to distant cortical and subcortical regions [38].

An important consideration in the trial design was the control group included for comparison. The majority of studies chose sham stimulation for the control arm to offset the potential placebo effect of the rTMS intervention. Some studies kept the same patient group, however had a control site (occipital) for stimulation, and some included healthy controls as their control group. The method used for ideal sham stimulation has been debated. Sham stimulation comprises three main methods. One of the earlier methods has been the use of a real TMS coil tilted at an angle, presumably not discharging substantial amounts of magnetic energy into the brain. The second method has been the use of a sham coil that is similar in appearance and making the same sound as a real TMS coil. One problem with this method was the potential of unmasking participants at high TMS intensities (>90% intensity) as the regular coil induced a twitching sensation on the scalp. The third method comprises electrical stimulation of the scalp muscles over the targeted site and a clicking sound is created by a real coil placed close to the site and not over the site [51]. We found all studies except for two employed a proper sham coil for stimulation. In our subgroup analysis of studies with sham coil, the overall rTMS benefits continued to show significance.

Medication status is another important consideration while interpreting the effects of rTMS, although the role of dopaminergic medications is currently not clear. According to a previous notion, dopaminergic medications were proposed to have a potential to mask the effects of rTMS therapy which was referred to as a "ceiling effect" [8]. A recent large study by Shirota et al noted rTMS benefits while the patients took their dopaminergic medications [11] Similarly Aria et al found positive results with rTMS regardless of the medication status. [29]

Indeed, a treatment intervention with significant impact on clinical practice must demonstrate benefits that are clinically meaningful, long lasting and outweigh the side effects. After the success of single rTMS

session, many studies began to employ multiple sessions based on the widely held belief that repeated sessions resulted in cumulative benefits [48]. We conducted a separate analysis for such studies to determine if rTMS therapy had cumulative and long term benefits. We found motor improvements were sustained for an average follow-up of 6 weeks after the therapeutic sessions were completed. Upon specific examination of adverse effects, we found no report of serious effects. Some studies reported benign side effects such as: mild headache, neck pain, a mild burning sensation over the scalp, and increased salivation [31]. For example, Dragasevic et al, reported four out of ten patients developed a light burning sensation over the scalp during stimulation, and three patients to develop a mild tension headache. Most studies excluded patients with a seizure disorder in order to comply with the safety guidelines for rTMS[52]. In the theta burst stimulation study, special attention was provided to the possibility of increased seizure risk; EEG electrodes were applied over the scalp and the forearm to monitor any increase in cortical excitability or epileptiform activity during the course of treatment [34].

The literature on the use of rTMS for levodopa induced dyskinesia, objective bradykinesia and gait measures is sparse and overall disappointing [25,31]. Based on the current available information, the results are conflicting and no clear treatment protocol has yet been defined. Although some of the previous high frequency studies in the range of 25 Hz demonstrated positive improvements [26], a Class I study that used theta burst stimulation (50Hz) failed to demonstrate any significant improvements in gait and bradykinesia [10]. The authors felt these discrepancies were largely related to methodological differences in that the circular coil used in the theta burst study has a wider spread of stimulation which may have offset the benefits of stimulating focal leg and hand areas.

In summary, with recent publication of several large sample studies, rTMS therapy has been demonstrated to be an effective treatment for motor symptoms in PD. The benefits are sustained at a follow-up period of about 6 weeks. Although the rTMS therapy requires a specialized setup and a skilled personnel, however it is easy to administer, and is well tolerated by most patients. Although studies included in our

analysis reported improvements in the UPDRS motor scale regardless of stimulation frequency, it was not clear if any particular item of the scale was more likely to demonstrate a treatment response. The mechanisms underlying rTMS actions remain largely unknown; the individual differences in pathophysiology likely play an important role in impacting the treatment outcomes. Future studies should be directed towards determination of optimal stimulation parameters. It may also be reasonable to conclude that rTMS therapy may have greater benefits if the dose and stimulation parameters are personalized in individuals to address specific symptoms.

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Figure legend:

Figure 1: Pooled mean difference between treatment and control groups when comparing baseline and post treatment motor scores. The figure shows all controlled studies together and then presents data when individual factors such as low frequency, high frequency, long and short term follow-up, and studies that specifically included a sham coil were separately examined. The scatter plot shows the point estimates with 95% confidence interval error bars. The number of studies included and the p value for each comparison is presented.

Figure 2: Pooled mean difference between treatment and control groups with baseline values ignored. The figure shows all controlled studies together and then presents data when individual factors such as low frequency, high frequency, long and short term follow-up, and studies that specifically included a sham

coil were separately examined. The scatter plot shows the point estimates with 95% confidence interval error bars. The number of studies included and the p value for each comparison is presented.

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Table 1: Study characteristics of low frequency stimulation studies

Study	Age (Mean ±SD)	Disease duration (Mean ±SD)	Medication	HY [1] stage (Mean ±SD)	Design	Site	Coil	Intensity	Frequency	No. of Stimuli	Duration	Evaluation time	Total sample
Shimamato 2001	65.1 ±8	7 ± 4.2	ON	3.1 ± 0.9	controlled blinded	frontal	C	0.4 T	0.2	60	8 weeks (1/week)	immediate	18
Dragasevic 2002	59.9 ± 8.5		ON	2 ± 0.7	uncontrolled	bilateral frontal	C	110% AMT [2]	0.5	200	10	2 hours & 20 days	10
Ikeguchi 2003	68.8 ± 6.8	7.8 ± 4.5	ON	2.9 ± 1.1	controlled	bilateral frontal	C	70% output	0.2	60	2 weeks (3/week)	immediate	16
Okabe 2003	67.2 ± 8.2	8.8 ± 5.1	OFF	3.1 ± 0.9	RCT [3] blinded	vertex	C	110% RMT [4]	0.2	100	8 weeks (1/week)	4&8 weeks	85
Buhmann 2004	58.4 ± 10.5		ON	2.1 ± 0.6	uncontrolled	PMD [5]	F8	80% AMT	1	1200	1	immediate	19
Lefauheur 2004	64 ± 6.9	11 ± 3.4	OFF	3.4 ± 0.7	RCT blinded	left M1 [6]	F8	80% RMT	0.5	600	1	immediate (20 min)	12
Baumer 2009	62.2 ± 6.5	10.7 ± 2.9	OFF	3.1 ± 0.6	uncontrolled	PMD	F8	80% AMT	1	1200	1	immediate	15
Aria 2010			ON		RCT	vertex	C	90% RMT	1	100	1	immediate & 1 week	18
Filipovic 2010	64.5 ± 9.4	15.6 ± 5.6	OFF	3.3 ± 2.2	controlled blinded	M1	F8	90% RMT	1	1800	1	1 day	10
Shirota 2013	68.8 ± 7.6	8.5 ± 7.3	ON	2.9 ± 1.1	RCT double blind	SMA [7]	F8	110% AMT	1	1000	8 weeks (1/week)	1 & 12 weeks	106

[1] HY: Hoehn and Yahr scale
[2] AMT: active motor threshold
[3] RCT: randomized controlled trial
[4] RMT: rest motor threshold
[5] PMD: premotor dorsal cortex
[6] M1: primary motor cortex
[7] SMA: supplementary motor area

Table 2: Study characteristics of high frequency stimulation studies

Study	Age Mean ± SD	Disease duration Mean ± SD	Medication	HY stage Mean ± SD	Design	Site	Coil	Intensity	Frequency	No of stimuli	Duration of stimulation	Evaluation time	Total Sample
Siebner 2000	57 ± 11	5.5 ± 3.4	OFF	.	controlled	M1	F8	90% MT	5	2250	1	1 hour	12 [1]
Khedr 2003	57.8 ± 9.2	3.5 ± 2.3	OFF	.	RCT blinded	M1	F8	120% RMT	5	2000	10 days	immediate & 1month	36
Lefauheur 2004	64 ±2	11 ±1	OFF	3.4 ± 0.2	RCT, blinded	Left M1	F8	80% RMT	10	2000	1	immediate	12
Fregni 2004	65.7 ± 7.8	7.5 ± 8.3	OFF	2.1 ± 1.2	RCT blinded	Left DLPFC	F8	110% RMT	15	3000	2 weeks (5/week)	immediate	42
Mir 2005	63.2 ± 6.8	5.8 ± 3.2	ON (rTMS)	2.2 ± 0.3	controlled blinded	PMD	F8	90% AMT	5	1500	1	immediate	20
Khedr 2006	58 ± 10.6	3.6 ± 2.1	OFF	2.6 ± 0.6	controlled	Bilateral M1	F8	100% MT	25	3000	6 days	1 month	55
Lomarev 2006	63 ± 10	13.8 ± 6.8	ON	.	RCT double blind	Bilateral DLPFC	F8	100% RMT	25	1200	4 weeks (2/week)	immediate & 1month	18
del Olmo 2007	61.7 ± 5.2	8.1 ± 5.2	ON	2.2 ± 0.6	randomized controlled	DLPFC	F8	90% RMT	10	450	10 days	immediate	13
Sedlackova 2009	63.7 ± 6.7	7.8 ± 2.3	OFF	.	controlled unblinded	PMD	F8	100% RMT	10	1350	1	Immediate (30 min) & 1 month	10
Benninger 2009	62.6 ± 9.6	.	ON	2.3 ± 0.4	uncontrolled	M1	C	90% AMT	50	1000	1	immediate	10
Pal 2010	68.5 ± 7.9	6 ± 2.9	ON	2 ± 0.5	RCT double blind	DLPFC	F8	90% RMT	5	600	10	1& 30 days	22
Benninger 2011	62.1 ± 6.9	10.8 ± 7.1	ON	2.6 ± 0.2	RCT double blind	M1+ DLPFC Bilaterally	C	80% AMT	50Hz theta burst	.	2 (4/week)	1 day & 1 month	26
Shirota 2013	67.9 ± 8.4	7.8 ± 6.6	ON	2.8 ± 1.3	RCT double blind	SMA	F8	110% AMT	10	1000	8 (1/week)	1 & 12 weeks	106

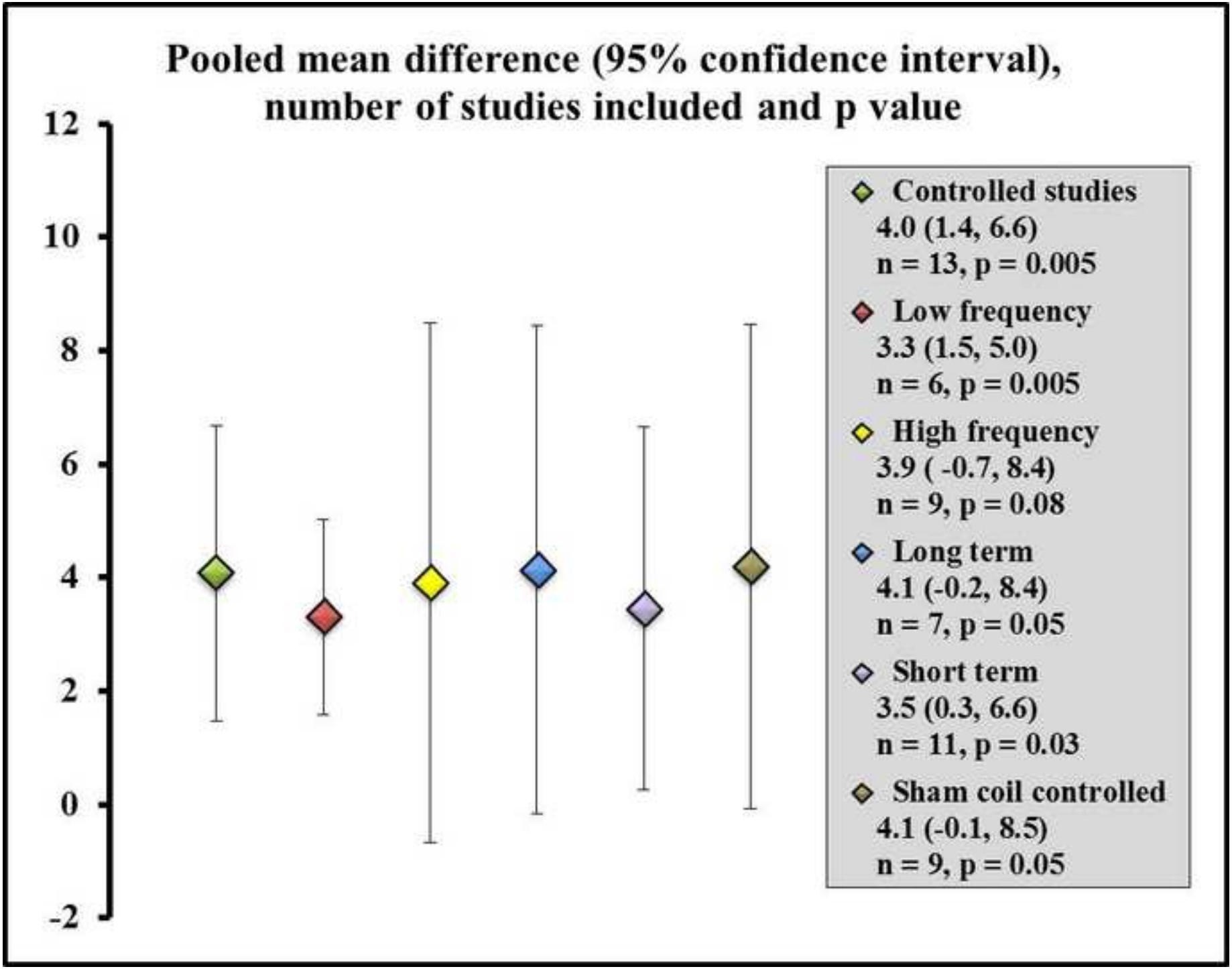
See table 1 foot notes for table abbreviations

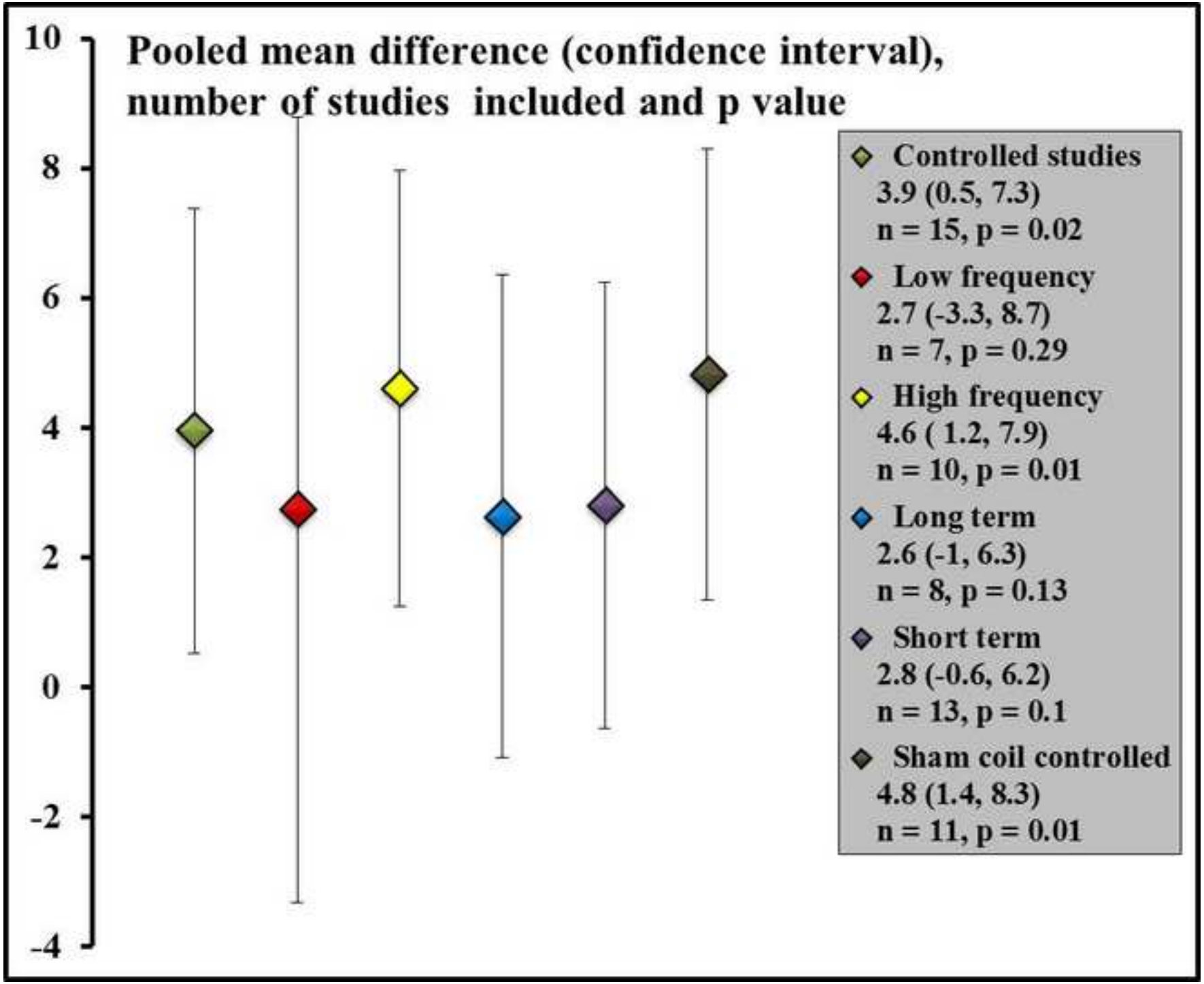
Table 3A: Scoring of articles according to Oxford scale, PEDro scale and AAN classification

	Study	Oxford Scale	PEDro Scale	AAN Classification
1	Siebner et al 2000	Level 4	3/10	Class III
2	Shimamato et al 2001	Level 4	5/10	Class III
3	Dragasevic et al 2002	Level 4	3/10	Class III
4	Khedr et al 2003	Level 2	8/10	Class II
5	Okabe et al 2003	Level 2	7/10	Class II
6	Ikeguchi et al 2003	Level 4	4/10	Class III
7	Buhmann et al 2004	Level 4	3/10	Class III
8	Lefauheur et al 2004	Level 3	6/10	Class III
9	Fregni et al 2004	Level 2	7/10	Class II
10	Mir et al 2005	Level 3	5/10	Class III
11	Lomarev et al 2006	Level 2	7/10	Class II
12	Khedr et al 2006	Level 3	4/10	Class III
13	Del Olmo et al 2009	Level 2	5/10	Class III
14	Sedlackova et al 2009	Level 3	4/10	Class III
15	Benninger et al 2009	Level 4	4/10	Class III
16	Baumer et al 2009	Level 4	3/10	Class III
17	Pal et al 2010	Level 2	9/10	Class II
18	Filipovic et al 2010	Level 4	3/10	Class III
19	Aria et al 2010	Level 2	7/10	Class III
20	Benninger et al 2011	Level 2	9/10	Class I
21	Shirota et al 2013	Level 2	9/10	Class I

Table 3B: Criteria used for scoring in PEDro scale, Oxford scale and AAN classification

The Oxford Centre for Evidence Based Medicine levels are as follows:	**The Physiotherapy Evidence Database (PEDro) scale** is as follows:	**American Academy of Neurology** guidelines for therapeutic intervention
- 1a Systematic review with homogeneity of randomized controlled trials (RCTs) - 1b Individual RCT (with narrow confidence interval) - 1c All or none - 2a Systematic review (with homogeneity of cohort studies) - 2b Individual cohort study (including low quality RCT; e.g., < 80% follow-up) - 2c Outcomes[research, ecologic studies] - 3a Systematic review (with homogeneity) of case-control studies - 3b Individual case-control study - 4 Case series (and poor-quality cohort and case control studies) - 5 Expert opinion without explicit critical appraisal or based on physiology, bench research, or first principles	1. Eligibility criteria were specified. No/yes 2. Where subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received). No/yes 3. Where allocation was concealed. No/ yes where the groups were similar at baseline regarding the most important prognostic indicators. No/yes 4. Where there was blinding of all subjects. No/yes 5. Where there was blinding of all therapists who administered the therapy. No/yes 6. Where there was blinding of all assessors who measured at least one key outcome. No/yes 7. Where measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups. No/ yes 8. Where all subjects for whom outcome measures were available received the treatment or control condition as allocated, or, 9. Where this was not the case, data for at least one key outcome were analyzed by intention to treat. No/ yes 10. Where the results of between-group statistical comparisons are reported for at least one key outcome. No/yes 11. Where the study provides both point measures and measures of variability for at least one key outcome. No/ yes	**Class I** - Randomized, controlled clinical trial (RCT) in a representative population - Masked or objective outcome assessment - Relevant baseline characteristics are presented and substantially equivalent between treatment groups, or there is appropriate statistical adjustment for differences - Also required: a. Concealed allocation b. Primary outcome(s) clearly defined c. Exclusion/inclusion criteria clearly defined d. Adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*: 1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority 2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective) 3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment 4. The interpretation of the study results is based on a per-protocol analysis that accounts for dropouts or crossovers **Class II** - Cohort study meeting criteria a–e (see Class I) or an RCT that lacks one or two criteria b–e (see Class I) - All relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences - Masked or objective outcome assessment **Class III** - Controlled studies (including well-defined natural history controls or patients serving as their own controls) - A description of major confounding differences between treatment groups that could affect outcome** - Outcome assessment masked, objective or performed by someone who is not a member of the treatment team. **Class IV** - Did not include patients with the disease - Did not include patients receiving different interventions - Undefined or unaccepted interventions or outcome measures - No measures of effectiveness or statistical precision presented or calculable


Pooled mean difference (95% confidence interval), number of studies included and p value
12
10
8
6
4
2
0
-2
Controlled studies
4.0 (1.4, 6.6)
n = 13, p = 0.005
Low frequency
3.3 (1.5, 5.0)
n = 6, p = 0.005
High frequency
3.9 (-0.7, 8.4)
n = 9, p = 0.08
Long term
4.1 (-0.2, 8.4)
n = 7, p = 0.05
Short term
3.5 (0.3, 6.6)
n = 11, p = 0.03
Sham coil controlled
4.1 (-0.1, 8.5)
n = 9, p = 0.05


Pooled mean difference (confidence interval), number of studies included and p value
10
8
6
4
2
0
-2
-4
Controlled studies
3.9 (0.5, 7.3)
n = 15, p = 0.02
Low frequency
2.7 (-3.3, 8.7)
n = 7, p = 0.29
High frequency
4.6 (1.2, 7.9)
n = 10, p = 0.01
Long term
2.6 (-1, 6.3)
n = 8, p = 0.13
Short term
2.8 (-0.6, 6.2)
n = 13, p = 0.1
Sham coil controlled
4.8 (1.4, 8.3)
n = 11, p = 0.01