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PULSE

A Monthly Update on Advances in Neuromodulation

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Combining TMS and Antidepressant Therapies in Major Depressive Disorder

David Lee, MD reviewing Rakesh et al. Journal of Affective Disorders May 2024

This meta-analysis of 10 randomized controlled trials (RCTs) suggests that combined antidepressant and TMS therapy may be more effective in the management of patients with major depressive disorder, compared to similarly dosed antidepressant and sham TMS therapy. Despite data limitations, this study sheds light on the clinical consideration of whether it is more efficacious to pause or continue antidepressant treatment during the course of rTMS treatment.

Antidepressants are typically considered first line treatment among biological interventions for MDD. However, rTMS is an increasingly utilized alternative for patients who exhibit resistance or intolerance to one or more antidepressant treatments. The use of antidepressants

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throughout the course or rTMS remains largely under-investigated. The therapeutic effects of rTMS, when combined with antidepressants, are thought to involve cortical excitability and neuronal plasticity through distinct yet complementary pathways. Despite growing clinical use, little data exist regarding optimal protocols for combining rTMS and antidepressants, and current practices tend to rely on case-by-case assessments. This meta-analysis sought to clarify the efficacy of rTMS + antidepressant combination therapy in patients with MDD.

The authors screened over 750 studies from 2010 to 2023, identifying ten RCTs for inclusion in the meta-analysis. These trials included a total of 654 MDD patients, randomized into two groups: one receiving both antidepressants and active TMS, the other receiving the same dosing of antidepressants with sham TMS.

The classes of antidepressants studied included selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs), while TMS was applied at either low (1 or 5 Hz) or high (10–20 Hz) frequencies over the left or right DLPFC. The HAMD was used to assess treatment efficacy across all trials.

The meta-analysis revealed that patients receiving combination therapy had significantly greater reductions in HAMD scores compared to those receiving antidepressants and sham TMS. The overall effect size was substantial (Hedges' g = 1.95, CI: 0.27-1.73), indicating that combination therapy offered more robust symptom relief. Study results should be approached with care given the heterogeneity across study protocols, including variation in antidepressant class and rTMS treatment parameters. No evidence of publication bias was identified.

Impact : This meta-analysis provides compelling evidence that combined antidepressant and rTMS therapy is more effective than antidepressant therapy alone across MDD patients at various stages of treatment resistance and therapeutic trials. These findings suggest that not only should medications be safely continued as scheduled throughout TMS treatment, but TMS could potentially be considered earlier in the treatment algorithm. Future prospective, well-controlled studies are needed to confirm these findings and could further explore whether specific antidepressants or TMS parameter combinations yield better outcomes.

Rakesh G, Cordero P, Khanal R, Himelhoch SS, Rush CR. Optimally combining transcranial magnetic stimulation with antidepressants in major depressive disorder: A systematic review and Meta-analysis. Journal of Affective Disorders. 2024 May 11.

Magnetic Seizure Therapy Matches ECT in Efficacy with Fewer Cognitive Side Effects

Collin Price, MD reviewing Deng ZD, et al. JAMA Psych Mar 2023.

In a large, double-blind randomized clinical trial, MST showed comparable antidepressant efficacy to ECT while providing a superior cognitive safety profile. This trial suggests MST may be a promising alternative to ECT, especially for patients concerned about cognitive side effects, though ECT still demonstrated a faster remission time.

MDD is a leading global cause of disability and, when severe or treatment refractory, is often treated with ECT. This intervention is known for its high efficacy but significant cognitive risks. Magnetic Seizure Therapy (MST) is an investigational therapy designed to induce seizures through high-intensity magnetic stimulation rather than direct electrical current, potentially reducing adverse effects while maintaining efficacy. While early trials have demonstrated the cognitive advantages of MST, large-scale studies comparing its antidepressant effects with ECT are limited.

This RCT, conducted at three academic hospitals, randomized 73 patients aged 18 to 90 with a major depressive episode (MDD or bipolar disorder) to receive either MST (n=35) or ultra-brief pulse right unilateral ECT (n=38). The MST was administered at 100 Hz for 10 seconds, and ECT was delivered at six times the seizure threshold. Patients were treated three times per week and followed up for six months post-treatment. The primary outcome was the reduction in HAMD-24 scores, with a 50% reduction indicating response and a 60% reduction with a final score of ≤8 indicating remission. EEG-to-motor seizure duration was measured post-treatment, and global cognitive function was assessed pre- and post-treatment using the Mini-Mental State Examination (MMSE) and the Autobiographical Memory

Interview-Short Form (AMI-SF).

Only 53 (72.6%) of the patients who were randomized completed treatment (MST: 29; ECT: 24). Both MST and ECT demonstrated significant antidepressant effects, with no statistical difference between the two groups in remission or response rates. In the ITT sample, 18 (51.4%) patients in the MST group and 16 (42.1%) in the ECT group met criteria for response. In terms of remission, 13 (37.1%) patients in the MST group and 10 (26.3%) in the ECT group met criteria. In the completer group, efficacy rates were similar for MST (response: 58.6%; remission: 44.8%) but higher for ECT (62.5%; 41.7%). There was no significant difference between MST and ECT for response or remission in either analysis group. However, ECT required fewer treatments to achieve remission, with a mean (SD) of 6.7 (3.3) treatments compared to 9.0 (3.1) for MST ($\chi2=9.5$; $p = 0.002$). Global cognitive function was stable in both groups ($F = 1.9$, $P = 0.18$), but MST patients regained orientation faster ($F = 10.0$, $P = 0.003$) and had better recall of autobiographical memories ($t = 2.8$, $P = 0.01$). ECT had more severe adverse effects, including five serious adverse events (3 worsened depression, 1 transient BP increase, and 1 episode of prolonged post-ictal agitation); ECT also caused more frequent headaches ($t = 3.1$, $P = 0.002$), nausea ($t = 2.8$, $P = 0.006$), muscle pain ($t = 3.7$, $P < 0.001$), and confusion ($t = 2.2$, $P = 0.03$). MST had fewer side effects, including nausea and tendinitis, but no serious adverse events. The EEG-to-motor seizure duration ratio was significantly higher for ECT than MST ($t = -3.23$, $P = .002$), indicating broader seizure spread in ECT and potentially explaining the lower cognitive burden observed with MST.

Impact: This double-blind RCT is among the largest comparing MST and ECT for depression, providing compelling evidence that MST offers a balance of efficacy and enhanced cognitive safety. While ECT remains the faster treatment for inducing remission, MST's cognitive benefits make it a strong alternative, especially for patients at risk of cognitive decline. Future research should focus on optimizing MST protocols to enhance its antidepressant speed while maintaining its favorable cognitive profile.

Deng ZD, Luber B, McClintock SM, Weiner RD, Husain MM, Lisanby SH. Clinical Outcomes of Magnetic Seizure Therapy vs Electroconvulsive Therapy for Major Depressive Episode: A Randomized Clinical Trial. JAMA Psychiatry. 2023.

Connectivity-Guided iTBS vs rsfMRI-Targeted rTMS for TRD

Angela Broida, PhD, LCSW reviewing Morriss et al., Nature Medicine Jan 2024.

The optimization of repetitive transcranial magnetic stimulation (rTMS) treatment remains a central focus in both clinical practice and ongoing research. While researchers and clinicians work toward better understanding how treatment parameters impact outcomes, the most ideal approaches remain unclear. Morriss and colleagues detail a multicenter, double-blind, RCT (BRIGhTMIND) that compared two neuromodulation techniques for TRD. The trial tested whether connectivity-based iTBS (cgiTBS), using rsfMRI to target rAI (right anterior insula) and LDLPFC, could more effectively reduce depressive symptoms than the standard rTMS F3 site, guided by structural MRI over 26 weeks. The results highlight that personalized cgiTBS and standard rTMS offer similar therapeutic potential for TRD.

This RCT (BRIGhTMIND) enrolled patients aged 18 and older with moderate to severe TRD across five centers across the UK. Participants were randomly assigned to either cgITBS based on rsfMRI (n=128) or standard rTMS using structural MRI (n=127). The cgiTBS targeted rAI and LDLPFC, while rTMS stimulated LDLPFC alone. Participants underwent comprehensive assessments for eligibility using the Structured Clinical Interview for DSM-5 (SCID-5-RV), GRID-HDRS-17, and the MGH scale, with medical histories obtained from primary and secondary care records. Following randomization in a 1:1 ratio to receive either repetitive Transcranial Magnetic Stimulation (rTMS) or intermittent theta burst stimulation (cgiTBS), each participant received 20 sessions of treatment over 4 to 6 weeks. The rTMS group received 10 Hz stimulation (with 26 s ITI) at 120% resting motor threshold, delivering 3,000 pulses per session The cgiTBS group received triplet bursts of 50 Hz on a 5 Hz carrier wave over 10-second cycles (2 seconds on, 8 seconds off), totaling 600 pulses per "run" and, given 5 runs comprised each session (with each run separated by 5 minutes), 3,000 total pulses per session were delivered. Primary outcomes focused on changes in depression symptoms measured by GRID-HDRS-17 at baseline, 8, 16, and 26 weeks, with secondary outcomes assessing various mental health scales including the BDI-II, PHQ-9, and GAD-7.

Key findings indicate that both cgiTBS and structural MRI-guided rTMS demonstrated lasting effects on depression symptoms up to 26 weeks, though the lack of sham group and the timing of outcome assessments complicate the interpretation of these results. Both treatments were effective in reducing depressive symptoms, and there was no statistically

significant difference between the two groups. The primary outcome showed an adjusted mean difference of -0.31 points on the HAMD-17 score (95% CI -1.87 to 1.24, P = 0.689) between cgiTBS and rTMS groups. Both interventions were well tolerated, with two serious adverse events (mania and psychosis) possibly related to the stimulation. Previous research suggests that iTBS and 10 Hz rTMS may be equally effective for treatment-resistant depression (TRD), but some participants in the rTMS arm of this study required a reduction in stimulation intensity due to intolerability. The intensity and selection methods might have influenced outcomes, as a reduction in stimulation was found to correlate with a decrease in depressive symptoms. Additionally, while both treatment methods produced similar results, it remains uncertain whether precise targeting of the LDLPFC–rAI loop significantly enhances clinical efficacy.

Impact: This trial demonstrates that personalized cgiTBS is as effective as standard-site, structurally guided rTMS in reducing depressive symptoms in patients with TRD over six months. While no advantage was found for cgiTBS, the study underscores the potential of using functional neuroimaging-guided approaches for tailoring brain stimulation treatments while also addressing the necessity of precision targeting methodologies. These findings contribute to the ongoing exploration of neuromodulation techniques and may inform future strategies for improving neuromodulationtreatment outcomes.

Morriss, R., Briley, P.M., Webster, L. et al. Connectivity-guided intermittent theta burst versus repetitive transcranial magnetic stimulation for treatment-resistant depression: a randomized controlled trial. Nat Med 30, 403–413 (2024). https://doi.org/10.1038/s41591-023-02764-z

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)