HHS Public Access

Author manuscript

Brain Stimul. Author manuscript; available in PMC 2020 October 30.

Published in final edited form as:

Brain Stimul. 2019 ; 12(5): 1328–1329. doi:10.1016/j.brs.2019.06.016.

Repetitive Transcranial Magnetic Stimulation for depression relapse or recurrence: Naturalistic retreatment series outcomes

Andrew M. Fukuda,
Butler Hospital TMS Clinic and Neuromodulation Research Facility, 345 Blackstone Boulevard, Providence, RI, 02906, USA; Department of Psychiatry and Human Behavior, Alpert Medical School of Brown University, Box G-BH, Providence, RI, 02912, USA

Eric Tirrell,
Butler Hospital TMS Clinic and Neuromodulation Research Facility, 345 Blackstone Boulevard, Providence, RI, 02906, USA

A. Polly Gobin,
Butler Hospital TMS Clinic and Neuromodulation Research Facility, 345 Blackstone Boulevard, Providence, RI, 02906, USA

Linda L. Carpenter*
Butler Hospital TMS Clinic and Neuromodulation Research Facility, 345 Blackstone Boulevard, Providence, RI, 02906, USA; Department of Psychiatry and Human Behavior, Alpert Medical School of Brown University, Box G-BH, Providence, RI, 02912, USA

Keywords

Transcranial magnetic stimulation; Treatment resistant major depressive disorder; Retreatment; Neuromodulation; Naturalistic study

Introduction

Repetitive Transcranial Magnetic Stimulation (rTMS) is FDA approved for the treatment of pharmacoresistant major depressive disorder (TRD) [1,2]. Currently no standard of care for maintaining clinical benefits following a successful initial rTMS exists [3]. A common strategy in American TMS clinical practices is beginning a new course of TMS treatments once relapse/recurrence occurs. However, data regarding this approach to TMS retreatment (here-after abbreviated Retx) is sparse [4,5]. We aimed to characterize the course and outcomes of Retx for TRD in a naturalistic setting.

*Corresponding author. linda_carpenter_md@brown.edu (L.L. Carpenter).

Conflicts of interest

Dr. Carpenter, Mr. Tirrell, and Ms. Gobin have received clinical trials/research support from Neuronetics, Neosync, Feelmore Rx, and Janssen; Butler Hospital has received TMS research equipment from Nexstim and Neuronetics. Dr. Carpenter has received consulting income from Magsim LTD and Janssen. There was no funding from any commercial entity for the work presented in this report.

Methods

Standard FDA protocol for rTMS with figure-8 devices was initiated for all MDD patients in the Butler Hospital TMS Clinic [6,7]. For each session, stimulation at 120% of motor threshold was administered over the left dorsolateral prefrontal cortex at 10 Hz for 3000–4000 pulses/session. Slight variations from the standard protocol were made when 10 Hz stimulation was poorly tolerated [7] but the majority of patients followed the above protocol.

De-identified data of all MDD patients who received rTMS at Butler TMS Clinic from 2009 to 2018 was analyzed. All met eligibility criteria for insurance coverage of rTMS for primary MDD. Cases selected for analysis received an initial acute course of rTMS with clinical benefit and subsequently returned to receive at least 10 sessions in a repeat course of standard once-daily rTMS therapy. The Inventory of Depressive Symptoms-Self Report (IDSSR) and the 9-Item Patient Health Questionnaire (PHQ9) were outcome measures, administered at baseline and at end of treatment (post). Those without at least one of the outcome measures in either the initial or Retx were excluded.

Response was defined as a 50% reduction in score from baseline (prior to the first rTMS session in that series) to post-treatment (after final rTMS session in the series) and remission as post-treatment IDSSR ≤14 or PHQ9 ≤4. In order to quantify the magnitude of the initial clinical improvement that was lost at the point when patients presented for Retx, an index termed Severity of Relapse was calculated for both IDSSR and PHQ9 as follows: [(RetxBaseline – AcutePost)/(AcuteBaseline – AcutePost)] x 100%. When applicable, results are reported as mean ± standard deviation.

Results

A significant reduction in depression severity during Retx was seen via paired T-test between baseline and post-treatment PHQ9 (18.19 ± 4.60 to 5.90 ± 4.75, $p < 0.0001$) and IDSSR (44.21 ± 11.57 to 19.79 ± 10.62, $p < 0.0001$). %-change from baseline to post-treatment was significantly less for Retx compared to acute on both IDSSR (65.77 ± 17.54 and 53.36 ± 24.73, $p < 0.002$) and PHQ9 (75.08 ± 18.75 and 63.58 ± 27.83, $p < 0.02$). However, baseline scores were also significantly lower when starting Retx than at the baseline assessment for the initial series (IDSSR 48.64 ± 10.51 vs 44.21 ± 11.57, $p < 0.005$). A significant positive Spearman's correlation between time elapsed between series and depression severity upon presentation for Retx on both IDSSR and PHQ9 ($r = 0.353$ and $r = 0.360$, respectively, $p < 0.03$) was present.

Retx response rates measured via IDSSR and PHQ9 were 59.5% and 73.8%, respectively. 78.6% responded via either IDSSR or PHQ9. Retx remission rates using IDSSR and PHQ9 were 40.5% and 52.4%; 57.1% of the sample remitted when applying criteria from either measure. Patients achieving remission during the initial series were significantly more likely to achieve remission during Retx ($X^2 = 5.567$, $p < 0.02$) with an odds ratio of 4.7. Furthermore, when outcomes were examined as baseline-to-post-treatment %-change on IDSSR and PHQ9, significant positive Pearson correlations were seen between initial and Retx outcomes ($r = 0.432$, $p < 0.005$ and $r = 0.368$, $p < 0.02$ respectively), indicating that

greater magnitude of symptom improvement in the initial series predicted the same during Retx.

The severity of relapse index showed that the majority presented for Retx before the magnitude of improvement obtained during initial series was fully lost (52.5% on PHQ9 and 81.0% on IDSSR), consistent with advice given by clinic staff upon completion of initial course of rTMS. The majority were able to recapture the initial post-treatment state with post-Retx scores that were within 2 points on IDSSR (52.4% of pts) and PHQ9 (67.5%). No significant difference in age, time, baseline severity, degree of relapse was found between those who recaptured and those who did not. Additionally, no significant correlations were present between the degree of recapture and other variables.

Demographics and the response/remission rates for those receiving more than one retreatment are included in Table 1.

Discussion

Our data showed that naturalistic rTMS Retx successfully relieved symptoms in the majority of cases. About half the patients fully recaptured their prior level of improvement. The degree of improvement during initial series correlated with Retx improvement and initial remission was significantly associated with Retx remission. These findings are in accordance with another retrospective naturalistic study which showed that initial rTMS response was a significant predictor of repeat rTMS response in 16 patients [5]. Although a similar correlation was not found in the first naturalistic study that included both right, left and bilateral stimulation without a clear definition of “relapse,” the degree of symptomatic improvement post-Retx seen in our study was similar [4]. The naturalistically treated samples (our data [4,5],) had somewhat lower retreatment response rates than those seen in a 12-month prospective maintenance trial that used systematic serial assessment over time and a pre-defined threshold of clinical worsening triggered rTMS retreatment in medication-free patients [6].

These results suggest that Retx after relapse or recurrence is viable for those who respond well to an initial course of rTMS therapy, and a similar degree of improvement may be expected. However, not all patients are able to recapture their prior level of benefit, raising the question of whether a maintenance or rescue rTMS regimen, offered before the relapse has progressed to the point of meeting full episode and severity criteria, would improve long-term outcomes. Since there are currently no established predictor variables that forecast which patients will relapse following an initial rTMS course [2], watchful waiting and Retx remains the best available strategy until a more personalized medicine approach is available for determining whether and how many maintenance rTMS sessions at an individualized schedule can be delivered to achieve the most enduring state of symptom resolution.

Acknowledgements

This work was supported by NIMH R25 MH101076 (Dr. AM Fukuda) and by internal funds at Butler Hospital.

References

[1]. Carpenter LL, Janicak PG, Aaronson ST, Boyadjis T, Brock DG, Cook IA, et al. Transcranial magnetic stimulation (TMS) for major depression: a multisite, naturalistic, observational study of acute treatment outcomes in clinical practice. Depress Anxiety 2012;29(7):587–96. [PubMed: 22689344]

[2]. Dunner DL, Aaronson ST, Sackeim HA, Janicak PG, Carpenter LL, Boyadjis T, et al. A multisite, naturalistic, observational study of transcranial magnetic stimulation for patients with pharmacoresistant major depressive disorder: durability of benefit over a 1-year follow-up period. J Clin Psychiatry 2014;75(12): 1394–401. [PubMed: 25271871]

[3]. Rachid F Maintenance repetitive transcranial magnetic stimulation (rTMS) for relapse prevention in with depression: a review. Psychiatr Res 2018;262:363–72.

[4]. Fitzgerald PB, Benitez J, de Castella AR, Brown TL, Daskalakis ZJ, Kulkarni J. Naturalistic study of the use of transcranial magnetic stimulation in the treatment of depressive relapse. Aust N Z J Psychiatr 2006;40(9):764–8.

[5]. Kelly MS, Oliveira-Maia AJ, Bernstein M, Stern AP, Press DZ, Pascual-Leone A, et al. Initial response to transcranial magnetic stimulation treatment for depression predicts subsequent response. J Neuropsychiatry Clin Neurosci 2017;29(2):179–82. [PubMed: 27899052]

[6]. Philip NS, Dunner DL, Dowd SM, Aaronson ST, Brock DG, Carpenter LL, et al. Can medication free, treatment-resistant, depressed patients who initially respond to TMS Be maintained off medications? A prospective, 12-month multisite randomized pilot study. Brain Stimul 2016;9(2):251–7. [PubMed: 26708778]

[7]. Philip NS, Ridout SJ, Albright SE, Sanchez G, Carpenter LL. 5-Hz transcranial magnetic stimulation for comorbid posttraumatic stress disorder and major depression. J Trauma Stress 2016;29(1):93–6. [PubMed: 26748883]

Table 1.

Out of the 317 patients reviewed, 42 met criteria for Retx analysis. The left side of the table shows the demographic data for the patients for the Retx #1 series unless otherwise specified, where appropriate data is presented as mean ± standard deviation and the minimum value to maximum value in parenthesis. Of note, no significant difference was present between Index and Retx for the total # treatments (p = 0.201). The right side of the table shows the response/remission rate for each series, including those who came back for more than 1 retreatment. Due to the limited sample sizes, no further analyses for Retx #2–5 were performed.

Retx Demographic			N	Response(%)	Remission (%)
Age at Retx presentation	53.45 ± 12.27 (Range: 26 to 75)	Acute	42	93	59.5
Weeks elapsed between acute and Retx	51.2 ± 46.2 (Range: 10 to 248)	Retx #1	42	78.6	57.1
Total # Tx Index Series	35.36 ± 5.4 (Range: 21 to 52)	Retx #2	9	77.8	55.6
Total # Tx Retx Series	34.07 ± 7.1 (Range: 15 to 59)				
Sex (Female)	85.7% (n = 36)	Retx #3	6	66.7	50
Prior Hospitalization for MDD	73.8% (n = 31)	Retx #4	4	100	50
Prior ECT	38.1% (n = 16)	Retx #5	1	100	100