**Mini-CAT- Summer 2019**

**Clinical Question:**

Scenario: A 67 years old male with PMHx of HTN, HLD, Parkinson’s disease, aortic valve calcification s/p aortic valve replacement, mesenteric artery stenosis, and repeated fall c/o increasing muscle stiffness and keep shaking of hands, and family c/o loss of automatic movements. The patient’s family concerns these worsening motor symptoms.

Clinical question: In adult patients with Parkinson’s disease, how effective is repetitive transcranial magnetic stimulation (rTMS) in reducing motor symptoms, such as rigidity, bradykinesia, gait, and tremor?

**PICO Question:**

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| **P** | **I** | **C** | **O** |
| Parkinson’s disease | Repetitive transcranial magnetic stimulation | Sham controlled | Reduction of motor symptoms |
| Motor dysfunction | rTMS |  | Unified Parkinson  Disease Rating Scale |
| Adults |  |  | Adverse events |
|  |  |  | Improvement of bradykinesia |
|  |  |  | Improvement of rigidity |
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**Search Strategy:**

Key words used: Parkinson’s disease, motor function, repetitive transcranial magnetic stimulation, bradykinesia, rigidity, gait, tremor

Database: PubMed

Results found:

Repetitive transcranial magnetic stimulation Parkinson disease / limits: human, publications dates 10 years🡪79

Repetitive transcranial magnetic stimulation Parkinson disease motor/ limits: human, publications dates 10 years🡪 19

Database: Cochrane

Results found:

Repetitive transcranial magnetic stimulation Parkinson disease / limits: human, publications dates 10 years🡪 163

Non antibiotic uncomplicated diverticulitis management / limits: human, publications dates 10 years🡪 141

Database: JAMA

Results found:

Repetitive transcranial magnetic stimulation Parkinson disease / limits: academic article🡪 16

Repetitive transcranial magnetic stimulation Parkinson disease motor / limits: academic article, publications dates 10 years🡪 5

**How do I narrow down my articles?**

First of all, I tried to find articles that are reviewed articles; published in 10 years; the higher level of evidence, such as systemic review, meta-analysis, and RCTs; based on large sample size; and indexed for MEDLINE. Secondly, I read through abstract quickly and include articles that are published recently and a higher level of evidence, and intervention and control, the outcome of study must match my clinical questions. Especially, articles that match PICO search terms, for example, intervention with transcranial magnetic stimulation and outcomes of reductions in motor functions, such as bradykinesia, rigidity, tremor, gait and axial symptoms. For the selection of articles, systemic review and meta-analysis are my first choice, I did find a couple of systemic review and meta-analysis studies, and some of them are reviewing the same articles. I did not include those articles, and I tried to include those systemic reviews which reviewed different studies. The first two systemic reviews are the most precise systemic review I can find that compare repetitive transcranial magnetic stimulation (rTMS) and shame controlled in Parkinson’s disease. I also include 2 RCTs, which also compare rTMS and shame controlled.

**Articles Chosen** :

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| **Title** | **Effects of repetitive transcranial magnetic stimulation on motor symptoms in Parkinson disease: a systematic review and meta-analysis.**  [Chou YH](https://www.ncbi.nlm.nih.gov/pubmed/?term=Chou%20YH%5BAuthor%5D&cauthor=true&cauthor_uid=25686212)1, [Hickey PT](https://www.ncbi.nlm.nih.gov/pubmed/?term=Hickey%20PT%5BAuthor%5D&cauthor=true&cauthor_uid=25686212)2, [Sundman M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Sundman%20M%5BAuthor%5D&cauthor=true&cauthor_uid=25686212)3, [Song AW](https://www.ncbi.nlm.nih.gov/pubmed/?term=Song%20AW%5BAuthor%5D&cauthor=true&cauthor_uid=25686212)3, [Chen NK](https://www.ncbi.nlm.nih.gov/pubmed/?term=Chen%20NK%5BAuthor%5D&cauthor=true&cauthor_uid=25686212)4. [JAMA Neurol.](https://www.ncbi.nlm.nih.gov/pubmed/25686212) 2015 Apr;72(4):432-40. doi: 10.1001/jamaneurol.4380. |
| **Abstract** | AbstractIMPORTANCE: Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive neuromodulation technique that has been closely examined as a possible treatment for Parkinson disease (PD). However, results evaluating the effectiveness of rTMS in PD are mixed, mostly owing to low statistical power or variety in individual rTMS protocols. OBJECTIVES: To determine the rTMS effects on motor dysfunction in patients with PD and to examine potential factors that modulate the rTMS effects. DATA SOURCES: Databases searched included PubMed, EMBASE, Web of Knowledge, Scopus, and the Cochrane Library from inception to June 30, 2014. STUDY SELECTION: Eligible studies included sham-controlled, randomized clinical trials of rTMS intervention for motor dysfunction in patients with PD. DATA EXTRACTION AND SYNTHESIS: Relevant measures were extracted independently by 2 investigators. Standardized mean differences (SMDs) were calculated with random-effects models. MAIN OUTCOMES AND MEASURES: Motor examination of the Unified Parkinson's Disease Rating Scale. RESULTS: Twenty studies with a total of 470 patients were included. Random-effects analysis revealed a pooled SMD of 0.46 (95% CI, 0.29-0.64), indicating an overall medium effect size favoring active rTMS over sham rTMS in the reduction of motor symptoms (P<.001). Subgroup analysis showed that the effect sizes estimated from high-frequency rTMS targeting the primary motor cortex (SMD, 0.77; 95% CI, 0.46-1.08; P<.001) and low-frequency rTMS applied over other frontal regions (SMD, 0.50; 95% CI, 0.13-0.87; P=.008) were significant. The effect sizes obtained from the other 2 combinations of rTMS frequency and rTMS site (ie, high-frequency rTMS at other frontal regions: SMD, 0.23; 95% CI, -0.02 to 0.48, and low primary motor cortex: SMD, 0.28; 95% CI, -0.23 to 0.78) were not significant. Meta-regression revealed that a greater number of pulses per session or across sessions is associated with larger rTMS effects. Using the Grading of Recommendations, Assessment, Development, and Evaluation criteria, we characterized the quality of evidence presented in this meta-analysis as moderate quality. CONCLUSIONS AND RELEVANCE: The pooled evidence suggests that rTMS improves motor symptoms for patients with PD. Combinations of rTMS site and frequency as well as the number of rTMS pulses are key modulators of rTMS effects. The findings of our meta-analysis may guide treatment decisions and inform future research. |
| **Link** | **Link**: <https://www.ncbi.nlm.nih.gov/pubmed/25686212> |
| **PDF** |  |

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| **Title** | **Repetitive transcranial magnetic stimulation of the primary motor cortex in the treatment of motor signs in Parkinson's disease: A quantitative review of the literature.**  [Zanjani A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Zanjani%20A%5BAuthor%5D&cauthor=true&cauthor_uid=25786995)1, [Zakzanis KK](https://www.ncbi.nlm.nih.gov/pubmed/?term=Zakzanis%20KK%5BAuthor%5D&cauthor=true&cauthor_uid=25786995)1, [Daskalakis ZJ](https://www.ncbi.nlm.nih.gov/pubmed/?term=Daskalakis%20ZJ%5BAuthor%5D&cauthor=true&cauthor_uid=25786995)2, [Chen R](https://www.ncbi.nlm.nih.gov/pubmed/?term=Chen%20R%5BAuthor%5D&cauthor=true&cauthor_uid=25786995)3. [Mov Disord.](https://www.ncbi.nlm.nih.gov/pubmed/25786995) 2015 May;30(6):750-8. doi: 10.1002/mds.26206. Epub 2015 Mar 18. |
| **Abstract** | Abstract Parkinson's disease (PD) is a progressive disorder characterized by the emergence of motor deficits. In light of the voluminous and conflicting findings in the literature, the aim of the present quantitative review was to examine the effects of repetitive transcranial magnetic stimulation (rTMS) targeting the primary motor cortex (M1) in the treatment of motor signs in PD. Studies meeting inclusion criteria were analyzed using meta-analytic techniques and the Unified Parkinson's Disease Rating Scale (UPDRS) sections II and III were used as outcome measures. In order to determine the treatment effects of rTMS, the UPDRS II and III scores obtained at baseline, same day, to 1 day post rTMS treatment (short-term follow-up) and 1-month post stimulation (long-term follow-up) were compared between the active and sham rTMS groups. Additionally, the placebo effect was evaluated as the changes in UPDRS III scores in the sham rTMS groups. A placebo effect was not demonstrated, because sham rTMS did not improve motor signs as measured by UPDRS III. Compared with sham rTMS, active rTMS targeting the M1 significantly improved UPDRS III scores at the short-term follow-up (Cohen's d of 0.27, UPDRS III score improvement of 3.8 points). When the long-term follow-up UPDRS III scores were compared with baseline scores, the standardized effect size between active and sham rTMS did not reach significance. However, this translated into a significant nonstandardized 6.3-point improvement on the UPDRS III. No significant improvement in the UPDRS II was found. rTMS over the M1 may improve motor signs. Further studies are needed to provide a definite conclusion. KEYWORDS: Meta-analysis; Parkinson's disease; Review; Transcranial magnetic stimulation (rTMS); Treatment efficacy |
| **Link** | **Link:** <https://www.ncbi.nlm.nih.gov/pubmed/25786995> |
| **PDF** |  |

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| **Title** | **Multifocal repetitive TMS for motor and mood symptoms of Parkinson disease: A randomized trial.**  [Brys M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Brys%20M%5BAuthor%5D&cauthor=true&cauthor_uid=27708129)1, [Fox MD](https://www.ncbi.nlm.nih.gov/pubmed/?term=Fox%20MD%5BAuthor%5D&cauthor=true&cauthor_uid=27708129)1, [Agarwal S](https://www.ncbi.nlm.nih.gov/pubmed/?term=Agarwal%20S%5BAuthor%5D&cauthor=true&cauthor_uid=27708129)1, [Biagioni M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Biagioni%20M%5BAuthor%5D&cauthor=true&cauthor_uid=27708129)1, [Dacpano G](https://www.ncbi.nlm.nih.gov/pubmed/?term=Dacpano%20G%5BAuthor%5D&cauthor=true&cauthor_uid=27708129)1, [Kumar P](https://www.ncbi.nlm.nih.gov/pubmed/?term=Kumar%20P%5BAuthor%5D&cauthor=true&cauthor_uid=27708129)1, [Pirraglia E](https://www.ncbi.nlm.nih.gov/pubmed/?term=Pirraglia%20E%5BAuthor%5D&cauthor=true&cauthor_uid=27708129)1, [Chen R](https://www.ncbi.nlm.nih.gov/pubmed/?term=Chen%20R%5BAuthor%5D&cauthor=true&cauthor_uid=27708129)1, [Wu A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Wu%20A%5BAuthor%5D&cauthor=true&cauthor_uid=27708129)1, [Fernandez H](https://www.ncbi.nlm.nih.gov/pubmed/?term=Fernandez%20H%5BAuthor%5D&cauthor=true&cauthor_uid=27708129)1, [Wagle Shukla A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Wagle%20Shukla%20A%5BAuthor%5D&cauthor=true&cauthor_uid=27708129)1, [Lou JS](https://www.ncbi.nlm.nih.gov/pubmed/?term=Lou%20JS%5BAuthor%5D&cauthor=true&cauthor_uid=27708129)1, [Gray Z](https://www.ncbi.nlm.nih.gov/pubmed/?term=Gray%20Z%5BAuthor%5D&cauthor=true&cauthor_uid=27708129)1, [Simon DK](https://www.ncbi.nlm.nih.gov/pubmed/?term=Simon%20DK%5BAuthor%5D&cauthor=true&cauthor_uid=27708129)1, [Di Rocco A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Di%20Rocco%20A%5BAuthor%5D&cauthor=true&cauthor_uid=27708129)1, [Pascual-Leone A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Pascual-Leone%20A%5BAuthor%5D&cauthor=true&cauthor_uid=27708129)2. [Neurology.](https://www.ncbi.nlm.nih.gov/pubmed/27708129) 2016 Nov 1;87(18):1907-1915. Epub 2016 Oct 5. |
| **Abstract** | AbstractOBJECTIVE: To assess whether multifocal, high-frequency repetitive transcranial magnetic stimulation (rTMS) of motor and prefrontal cortex benefits motor and mood symptoms in patients with Parkinson disease (PD). METHODS: Patients with PD and depression were enrolled in this multicenter, double-blind, sham-controlled, parallel-group study of real or realistic (electric) sham rTMS. Patients were randomized to 1 of 4 groups: bilateral M1 ( + sham dorsolateral prefrontal cortex [DLPFC]), DLPFC ( + sham M1), M1 + DLPFC, or double sham. The TMS course consisted of 10 daily sessions of 2,000 stimuli for the left DLPFC and 1,000 stimuli for each M1 (50 × 4-second trains of 40 stimuli at 10 Hz). Patients were evaluated at baseline, at 1 week, and at 1, 3, and 6 months after treatment. Primary endpoints were changes in motor function assessed with the Unified Parkinson's Disease Rating Scale-III and in mood with the Hamilton Depression Rating Scale at 1 month. RESULTS: Of the 160 patients planned for recruitment, 85 were screened, 61 were randomized, and 50 completed all study visits. Real M1 rTMS resulted in greater improvement in motor function than sham at the primary endpoint (p < 0.05). There was no improvement in mood in the DLPFC group compared to the double-sham group, as well as no benefit to combining M1 and DLPFC stimulation for either motor or mood symptoms. CONCLUSIONS: In patients with PD with depression, M1 rTMS is an effective treatment of motor symptoms, while mood benefit after 2 weeks of DLPFC rTMS is not better than sham. Targeting both M1 and DLPFC in each rTMS session showed no evidence of synergistic effects. CLINICALTRIALSGOV IDENTIFIER: [NCT01080794](http://clinicaltrials.gov/show/NCT01080794). CLASSIFICATION OF EVIDENCE: This study provides Class I evidence that in patients with PD with depression, M1 rTMS leads to improvement in motor function while DLPFC rTMS does not lead to improvement in depression compared to sham rTMS. |
| **Link** | Link: <https://www.ncbi.nlm.nih.gov/pubmed/27708129> |
| **PDF** |  |
| **Title** | **Repetitive Deep TMS for Parkinson Disease: A 3-Month Double-Blind, Randomized Sham-Controlled Study.**  [Cohen OS](https://www.ncbi.nlm.nih.gov/pubmed/?term=Cohen%20OS%5BAuthor%5D&cauthor=true&cauthor_uid=29373395)1,2,3, [Rigbi A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Rigbi%20A%5BAuthor%5D&cauthor=true&cauthor_uid=29373395)4, [Yahalom G](https://www.ncbi.nlm.nih.gov/pubmed/?term=Yahalom%20G%5BAuthor%5D&cauthor=true&cauthor_uid=29373395)1,2, [Warman-Alaluf N](https://www.ncbi.nlm.nih.gov/pubmed/?term=Warman-Alaluf%20N%5BAuthor%5D&cauthor=true&cauthor_uid=29373395)1, [Nitsan Z](https://www.ncbi.nlm.nih.gov/pubmed/?term=Nitsan%20Z%5BAuthor%5D&cauthor=true&cauthor_uid=29373395)5, [Zangen A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Zangen%20A%5BAuthor%5D&cauthor=true&cauthor_uid=29373395)6, [Hassin-Baer S](https://www.ncbi.nlm.nih.gov/pubmed/?term=Hassin-Baer%20S%5BAuthor%5D&cauthor=true&cauthor_uid=29373395). [J Clin Neurophysiol.](https://www.ncbi.nlm.nih.gov/pubmed/29373395) 2018 Mar;35(2):159-165. doi: 10.1097/WNP.0000000000000455. |
| **Abstract** | AbstractPURPOSE: To study the effects of a repetitive deep transcranial magnetic stimulation (rDTMS) in patients with Parkinson disease using the H5 coil for the low-frequency stimulation of the primary motor cortex, followed by the high-frequency rDTMS of the prefrontal cortex. METHODS: The main outcome measures were the total and motor scores of the Unified Parkinson's Disease Rating Scale (UPDRS). Secondary measures included rating of depression and quantitative motor tasks. RESULTS: Forty-eight patients were randomized 1:1 into real or sham rDTMS treatment arms. Analyses (n = 42) of both UPDRS scores revealed a significant main effect for time between baseline and day 90 (end of treatment), indicating that there was an improvement of both scores over time in the whole sample. Although effects of treatment and time-by-treatment were insignificant, simple effects analysis of both measures was significant in the rDTMS group and reached a P-value of 0.06 in the sham group. The response rate was higher in patients with longer disease duration and higher motor UPDRS scores. Side effects were more common in the rDTMS group but were transient and tolerable. CONCLUSIONS: Although rDTMS treatment exhibited some motor improvements, we could not demonstrate an advantage for real treatment over sham. Further research is required to establish stimulation parameters that may induce potentially more beneficial outcomes, probably in patients with longer and more sever disease. |
| **Study** | RCT |
| **Link** | Link: <https://www.ncbi.nlm.nih.gov/pubmed/29373395> |
| **PDF** |  |

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| Author (Date) | Level of Evidence | Sample/Setting  (# of subjects/ studies, cohort definition etc. ) | Outcome(s) studied | Key Findings | Limitations and Biases |
| Chou YH, Hickey PT, Sundman M, Song AW, Chen NK(2015) | Systematic Review | 20 studies included, with a total of 470 patients; parallel or crossover RCTs that use a sham-controlled group or condition | Primary outcome:  -reduction of motor symptoms  By Unified Parkinson Disease Rating Scale (UPDRS)section III  Subgroup analysis:  -effects of stimulation site and frequency on motor symptoms | -There is a significant medium effect size favoring active repetitive transcranial magnetic stimulation over sham controlled in the reduction of motor symptoms in patients with Parkinson’s disease; the total effect size of rTMS on UPDRS-III score was 0.46 (95% CI, 0.29 to 0.64), indicating a medium effect size favoring active rTMS over sham rTMS (z = 5.18; P < .001). The mean score change in the UPDRS-III following active rTMS intervention was −6.42 (5.79), corresponding to a moderate clinically important difference.  -Subgroup analysis: there are no significant differences in the effect size between repetitive transcranial magnetic stimulation sites and between high-frequency and low-frequency stimulation. However, the different combinations of sites and frequency are significant: the combination of high-frequency that targeting at primary motor cortex (SMD, 0.77; 95% CI, 0.46-1.08; P<.001); and the combination of low-frequency that over frontal region (SMD, 0.50; 95% CI, 0.13-0.87; P=.008) are significant | -When assessing the motor functions using Unified Parkinson’s Disease Rating Scale, no specific results for each part of assessments is listed. For example, walking, tremor, freezing when walking, speech, facial expression, and rigidity  -Only 13 studies evaluated the incidence of adverse events. Adverse events are not listed in the results, no percentage is calculated or compared. No medical interventions are recorded either  -For risk of bias assessment in individual studies, 10 studies had incomplete data for risk of bias assessment, and one group of authors cannot be located  -Some uncontrolled variables, such as medication use, disease stage, side of onset, side of repetitive transcranial magnetic stimulation can confound the results must be addressed. For example, side effect of Levodopa use can lead to tremor as well |

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| Zanjani A, Zakzanis KK, Daskalakis ZJ, Chen R. (2015) | Systematic Review | 11 randomized, sham controlled trails are included with total of 246 patients with Parkinson’s Disease; 109 patients with active rTMS, 93 patients with sham, and 44 patient with both active and sham | Primary outcomes:  -Motor signs- section III  -ADLs -section II  By Unified Parkinson Disease Rating Scale (UPDRS), section II and section III | -There is a low but significant pooled effect size of 0.27 (95%CI=0.034 to 0.50; df=10; overlap percent=80; P=0.025) was seen, with most studies showing improvement. These results translate to an average of 3.88 (95%CI=0.97 to 6.80; df=10; P=0.0090) point improvement in UPDRS III compared with sham stimulation.  -For after 1 month, there is a nonsignificant pooled effect size of 0.31 (95%CI=20.00014 to 0.63; df=4; P=0.050). However, this translated to a significant, nonstandardized improvement of 6.29 points (95%CI=0.50 to 12.07; df=4; P=0.033) in UPDRS III compared with sham stimulation.  -For ADLs: no significant effect size is seen; there is a pooled nonsignificant effect size of 20.059 (95%CI=20.60 to 0.49; df=1; P=0.83) in short-term follow up; and a size of 0.15 (95%CI=20.39 to 0.70; df=1; P=0.58) in long-term | -Studies were screened for this review by title and/or abstract, rather than the entire article. This may have left room for relevant articles to be excluded from the review  -Each of studies included in this systematic review use a different combination of parameters, which make determining whether the effects observed were attributable to one factor alone difficult  -The interactions between various parameters are not considered in this analysis |

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| Brys M, Fox MD, Agarwal S, Biagioni M, Dacpano G, Kumar P, Pirraglia E, Chen R, Wu A, Fernandez H, Wagle Shukla A, Lou JS, Gray Z, Simon DK, Di Rocco A, Pascual-Leone A. (2016) | RCT | There are 4 groups of comparisons: Group 1- real primary motor cortex + real dorsolateral prefrontal cortex  Group 2- real primary motor cortex + sham dorsolateral prefrontal cortex  Group 3- sham primary motor cortex+ real dorsolateral prefrontal cortex  Group 4- double sham | Main outcome:  -Improvement in motor symptoms  -Rigidity, bradykinesia, tremor, gait and axial symptoms  Other outcomes  -Mood symptoms, depression  By Hamilton Depression Rating Scale (HAM-D) | -Improvement in motor symptoms with real stimulation; change was greater in the primary motor cortex group (-4.9 points) than in the double-sham group (-0.3 points; mean difference= -4.6, 95% CI -0.1 to -9.1, t= -2.1, p<0.05).  -There are improvements in the primary motor cortex group in UPDRS-III subscores of rigidity (mean difference= -0.5, 95% CI -1.4 to -0.8, t =3.0, p<0.01) and bradykinesia (mean difference=0.3, 95% CI -0.6 to -0.01, t=2.1, p<0.05) but not tremor, gait, or axial symptoms  -For the primary motor cortex and dorsolateral prefrontal cortex group, there is no significant improvement in the motor symptoms | -For the participants, there are more male than female patients in different groups. Besides age and sex, the study does not inform other demographics information  -Sample sizes for each group is small, only 12-20 participants for each group  -There are 49% participants correctly guessed the stimulation status, real vs. sham, which may indicate low efficacy of blinding method used |

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| Cohen OS, Rigbi A, Yahalom G, Warman-Alaluf N, Nitsan Z, Zangen A, Hassin-Baer S. (2018) | RCT | 48 patients include in this study; 26 patients in active treatment group and 22 patients in sham group | Main outcomes:  -Total and motor scores by using Unified Parkinson’s Disease rating Scale (UPDRS)  Secondary outcomes:  -Rate of depression by Beck Depression Inventory (BDI)  -Quantitative motor tasks by Timed Up and Go test (TUG) and Digit span test (forward and backward) | -The total score decreased over time in the whole sample (baseline estimate: M=43.1, SE=1.9; day 90 estimate: 39.6, SE=1.4; F1,39=11.8; P=0.001); no significant effects for treatment (P=0.63) or for time-by treatment interaction (P=0.45) are observed.  -Motor scores decrease over time in the whole sample (baseline estimate: M =28.8, SE=1.4; day 90 estimate: 26.6, SE =1.1; F1,39 =7.6; P=0.009). Main effects for treatment are insignificant (P=0.93 and 0.20, respectively) as was the time by-treatment interaction effect (P=0.51).  -For secondary outcomes: improvement over time in the whole sample on these tasks; a significant main effect for time  is found in most cognitive and motor tasks, for example, digit span forward  and backward; and Timed Up and Go.  - Adverse events are more common in the real treatment group than those in the sham group (16 vs. 9, respectively, x2=3.6, df=1, P=0.06); however, they are generally transient, and the  interventions are well tolerated. | -For the group characteristics, there are more patients in the sham group are taking levodopa, and as the result, the levodopa-equivalent daily dose is higher than active treatment group, which will lead to differences when compare between these two groups  -For subanalysis, the response rate may be higher in patients with more severe disease and in those with longer disease duration which may lead to bias and different results  -Sample size for this study is small, which only has 48 patients in total; and the study time is 3 months only, which may not indicate long-term effects of rTMS |

**Conclusion(s):**

Article1 (systemic review) concludes that there is a significant medium effect size favoring active repetitive transcranial magnetic stimulation over sham-controlled in the reduction of motor symptoms in patients with Parkinson’s Disease. Also, the different combinations of sites and frequency are significant: the combination of high-frequency that targeting at the primary motor cortex and the combination of low-frequency that over the frontal region are significant. For adverse events, few patients complain of headache, and intervention is generally tolerated.

Article 2 (systemic review), most studies show motor improvement compared with sham stimulation, but due to small sample sizes, definitive conclusions cannot be drawn. No significant effect size is seen in ADLs improvement.

Article 3 (RCT) concludes that rTMS in the primary motor cortex is an effective treatment of motor symptoms in patients with Parkinson’s disease. For adverse events, 68% of participants report headache and neck pain, which are mild and transient.

Article 4 (RCT) concludes that rTMS showed some benefit on motor outcomes of patients with Parkinson’s Disease but failed to show a significant advantage over sham treatment. For the adverse events, it is more common in the real treatment group, but it is transient.

Overall, all 4 articles have the same conclusions that rTMS show motor function improvements in patients who have Parkinson’s Disease. Interventions are generally tolerated, adverse events, such as headache and neck pain are reported, which is transient and does not require medical intervention. However, article 2 states cannot draw a definitive conclusion based on small sample size; and article 4 also states it failed to show a significant advantage over sham treatment.

**Clinical Bottom Line:**

Article 1 is a systemic review, which includes20 studies, and it is based on a larger sample size with 470 participants. They measure the reduction of motor symptoms, and also the effects of stimulation site and frequency on motor symptoms. Article 1 also shows the combination of high-frequency that targeting at the primary motor cortex and the combination of low-frequency that over the frontal region are significant as well. Article 2 is a systemic review, and it assesses the motor sign and ADLs of patients. Article 3 and Article 4 are RCTs exam the efficacy of rTMS. The exposures to active treatment and sham-controlled, and measure the outcomes and adverse events. Even though they are based on small sample sizes, the experimental study design is a good standard for evaluating efficacy in clinical research and constitute evidence for medical treatments.

In clinical practice, Parkinson’s disease cannot be cured, but medications can help control symptoms. Medications like Carbidopa-levodopa, dopamine agonists, or anticholinergics can help with the management of walking, movement, and tremor. And as the disease progress, surgical procedures, deep brain stimulation, may get involved. Surgeons will implant electrodes into the brain, and electrodes are connected to a generator implanted in the chest. Unlike deep brain stimulation, repetitive transcranial magnetic stimulation (rTMS) is a noninvasive procedure that uses magnetic fields to stimulate nerve cells in the brain to improve motor functions.

In conclusion, the clinical recommendation is based on the evidence found in the systemic and RCT studies, in patients with Parkinson’s disease, repetitive transcranial magnetic stimulation (rTMS) shows beneficial outcomes in motor function. For my patient, I will recommend him to get this noninvasive rTMS treatment if his symptoms getting worse or medication control is unsuccessful. When discussing the side effects of rTMS to the patients, we would inform them about headache and neck pain, which should be mild and do not require medical treatment. However, due to small sample size and different conclusions in different stimulation sites, primary motor cortex and/or dorsolateral prefrontal cortex, and different intensity, low-frequency and high-frequency, more studies based on larger sample size should be done to further investigate rTMS efficiency, stimulation site, and intensity.