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# REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION FOR FIBROMYALGIA: AN INTERNATIONAL MULTICENTER CONTROLLED TRIAL

TU537

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## Background

Noninvasive repetitive transcranial magnetic stimulation (rTMS) has been shown to control pain in neuropathic pain when delivered to the primary motor cortex (M1). It has also shown analgesic effects in people with fibromyalgia (PwF) in two pioneering single-center studies. Here we report on the first international multicenter study. The present double blind sham controlled trials assessed whether induction sessions, followed by spaced maintenance sessions could improve pain and related symptoms in PwF.

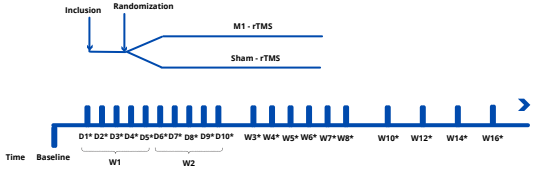
## Aim

To evaluate the analgesic effects of rTMS on FM patients targeting the primary motor cortex.

## Methods

The respective Ethics review boards from all the participating centers approved the study, and all participants provided informed consent before implementing any study protocol, registered under No. 5.315.085 in the coordinating center. This study was registered under clinicaltrials.gov under protocol NCT03658694. The main outcome was the number of responders (reduction of ⩾50% in pain intensity at week 8 compared to baseline), measured on a 11-point numerical rating scale (NRS) ranging from 0 to 10. Secondary outcomes included the Fibromyalgia Impact Questionnaire (FIQ), Global Impression of Change (GIC), mood (Hospital Anxiety and Depression Scale (HADS), and the Brief Pain Inventory (BPI). Adverse events were assessed by a standardized questionnaire. Blinding assessments was also assessed with questionnaires.

**Figure 1:** Study design.




Legend: TMS session (*), day (D), Week (W). Baseline assessment was performed on baseline, week 8 (w8) and week 16 (w16), and included sociodemographic; brief pain inventory – short form; fibromyalgia impact questionnaire; hospital anxiety and depression scale; global impression of change (clinician and participant versions), blinding assessment (quality of blinding assessment); the American College of Rheumatology 2016 criteria (symptom severity score and generalized pain index) occurred during the baseline visits, W8, and W16. In every rTMS session side effects were assessed, on the last day of the study week 16 blinding was added to the assessment.

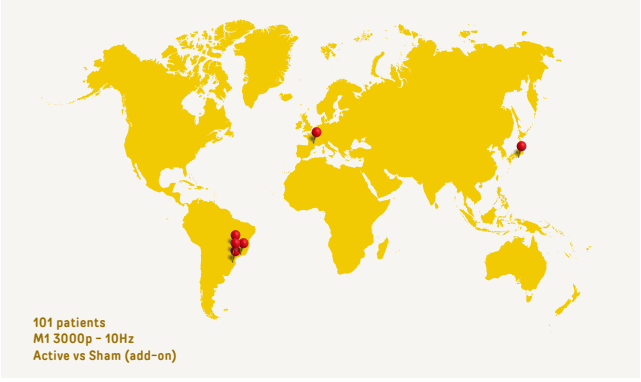
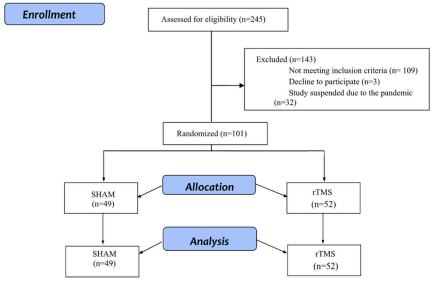



**Figure 2:** Study selection flow chart.



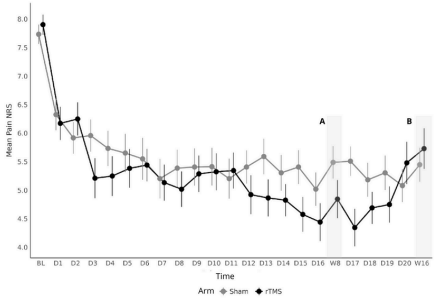

Legend: Repetitive Transcranial Magnetic Stimulation (rTMS)

**Table 1:** Estimate differences and probability of the hypothesis for W8 and W16 for Pain instruments and Improvement of Clinician and patient CGI.

| Outcomes | Estimate difference | Probability of hypothesis |
|---|---|---|
| *Week 8* | | |
| 50% Reduction Pain NRS | 1.11 (0.232, 2.09) | 99.4 % |
| BPI pain severity | -0.529 (-1.21, 0.192) | 92.6 % |
| BPI pain interference | 0.17 (-1.02, 0.693) | 65.8 % |
| BPI pain relief during the last 24h | 0.467 (-8.07, 8.5) | 45.9 % |
| BPI Overall activity 24h | 0.439 (-1.43, 0.589) | 79.9 % |
| BPI Mood 24h | 0.326 (-0.724, 1.41) | 26.7 % |
| BPI Walking 24h | 0.045 (-0.992, 1.08) | 46.6 % |
| BPI Work 24h | -0.578 (-1.58, 0.43) | 86.9 % |
| BPI Relationship with People 24h | -0.165 (-1.24, 0.933) | 61.7 % |
| BPI Sleep 24h | -0.846 (-2.05, 0.339) | 92.3 % |
| BPI Ability to Enjoy Life 24h | -0.352 (-1.4, 0.722) | 74.3 % |
| FIQ | -2.95 (-9.72, 3.83) | 80.1 % |
| HADS anxiety | -0.255 (-1.93, 1.43) | 61.8 % |
| HADS depression | 0.421 (-1.2, 1.99) | 29.7 % |
| Improvement in patient CGI | 0.759 (-0.041, 1.57) | 96.8 % |
| Improvement in clinician CGI | 0.548 (-0.301, 1.45) | 88.8 % |

Legend: Data are presented as mean (±SD) for the experience of pain and as absolute numbers with percentages for categorical variables.

**Figure 3:** Pain intensity during the study.




Legend: Numerical Rating Scale (NRS), day (D), Week (W). A = at week 8 the Bayesian analysis shows a 99.4% probability of a 50% pain reduction, in the active group versus sham, with an odds ratio of 3.04. Frequentist analysis supported these results (responders=40.4%, non-responders=18.4%; p=0.028). B= At week 16, the probability of pain response was 34.2%, odds ratio of 0.815.

## Results

Pre-planned single-levelBayesian models showed 99.4% probability of achieving 50% reduction in pain at week 8 in theactive arm compared to sham (estimated difference: 1.11 (0.232; 2.09)), oddsratio (OR): 3.04 (1.26,8.06). Frequentist analyses confirmed these findings (responders = 40.4%, non-responders=18.4%; p=0.028), NNT=4.54, effect size: 0.49). Additionally, by week 16, there was a notable reduction in effect: 34.2% (OR: 0.815 (0.313;2.1). At week 8, theprobability of active rTMS being superior toshamstimulation in secondary outcomes is presented in Table 1 below.

## Conclusions

This international multicentric study suggests that rTMS targeting the M1 has significant analgesic effects in PwF, after the induction after the maintenance phase, with weaning of the analgesic effects with stimulation sessions occurring every 2 weeks.

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