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Impact of prior treatment on remission with intermittent theta burst versus high-frequency repetitive transcranial magnetic stimulation in treatment resistant depression

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ABSTRACT

Background: Multiple prior treatment failures are associated with reduced rates of remission to subsequent antidepressant treatment, including rTMS. The degree of treatment resistance that is especially predictive of inferior outcome is uncertain. Intermittent theta burst stimulation (iTBS) is a newer form of rTMS where less is known regarding clinical predictors of remission. The THREE-D study demonstrated that iTBS is non-inferior to 10 Hz rTMS for the treatment of depression.
Objective: Determine if the number and type of prior pharmacotherapy trials affect the rate of remission with two types of rTMS.
Method: Compare remission rates based on prior pharmacotherapy using data from the THREE-D trial (NCT01887782).
Results: No differences in remission rates were noted between the three levels of treatment resistance, however, participants with 3 compared to <3 treatment failures had lower rates of remission: 17.3% versus 29.4% (χ^2 4.87; df = 1; p = 0.03).
Conclusions: Three or more treatment failures may be associated with lower remission rates with rTMS.

Introduction

Repetitive transcranial magnetic stimulation (rTMS) is approved by multiple health regulatory bodies for the treatment of major depressive episodes in patients not responding to treatment [1]. A higher degree of treatment resistance is a clinical factor consistently associated with worse treatment outcomes in pharmacotherapy [2], electroconvulsive therapy (ECT) [3] and rTMS [4–6]. A newer form of rTMS called intermittent theta burst stimulation (iTBS) has recently emerged as a similarly effective treatment.

The THREE-D study demonstrated that iTBS is a non-inferior treatment compared to 10 Hz rTMS in patients with treatment resistant depression (TRD) [7]. Using data from this trial, we examined the rate of remission with two types of rTMS (iTBS and 10Hz rTMS) delivered to the left dorsolateral prefrontal cortex (DLPFC) based on the number and type of prior pharmacotherapy trials in the current episode. We hypothesized that a greater number of treatment failures would be associated with lower remission rates across both treatments.

Methods

The methods of the THREE-D trial are described elsewhere [7]. In brief, the trial was a randomized non-inferiority clinical trial without a sham control, in depressed adults with TRD. Participants were also included if they were intolerant of two separate

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antidepressant trials in the current episode. A medication trial was classified as intolerant by the following criteria: 1) less than 4 weeks duration or 2) the highest dose achieved was less than the therapeutic dose for greater than 4 weeks. The maximum number of previous adequate trials allowed was three. Participants were randomly allocated to 10 Hz rTMS or iTBS of the left DLPFC. Randomization was stratified by study site and failure of more than one adequate antidepressant trial as this clinical factor has been previously associated with poor response to rTMS [1]. Approval was obtained from the institutional review boards and registered with ClinicalTrials.gov (NCT01887782).

The primary outcome in the trial was reduction in Hamilton Rating Scale for Depression (HRSD-17) score from baseline to end of treatment. Remission was defined as HRSD-17 < 8. Participants received 10 Hz rTMS (120% resting motor threshold; 10 Hz frequency; 4 s on and 26 s off; 3000 pulses per session; total duration of 37.5 min) or iTBS (triplet 50 Hz bursts, repeated at 5 Hz; 2s on and 8 s off; 600 pulses per session; total duration of 3 min 9 s). Participants continued on current medication, but no dose increases were allowed for a minimum of 4 weeks prior to treatment and the duration of treatment.

The Antidepressant Treatment History Form (ATHF) [8] was used to measure the number and type of prior pharmacotherapy. An adequate dose was determined based on the recommended therapeutic dose for each medication and a minimum of 4 weeks at this dose. We used Pearson's chi square tests to compare remission rates between participants categorized by different degrees of treatment resistance at the primary endpoint following the treatment protocol. We also investigated the impact of the type of antidepressant trials in the episode on remission rates using Fisher's exact test, comparing those who had taken a particular class, with those who had not (i.e. serotonin-norepinepnhrine reuptake inhibitors).

An intention to treat analysis was performed with participants lost to follow up assumed to not have achieved remission. An analysis with only subjects who were able to complete the treatment schedule until the primary endpoint of 4 weeks was also conducted. All statistical analyses were conducted using statistical software (SPSS 24.0; IBM Inc.).

Results

414 participants were included in the current analysis with 385 achieving the primary completion timepoint (see Table 1). Among all participants, 217/414 (52.4%) had one or no adequate antidepressant trial, 116/414 (28.0%) had two and 81/414 (19.6%) had three. Among these groups, there was no statistically significant difference between the respective remission rates of 29.0%, 30.2% and 17.3% (χ^2 4.92; df = 2; p = 0.09). However, an analysis comparing remission rates in those with three prior treatment failures compared to those with 2 or fewer previous adequate treatment trials showed a statistically significant difference of 17.3% versus 29.4% (χ^2 4.87; df = 1; p = 0.03). There were no significant differences in remission rates for the different levels of treatment resistance within the 10 Hz rTMS (χ^2 3.51; df = 2; p = 0.17) and iTBS subgroups (χ^2 1.79; df = 2; p = 0.41), although the lower observed remission rates with three failed trials persisted and was similar in both treatment arms. The results were similar in the completer analysis.

The most common prior pharmacotherapy was selective serotonin reuptake inhibitors 143/414 (34.5%) and serotonin norepinephrine reuptake inhibitors 124/414 (30.0%). There were no statistically significant differences in remission rates based on the antidepressant classes used in the current episode.

Discussion

The present study did not find a significant difference in the remission rates with rTMS to left DLPFC among patients that had not responded to one (or fewer), two or three medication trials. However, when those who had failed three adequate treatment trials were compared to the those with two or fewer trials a lower remission was found. There were no significant differences in the observed remission rates with the 10 Hz rTMS or iTBS based on prior treatment failures. We did not find any significant differences in remission rates based on type of prior pharmacotherapy.

Our analysis supports previous findings that a higher level of treatment resistance may confer a less favorable outcome with rTMS [4,6]. Despite the lack of a sham control, the present analysis suggests that two or fewer failed antidepressant trials may be associated with better outcomes whereas earlier sham-controlled data suggested that better outcomes were associated with one or fewer failed trials [6]. The finding that three failed trials may confer a less favorable outcome compared to lower levels of treatment resistance with rTMS requires replication in larger samples that have well-characterized prior treatment histories. Importantly, the lack of difference in remission rates based on number of prior treatment failures further reinforces that the clinical performance of iTBS is very similar to 10 Hz rTMS.

Table 1
Demographic, clinical factors and remission rates by number of previous adequate treatment trials.

Number of previous adequate treatment trials	<=1 (n = 217)[a]	2 (n = 116)	3 (n = 81)	Statistical test
Age, mean (SD)	43.3 (11.4)	41.5 (11.7)	41.3 (11.3)	F = 1.29 (df = 2, p = 0.28)
Female, n (%)	129 (59.4)	64 (55.2)	53 (65.4)	χ2 = 2.08 (df = 2, p = 0.35)
Years of education, mean (SD)	16.3 (3.3)	16.3 (2.8)	16.3 (3.1)	F = 0.01 (df = 2, p = 0.99)
Previous ECT, n (%)	13 (6.0)	3 (2.6)	4 (4.9)	χ2 = 1.91 (df = 2, p = 0.39)
Current psychotherapy, n (%)	84 (38.7)	45 (38.8)	38 (46.9)	χ2 = 1.81 (df = 2, p = 0.41)
Age of onset, mean (SD)	21.0 (11.8)	20.6 (10.5)	21.1 (11.3)	F = 0.47 (df = 2, p = 0.63)
Episode duration in months, mean (SD)	20.7 (25.6)	26.6 (32.1)	25.7 (23.1)	F = 2.20 (df = 2, p = 0.11)
Concurrent antidepressant, n (%)	164 (75.6)	88 (75.9)	66 (81.4)	
Concurrent antidepressant combination, n (%)	29 (13.4)	36 (31.0)	26 (32.1)	
Concurrent augmentation, n (%)	27 (12.4)	25 (21.6)	81 (30.9)	
Concurrent lithium, n (%)	3 (1.4)	5 (4.3)	5 (6.2)	
Remitters - total sample, n (%)[b]	63 (29.0)	35 (30.2)	14 (17.3)	χ2 = 4.92 (df = 2, p = 0.09)
Remitters - 10 Hz rTMS, n (%)	29 (26.9)	17 (28.8)	5 (13.2)	χ2 = 3.51 (df = 2, p = 0.17)
Remitters - iTBS, n (%)	34 (31.2)	18 (31.6)	9 (20.9)	χ2 = 1.79 (df = 2, p = 0.41)

[a] 32/217 (14.7%) of group with no previous adequate trials (but at least two antidepressant trials which they could not tolerate).
[b] In an analysis comparing remission rates for 3 versus <3 previous treatment trials, there was a statistically significant difference: 14/81 (17.3%) versus 98/333 (29.4%) (χ^2 4.87; df = 1; p = 0.03) among all participants and 14/76 (18.4%) versus 98/309 (31.7%) (χ^2 5.23; df = 1; p = 0.02) among completers only.rTMS: repetitive transcranial magnetic stimulation, iTBS: intermittent theta burst stimulation, χ^2: chi-squared test, df: degrees of freedom.

The clinical implications of these findings reinforce the need to evaluate prior treatment history in distinguishing patients who are being considered for rTMS. The failure of multiple treatment trials may represent a more complex underlying biological phenotype in TRD [9]. The study highlights the need to identify biomarkers to identify these patients prospectively and supports the practice of considering rTMS as a treatment option earlier in the treatment algorithm.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.07.011.

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