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Can Early Treatment Response Serve as a Predictor of Antidepressant Outcome of Repetitive Transcranial Magnetic Stimulation?

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Dear Editor,

Clinically relevant markers to predict therapeutic response to Transcranial Magnetic Stimulation (TMS) for Major Depressive Disorder would curtail potentially futile burden on available resources and aid in redirecting or modifying treatment course. To this end, biomarkers such as magnetic resonance imaging and electroencephalography have been studied with some promising results but currently not at a clinically translatable state [1].

A retrospective study reported that a lack of clinical response after 10 sessions of TMS treatment had a negative predictive value (NPV) of around 88%, meaning overall non-response (following the 20 session TMS treatment course used) could be predicted with 88% accuracy [2]. However, this result may not account for the possibility of late-response to TMS (i.e significant symptom improvement after 20 treatment sessions), and may overestimate predictability of non-response to TMS based on early response. Using patient data from Butler Hospital's TMS Clinic, NPVs calculated based on 20 treatment sessions were compared with those calculated using the full 36 treatment course. This allowed for an exploration of the trend of predictability of non-response in patients whose course of TMS extends beyond 4 weeks.

Data from 248 patients treated at Butler Hospital's TMS clinic from 2009–2019 were reviewed in a de-identified dataset. Treatment was initiated at 10 Hz delivered to left dorsolateral prefrontal cortex (DLPFC) daily at 120% maximum intensity relative to their motor threshold for a minimum of 3000 pulses/session. Deviations from the standard protocol occurred in situations with poor tolerability and resulted in a change to 5 Hz stimulation [3].

Change in depression severity was measured by Inventory of Depressive Symptomatology Self Report (IDS-SR) and Patient Health Questionnaire-9 (PHQ-9) scores based on %

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reduction from pretreatment baseline to after weeks 2, 4, and final treatment [4,5]. Scores at week 4 (following 20 sessions) and scores after the final treatment in the series (typically after session 36) were used to determine outcomes based on % change relative to baseline.

Non-response was defined as <50% decrease in scores relative to baseline, as well as by a data driven change threshold based on kernel density estimates of overall % change in both IDS-SR and PHQ-9 scores for the entire sample. Cases were included in this analysis only if they had completed self-rated depression assessment scales at baseline and following weeks 1 and 2, corresponding with a minimum of 10 treatment sessions; last-observation carried forward scores were used for defining outcomes in cases where TMS was stopped prematurely. Using MATLAB R2017a, prediction models of TMS non-response (based on either 10% or 20% threshold improvement at week 2) were tested and quantified in confusion matrices.

The patient population included in this analysis consisted of adults (70% female, mean age 54.5 ± 15.2) with treatment resistant depression. Of the 248 patients, 64% had been previously hospitalized for depression, and 28% had received prior electroconvulsive therapy (ECT). Patients received an average total of 35.5 ± 5.6 TMS sessions in the initial course of treatment.

Application of kernel density estimates for IDS-SR and PHQ-9 data from our sample revealed threshold % change scores for categorical response as 34% (IDS-SR) and 47% (PHQ-9). Less than 20% IDS-SR improvement at week 2 was associated with an NPV of 72.3% when using final outcomes, and 93.1% when using week 4 outcomes. Similarly, using a more stringent <10% improvement at week 2, NPVs were 76.8% and 95.1% when using final and week 4 outcomes, respectively (Table 1). Less than 20% improvement at week 2 in PHQ-9 scores yielded an NPV of 58.9% for final outcomes, and 85.5% for week 4 outcomes; with <10% improvement at week 2, NPVs were 62.7% and 90.4% for final and week 4 outcomes, respectively (Table 1). Symptom worsening in the first two weeks (<0% improvement) showed a similar trend, with reduced NPVs when using final scores rather than scores at week 4 for all parameters tested.

The ability to reliably predict treatment outcomes with early indicators could be a valuable tool for avoiding non-efficacious courses of treatment [6]. This has been shown in a recent study where lack of at least a 20% improvement with pharmacotherapy at end of week 2 had a 93% NPV of achieving remission by end of week 12 [7]. We replicated methods from a study that found lack of response to 20 TMS treatments could be predicted with 88.2% accuracy if the patient did not achieve ≥20% improvement after 10 treatments [2]. In our naturalistically treated TMS clinic population, the NPV was 93.1% using that same predictor model, however, the NPV sharply dropped by 20.8% when the course of treatment was extended beyond week 4; we could only correctly forecast a bad TMS outcome (non-response) 72.3% of the time when outcomes reflected longer courses of TMS therapy.

These findings provide evidence for the possibility of late-responders to TMS: those who do not meet response threshold after 20 treatments eventually may convert to a responder when the treatment course is extended beyond 20 treatments, as is done in many clinical settings.

Patients often seek TMS in cases of subsequent depressive relapse, and data suggest that those who achieved categorical responder status during their initial course of TMS are likely to benefit with TMS retreatment [8]. Therefore, missing a responder during the acute course could have long term consequences. Our findings suggest that depressed patients who do not experience symptom benefit during the first few weeks should still be encouraged to continue a longer course of TMS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declaration of competing interest

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Table 1.

Negative Predictability Values (NPVs)[a] for Response to TMS (defined by 50% improvement standard or by Response criteria determined by Kernel Density Estimate)

		Wk 2 < 0% Improved		Wk 2 < 10% Improved		Wk 2 < 20% Improved	
		T_{20} NPV	**T_F NPV**	**T_{20} NPV**	**T_F NPV**	**T_{20} NPV**	**T_F NPV**
IDS-SR	50%*	97.0	84.8	95.1	76.8	93.1	72.3
	34%**	97.0	69.7	91.5	61.0	80.8	54.6
PHQ-9	50%*	90.4	65.9	90.4	62.7	85.5	58.9
	47%**	90.2	65.9	90.4	61.4	84.7	58.1

[a]NPVs based on % improvement at Week 2, corresponding with completion of 10 TMS sessions. All NPVs reported in %. For all parameters tested, NPVs were lower when overall outcome was determined using final scores vs. those collected at week 4 (treatment 20). T_{20} = Treatment session #20; T_F = Final treatment session;

*standard 50 % improvement criterion applied to define response;

**data- driven % improvement criterion for defining response based on Kernel Density Estimate (see supplemental data figures 1 and 2)