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PULSE

A Monthly Update on Advances in Neuromodulation

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Early Nonresponse Fails to Predict Final Nonresponse with rTMS for Depression

Erin M Hegarty reviewing Sackeim et al. Brain Stimul. 2024 Mar-Apr

This large naturalistic study of patients treated with rTMS for MDD found that early symptom improvement, particularly by session 10, modestly predicted final response. However, lack of early improvement was a poor predictor of nonresponse, challenging prior assertions that nonresponse at session 10 reliably predicts ultimate nonresponse.

Predicting nonresponse early in a course of treatment for depression can reduce the financial, emotional, and clinical burden caused by ineffective treatments. Such prognostication would be especially valuable for rTMS, which typically requires daily treatment for six or more weeks. Prior studies have suggested that early symptom change at 10 sessions strongly predicts response to a full course of treatment, though many involved shorter rTMS courses (20–25 sessions). This study aimed to evaluate whether early symptom improvement could

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reliably predict nonresponse at the end of a full standard course of rTMS (36 sessions).

This study analyzed data from the NeuroStar Advanced Therapy Outcomes Registry, including 7215 adults with a primary diagnosis of MDD and pre-test PHQ-9 score ≥10.Patients without an MDD primary diagnosis or with comorbidities aside from anxiety were excluded. Patients were categorized into three groups based on the number of acute rTMS sessions received: exactly 36 (n=3591), <36 (n=2649), and >36 (n=975). PHQ-9 scores, collected at baseline and after 10, 20, 30, and the final sessions, were used to assess depression severity. Outcomes included final PHQ-9 score, absolute and percent change from baseline, response (≥50% reduction in PHQ-9), and remission (PHQ-9 < 5). To evaluate the predictive value of early symptom change, the authors calculated ROC curves and AUC values at each interim assessment. For each timepoint and treatment group, the thresholds used to define early symptom improvement were identified using two approaches: the Youden Index, which selects the cutoff that maximizes sensitivity and specificity, and a fixed false-positive rate of 10%, which constrains the proportion of patients incorrectly identified as nonresponders. These thresholds were applied to interim PHQ-9 changes to estimate the likelihood of final treatment response or nonresponse, allowing for calculation of positive (PPV) and negative (NPV) predictive values.

Patients who completed exactly 36-sessions had significantly better outcomes across all measures, including endpoint PHQ-9, raw and percentage change, and response and remission rates. Using thresholds derived from the Youden Index, early symptom improvement in both the 36-session and >36-session groups was a more reliable predictor of final response than nonresponse at all timepoints. The PPV of early symptom improvement increased with additional sessions but generally remained below 80% in both groups. Moreover, false positive rates (FPR) were high, particularly at earlier timepoints (e.g., 0.4 at session 10 in the >36-session group). This limited the clinical utility of the Youden Index-derived thresholds as a guide for stopping treatment early. Even in the <36-session group, which unsurprisingly had higher rates of final nonresponse and shorter intervals between assessments and final measurements, the PPV for nonresponse was still less than 80% at 30 sessions. Although FPR declined across successive measurement points in all groups, it too remained too high to be clinically useful. When using the other method for determining the threshold for symptom improvement, which fixed the FPR at 10%, the PPV was not significantly higher than the Youden Index method for the 36-session and >36-session groups. In the <36-session group, the PPV reached 85% at session 20 using this method, which the authors noted may be of some clinical utility for early treatment decisions.

Impact: This large retrospective registry study demonstrates that nonresponse after 10 sessions of rTMS is a poor predictor of final treatment nonresponse. While early symptom improvement did predict final response, lack of early improvement consistently failed to identify nonresponders with sufficient accuracy to guide clinical decisions. High false-positive rates limited clinical utility, though one threshold in the <36-session group showed potentially useful predictive value at session 20; still, these findings do not support early treatment termination based on early nonresponse. Several limitations warrant cautious interpretation, including no external validation, reliance on the PHQ-9, and heterogeneity in real-world clinical settings. These results reinforce the importance of completing a full 36-session course—associated with the best clinical outcomes—and caution against using early symptom stagnation alone to alter treatment plans.

Sackeim HA, Aaronson ST, Carpenter LL, et al. When to hold and when to fold: Early prediction of nonresponse to transcranial magnetic stimulation in major depressive disorder. Brain Stimul. 2024;17(2):272-282. doi: 10.1016/j.brs.2024.02.019

ECT More Effective than rTMS for Depression in Patients Receiving Both

Mandeep Singh, MD, MBA reviewing Strandberg et al. J ECT 2024 June

In this register-based observational crossover study, patients with depression treated with both ECT and rTMS experienced significantly greater reductions in depressive symptoms following ECT. ECT was also associated with higher response and remission rates, with superiority consistent across age and baseline severity subgroups.

ECT and rTMS are both effective treatment modalities for difficult-to-treat depression. Although studies show ECT is more effective than rTMS in certain subtypes of MDD (particularly psychotic and

melancholic), the data are less clear regarding nonpsychotic MDD. This study leverages a crossover design in which all participants received both ECT and rTMS, enabling a direct within-subject comparison to better understand their relative antidepressant effects.

This register-based retrospective observational crossover study enrolled 138 Swedish adults who received both ECT and rTMS for depression and completed MADRS-Self Report (MADRS-S) scales before and after each type of treatment between 2012 and 2021. ECT was usually administered three times per week. Of these, 111 (80.4%) received ECT first, while 27 (19.6%) received rTMS first. During the first ECT treatment, 134 (97.1%) received unilateral electrode placement, while 4 (2.9%) had bitemporal placement. ECT involved a mean of 7.9 sessions (SD: 3.2) with typical parameters: 0.5±0.1 ms pulse width, 833±63 mA current, 247±113 mC charge, and 6±1.2 second duration. rTMS was administered five times per week, with a mean number of treatments of 22.0 (SD: 7.2). iTBS was the most common stimulation protocol (123 cases; 89.1%), and left DLPFC was the most common stimulation target (127 subjects; 92%). The majority of cases received a stimulation intensity of 120% of MT (108 cases; 78.3%), followed by <110% (8; 5.8%) and 110%-119% (2 cases; 1.4%). Reduction in MADRS-S score after treatment was the primary outcome measure. Secondary outcome measures included remission (MADRS-S score <10 after treatment), response (≥50% decrease in MADRS-S from baseline to posttreatment), and clinically meaningful change (CMC; MADRS-S score reduction >6 from baseline).

Among the 138 included patients, the mean age during ECT and rTMS was 41 and 43 years, and 110 (79.9%) patients were diagnosed with unipolar depression while 28 (20.1%) had bipolar depression. ECT produced a significantly greater reduction in MADRS-S scores than rTMS (mean reduction: 15.0 vs. 5.6; $p < 0.0001$). Response and remission rates were also significantly higher with ECT (38% and 28%, respectively) compared to rTMS (15% and 8%; all $p < 0.0001$), as was CMC (80.4% vs. 44.2%; $p < 0.001$). These results were consistent across subgroups: in patients under 40 and those 40 or older, ECT resulted in significantly greater symptom reduction ($p < 0.0001$). Similarly, patients with higher baseline severity (MADRS-S ≥35) had greater mean score improvements with ECT (19.1 vs. 7.5), as did those with less severe symptoms (10.8 vs. 3.6; both $p < 0.0001$). ECT also outperformed rTMS regardless of whether it was given before or after rTMS (ECT first: 14.7 vs. 5.3; rTMS first: 15.3 vs. 5.9; both $p < 0.0001$). No clinical subgroups favored rTMS over ECT, and multivariable analyses revealed no patient characteristics that predicted greater benefit from rTMS. There were also no reported differences in stimulation parameters by treatment sequence for either modality.

Impact: This registry-based study reinforces the superior antidepressant efficacy of ECT compared to rTMS in a real-world population. Response rates—38% after ECT and 15% after rTMS—were lower than typically reported, likely reflecting a more treatment-refractory population. The fact that 80% of patients received ECT first suggests clinicians viewed these cases as more severe, potentially influencing the results shown here. Notably, even among younger and less severely depressed individuals—groups often more responsive to rTMS—ECT remained superior. However, interpretation is further limited by the relatively low mean number of rTMS sessions, which may have reduced the maximal antidepressant benefit observed for rTMS. Future research should focus on identifying subgroups of patients who would be more responsive to rTMS than ECT.

Strandberg P, Nordenskjöld A, Bodén R, Ekman CJ, Lundberg J, Popiolek K. Electroconvulsive Therapy Versus Repetitive Transcranial Magnetic Stimulation in Patients With a Depressive Episode: A Register-Based Study. J ECT. 2024;40(2):88-95. doi:10.1097/YCT.0000000000000971

Pragmatic 5-Day Accelerated iTBS Yields Rapid and Durable Antidepressant Effects Without MRI-Based Targeting

Meghan Y. Reddy, MD reviewing Luehr et al. Brain Stimul. 2024 Jul

This pilot study evaluated a pragmatic 5-day iTBS protocol for TRD as an accelerated and accessible alternative to both conventional rTMS and the technically complex SAINT protocol. The study demonstrated rapid and sustained improvements in depressive symptoms without serious adverse effects.

A standard rTMS protocol for depression involves 36 once-daily treatment sessions over 8–10 weeks. In contrast, the Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT) protocol has shown rapid antidepressant effects in just 5 days by consolidating 10 treatment sessions per day of iTBS and using fMRI-guided personalized targeting with stereotactic neuronavigation. Though early results have been impressive, these technical demands limit SAINT's real-world feasibility. This study evaluated a modified, pragmatic alternative to assess whether a simplified

protocol could deliver comparable results.

This prospective, open-label study enrolled 21 outpatients with TRD at a Minnesota mental health clinic. Inclusion criteria included a DSM-5 primary diagnosis of MDD, documented failure of at least one adequate antidepressant trial during the current episode, and a MADRS ≥20 at both screening and baseline. Exclusion criteria included bipolar disorder, psychotic symptoms, autism, OCD, an active SUD, or recent rTMS treatment. Participants underwent 36 iTBS sessions over 5 days (600 pulses per session, 8 sessions/day). Coil placement was determined using the Beam F3 method, and treatments were delivered using the NeuroStar System (v3.6). Stimulation intensity progressively increased from 90% to 120% RMT, or the maximum tolerated level. Depression and anxiety symptoms were assessed using the MADRS, QIDS-Self Report (SR), PHQ-9, and GAD-7 at baseline, end of treatment, and 4-weeks follow-up. Interim assessments (all except MADRS) were also completed daily. The primary outcome was change in MADRS at 4 weeks, while secondary outcomes included change in other scales, response (≥50% reduction from baseline), and remission (MADRS ≤9, QIDS-SR ≤5, and PHQ-9/GAD-7 ≤4). Statistical analyses included repeated-measures ANOVAs with Huynh-Feldt correction and Bonferroni corrected t-tests. One participant was excluded from efficacy analyses because they could not tolerate a stimulation intensity of at least 90% RMT. In the remaining 20 participants, MADRS scores showed a statistically significant reduction across all three time points ($p < 0.0001$), with a large effect size ($d = 2.2$) from baseline to 4-week follow-up. Mean MADRS scores decreased from 32.5 ± 6.1 at baseline to 17.2 ± 9.9 at 4 weeks. MADRS response and remission ates at 4-week follow-up were 70% and 55%, respectively. QIDS-SR, PHQ-9, and GAD-7 mirrored MADRS findings, showing consistent antidepressant and anxiolytic effects. The protocol was well-tolerated, with no serious adverse events and minor adverse events limited to physical discomfort during stimulation (15%), headache (25%), and fatigue (10%).

Impact: This prospective, open-label trial found that a pragmatic 5-day iTBS protocol—using standard pulse count, session number, and targeting—was feasible, safe, and effective for TRD. These results suggest that key elements of the SAINT protocol, such as fMRI-guided targeting, may not be essential for achieving robust clinical outcomes. However, limitations including the small sample size and open-label design underscore the need for randomized controlled trials to confirm efficacy and explore the durability of such accelerated TMS protocols.

Luehr JG, Fritz E, Turner M, Schupp C, Sackeim HA. Accelerated transcranial magnetic stimulation: A pilot study of safety and efficacy using a pragmatic protocol. Brain Stimul. 2024;17(4):860-863. doi:10.1016/j.brs.2024.07.009

Sustained Remission Using Accelerated TBS for TRD in Autism

Mohamad Shamas, PhD reviewing Blank et al. J Autism Dev Disord. 2024 May

This small open-label trial evaluated accelerated TBS for TRD in adolescents and young adults with autism spectrum disorder (ASD). The results showed sustained remission in 50% of participants and partial remission in 30%, with minimal side effects, supporting the need for larger controlled studies.

Autistic individuals are disproportionately affected by MDD, which contributes to significant functional impairments and heightened suicide risk, especially among those without intellectual disability. Traditional treatments for MDD often prove ineffective or poorly tolerated in this population. While rTMS is well-established for MDD, its conventional protocols may be poorly tolerated by autistic individuals due to sensory sensitivities and treatment burden. Accelerated TBS, a condensed and potentially better-tolerated rTMS protocol, may address these limitations. This study evaluated the clinical effectiveness, tolerability, and cognitive effects of unilateral vs. bilateral prefrontal accelerated TBS in adolescents and young adults with ASD and TRD.
This open-label prospective clinical trial enrolled participants aged 12–26 who were diagnosed with ASD and TRD. Key exclusion criteria included significant unrelated psychiatric or neurological conditions (including active suicidality and epilepsy), IQ below 80, recent substance use, or prior rTMS treatment. Participants were randomly assigned to receive either unilateral iTBS to the left DLPFC or bilateral stimulation combining iTBS to the left DLPFC and cTBS to the right DLPFC. Each TBS session consisted of

600 pulses delivered using a Magstim Horizon Performance device with intensity titrated to 90% RMT over the first two days. Treatments were administered three times daily, with 50-minute breaks, over ten days, with follow-up assessments 1, 4, and 12 weeks post-treatment. The primary outcome was change in HDRS-17 scores, while secondary outcomes included BDI-II, QIDS, Columbia-Suicide Severity Rating Scale (C-SSRS), GAD-7, Pittsburgh Sleep Quality Inventory (PSQI), and Social Responsiveness Scale (SRS). Cognitive and neuromuscular function were assessed using the NIH Cognitive Toolbox and Grip Strength Test. A linear mixed model was used to identify any main effects of time or treatment arm, as well as their potential interaction effect on each outcome measure.

Ten participants were randomized equally to either unilateral or bilateral accelerated TBS, with comparable baseline characteristics across groups. One subject randomized to the bilateral group subsequently received a borderline personality disorder diagnosis and was included in primary analyses but excluded from exploratory correlations. There were no significant differences between treatment groups on any outcome, and no group-by-time interaction effects were observed; thus, all findings reflect the combined sample across both treatment arms. TBS resulted in significant reductions in depression severity over time on the HDRS-17 ($p < 0.001$), with post-hoc tests showing reductions from baseline at all follow-up timepoints (all p's < 0.05). By Week 12, five participants reached full remission (HDRS-17 ≤ 7; 50%) and three achieved partial remission (30%; HDRS-17 < 14). Significant improvements were also seen on secondary outcomes, with the BDI-II and QIDS showing consistent reductions from baseline at Weeks 1, 4, and 12 ($p < 0.01$). The GAD-7 showed a significant main effect of time ($p = 0.028$) and a significant reduction from baseline at Week 12 post-treatment ($p = 0.039$), but no significant differences at Week 1 or 4. PSQI scores showed improved sleep quality with a main treatment effect ($p = 0.018$) and improvement in sleep ratings at Week 4 ($p = 0.023$). For fluid cognition, a significant improvement was observed at Week 4 ($p = 0.031$) and Week 12 ($p < 0.001$). Grip strength did not show significant effects over time, but the main effect of group trended toward significance ($p = 0.05$). No serious adverse events occurred; mild, transient headaches were reported in four participants.

Impact: This exploratory study supports the safety and efficacy of accelerated TBS for TRD in youth with ASD, a population with few effective and well-tolerated options. With five of the ten subjects achieving remission and cognitive improvement at 12 weeks post-treatment, along with minimal side effects, accelerated TBS is a promising treatment option. However, interpretation is limited by the small sample size, open-label design, absence of a sham control, and the higher pulse dose delivered in the bilateral group. Future research is needed with larger, sham-controlled studies for validation.

Blank E, Gilbert DL, Wu SW, et al. Accelerated theta burst transcranial magnetic stimulation for refractory depression in autism spectrum disorder. J Autism Dev Disord. 2025;55(4):940-954. doi:10.1007/s10803-024-06244-2.

cTBS (continuous theta burst stimulation)
DBS (deep brain stimulation)
dTMS (deep transcranial magnetic stimulation)
ECT (electroconvulsive therapy)
HFL (high frequency left, 10 Hz stimulation to left DLPFC)
HF-rTMS (high frequency repetitive transcranial magnetic stimulation; 10 Hz unless otherwise stated)
iTBS (intermittent theta burst stimulation)
MST (magnetic seizure therapy)
TBS (theta-burst stimulation; TMS delivered as triplet burst pulses at 50 Hz, repeated at 5 Hz)
TENS (transcutaneous electrical nerve stimulation)
TMS (transcranial magnetic stimulation)
rTMS (repetitive transcranial magnetic stimulation)
tDCS (transcranial direct current stimulation)
tACS (transcranial alternating current stimulation)
TPS (transcranial pulse stimulation)

BOLD (blood oxygen level dependent)
DTI (diffusion tensor imaging)
EEG (electroencephalography)
EMG (electromyography)
fMRI (functional magnetic resonance imaging)
MRI (magnetic resonance imaging)
MT (motor threshold)
RMT (resting MT)

ADHD (attention-deficit/hyperactivity disorder)
AUD (alcohol use disorder)
GAD (generalized anxiety disorder)
MDD (major depressive disorder)
OCD (obsessive compulsive disorder)
PTSD (post-traumatic stress disorder)
SUD (substance use disorder)
TRD (treatment resistant depression)

BAI (Beck Anxiety Inventory)
BDI (Beck Depression Inventory)
CGI (clinical global impression scale)
HAM-A (Hamilton Anxiety Rating Scale)
HAM-D / HDRS (Hamilton Depression Rating Scale)
MADRS (Montgomery-Asberg Depression Rating Scale)
MoCA (Montreal Cognitive Assessment)
PANSS (Positive and Negative Symptom Scale)
QIDS (Quick Inventory of Depressive Symptomatology)
YBOCS (Yale-Brown Obsessive Compulsive Scale)

ANOVA (analysis of variance)
AUC (area under the curve)
CI (confidence interval)
FDA (United States Food and Drug Administration)
ICA (independent component analysis)
ITT (intention to treat)
OR (odds ratio)
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)
RCT (randomized controlled trial)
ROC (receiver operating characteristic)
SMD (standard mean difference)

BA (Brodmann area)
DLPFC (dorsolateral prefrontal cortex)
DMPFC (dorsomedial prefrontal cortex)
M1 (primary motor cortex)
mPFC (medial prefrontal cortex)
OFC (orbitofrontal cortex)
SMA (supplementary motor area)