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PULSE

A Monthly Update on Advances in Neuromodulation

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Standard iTBS Outperforms Accelerated Protocol in Depression Treatment

Mohamad Shamas, PhD reviewing Dragon K et al. Behav Brain Res. 2024 Nov

This retrospective study compared the effectiveness and tolerability of standard and accelerated iTBS (aiTBS) protocols for treating depression. While both protocols significantly improved depressive symptoms, aiTBS was associated with lower response rates, tolerability, and patient satisfaction compared to the standard, four-week iTBS protocol.

iTBS, a well-established rTMS pulse type for the treatment of depression, provides significant symptom relief with shorter session times. While the standard iTBS protocol spans several weeks with daily sessions, accelerated iTBS (aiTBS) condenses treatment into one week with multiple session per day, potentially offering more rapid and cost-effective results. However, uncertainties remain regarding whether this condensed approach achieves the same clinical efficacy and

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tolerability as standard iTBS. This retrospective analysis compared the two protocols' outcomes and logistical advantages in patients with depression.

This retrospective study reviewed the clinical records of 66 patients with unipolar or bipolar depression treated with rTMS at a psychiatric hospital in Germany, provided they completed at least 15 sessions with sufficient stimulation intensity (>100% RMT) and had complete pre- and post-treatment assessments. Patients received either aiTBS (five sessions per day for five days, n=32) or standard iTBS (one session per weekday for four weeks, n=34). Both protocols targeted the left DLPFC using the 5-cm rule and delivered 1200 pulses using a MagVenture system. Depressive symptoms were assessed using the HAMD-21 and the Major Depression Inventory (MDI) before and after treatment, with response (≥50% symptom reduction) and remission (HAMD-21 ≤7; MDI ≤10) rates as primary outcome measures. Statistical analyses included mixed ANOVAs, t-tests, and chi-square tests, with Bonferroni correction for multiple comparisons; effect sizes were reported using Cohen's d, η^2, and φ.

The standard iTBS protocol showed trends toward higher response (38% HAMD-21, 35% MDI) and remission rates (29% HAMD-21, 44% MDI) compared to aiTBS, which had response (19% HAMD-21, 16% MDI) and remission rates (16% HAMD-21, 25% MDI), though these differences were not statistically significant and had small effect sizes. Notably, reported MDI remission rates were higher than response rates across both groups, suggesting lower baseline severity on this measure. The standard iTBS group had significantly lower end-of-treatment scores on both HAMD-21 ($d = 0.59$, $p = 0.02$) and MDI ($d = 0.73$, $p = 0.004$). Although 6 patients dropped out early due to side effects in the standard iTBS group, compared to none in the aiTBS, tolerability was statistically worse for aiTBS. The incidence of mild side effects, such as headaches, was significantly higher among completers in the aiTBS group (34%) compared to the standard iTBS group (15%; $\chi 2 = 8.08$, $p = 0.004$). Patient and clinician satisfaction was qualitatively reported to be lower for aiTBS, primarily due to logistical burdens, while standard iTBS was perceived more favorably due to the longer treatment duration fostering deeper clinician-patient relationships. However, no formal statistical analysis of satisfaction was conducted.

Impact: This retrospective analysis of depressed patients receiving standard vs. accelerated iTBS courses suggests that standard iTBS provides superior efficacy, tolerability, and patient satisfaction compared to accelerated protocols, supporting its continued use as the preferred option for treating MDD. While aiTBS offers the advantage of rapid completion, its lower response and remission rates and logistical challenges warrant further optimization of parameters such as session frequency and pulse dosage before broader implementation. This study was limited by a small sample size, lack of randomization and blinding, short follow-up, and restricted generalizability, leaving questions about long-term efficacy and the potential optimization of aiTBS protocols unanswered.

Dragon K, Janthur C, Hebel T, et al. Four weeks standard vs. one week accelerated intermittent Theta Burst Stimulation for the treatment of depression: A retrospective analysis. Behav Brain Res. 2025;479:115361. doi:10.1016/j.bbr.2024.115361.

Extended Course of Accelerated iTBS Shows Limited Remission in Depressed Patient Needing ECT

Mandeep Singh, MD, MBA reviewing Goodman et. al., Neuropsychopharmacology, 2024 Oct

In this open-label trial, severely depressed patients eligible for ECT were instead treated with an extended course of accelerated iTBS (aiTBS). Although positive clinical outcomes were noted, fewer than 20% of subjects achieved remission by the end of the acute phase, suggesting aiTBS may not be a suitable alternative to ECT in this population.

ECT remains among the most effective treatments of severe depression but is associated with cognitive side effects, poor public perception, and limited access. Traditional once-daily rTMS, including iTBS, is often thought to be less effective for severe depression; however, accelerated protocols have shown promise in patients with severe and refractory symptoms. This study, conducted during COVID-19-related restrictions on access to ECT, examined the efficacy of aiTBS among severely depressed patients who would have otherwise received ECT.

Using a prospective open-label design, 172 severely depressed patients referred for ECT were recruited to instead receive aiTBS. Inclusion required a prior response to ECT or symptom severity warranting ECT, with exclusions for recent substance use disorders, bipolar disorder,

psychotic disorders, or major neurological/physical illness. Each treatment session consisted of 600 pulses of iTBS at 110% MT targeting the left DLPFC (determined by the modified BeamF3 method). Each treatment day consisted of 8 sessions, with an acute phase consisting of 10 days (80 total sessions) followed by a taper phase of 2 days per week for 2 weeks then 1 day per week for 2 weeks. Responders (>50% HDRS reduction) entered a 6-month symptom-driven relapse prevention phase; non-responders were discontinued from the trial. The primary outcome was the percentage of patients achieving remission on HDRS between baseline and the end of the acute phase.

By acute phase completion (n=155), the per-protocol response and remission rates were 25.2% and 16.1%, respectively, with 29.4% mean HDRS reduction (d = 1.02, p < 0.001). Tapering phase results (n=115) showed increased response (49.6%) and remission rates (34.8%) with a 42.6% mean HDRS reduction from baseline (d = 1.29, p < 0.001). During the relapse prevention phase (n=61), HDRS scores improved by 60.1% (d = 1.93, p < 0.001). Among taper-phase responders (n = 22), 27.3% remained responders and 40.9% achieved remission, while among remitters (n = 39) 53.8% maintained remission and 10.3% converted to responders. Overall, 10 patients responded, 30 remitted, and 7 experienced a full relapse. Outcomes did not differ by complexity factors such as inpatient admission, personality disorder, history of trauma, alcohol abuse, or psychosis. aiTBS was well tolerated, with headaches (38.4%) being the most common side effect, low pain ratings (2.0 ± 1.9), and a 1.2% discontinuation rate; no seizures occurred.

Impact: This open-label trial highlights aiTBS as a safe and effective treatment for severly depressed patients though remission rates were lower than would be expected with ECT (often cited as 50-80%). Compared to the Stanford Neuromodulation Therapy (SNT) protocol—which delivers 1800 pulses per session over 10 daily sessions for five days via fMRI-guided neuronavigation and achieves remission rates up to 79%—the lower efficacy of the current protocol suggests that pulse number and precision targeting may be important for optimizing aiTBS outcomes. Importantly, aiTBS showed excellent tolerability, with a lower rate of adverse effects compared to ECT, which often leads to cognitive impairments and dropout. Future research should refine stimulation parameters and targeting to enhance efficacy while maintaining aiTBS's favorable safety profile as a non-invasive ECT alternative.

Goodman MS, Trevizol AP, Konstantinou GN, et al. Extended course accelerated intermittent theta burst stimulation as a substitute for depressed patients needing electroconvulsive therapy. Neuropsychopharmacology. Published online October 23, 2024. doi:10.1038/s41386-024-02007-w

Continuation and Maintenance ECT Associated with Lower Rehospitalization Rates and Treatment Costs

Visesha Kakarla, MD reviewing Jorgensen et al., JAMA Psychiatry, 2024 Sept

This national registry study from Denmark reviewed the clinical and economic outcomes of patients who underwent continuation or maintenance ECT (c/mECT) after acute ECT (aECT). The findings highlight that c/mECT significantly reduces psychiatric rehospitalizations and associated costs, although there was no significant difference in suicidal behaviors.

ECT is a cornerstone treatment for severe psychiatric conditions, including treatment-resistant depression and schizophrenia. However, relapse rates after aECT are estimated at 60%-80% in the absence of relapse-prevention strategies like pharmacotherapy and/or ongoing ECT. Continuation (cECT) and maintenance ECT (mECT) have emerged as strategies to sustain remission, yet large-scale evidence supporting their utility remains limited.

This national cohort study included 19,944 patients from the Danish National Patient Registry who underwent ECT between 2003 and 2022. Using treatment dates of ECT sessions, aECT was defined as ≥3 treatments spaced <7 days apart; cECT as ≥3 treatments spaced 7–90 days apart following an aECT series and within 180 days from the first cECT session; and mECT as sessions starting ≥181 days after the first cECT. Treatments separated by ≥91 days were categorized as separate episodes, and those with inconsistent intervals or ≤3 treatments were excluded. Primary outcomes included rates of rehospitalization (≥2 days in a psychiatric ward) and suicide attempts over six- and 12-month follow-ups. Statistical methods included Cox regression to compare hazard ratios (HR), propensity score matching to study moderators, and Poisson regression to assess outcomes before and after aECT. Economic outcomes compared hospitalization and ECT costs across three periods: 180 days before aECT, 180 days after, and the subsequent 180 days.

A total of 1533 patients (7.7%)

received c/mECT, with 516 (2.6%) receiving mECT. Compared with the aECT-only group, c/mECT patients were more likely to be diagnosed with schizophrenia (OR: 2.14, 95% CI: 1.86-2.46) and schizoaffective disorder (OR: 2.42, 95% CI: 1.90-3.09) and less likely to be diagnosed with unipolar depression (OR: 0.56, 95% CI: 0.51-0.62). c/mECT was associated with significantly lower rates of rehospitalization compared with aECT-only with HR of 0.68 (95% CI: 0.58-0.87) during the first 180 days after aECT and 0.62 (95% CI: 0.50-0.76) during the subsequent 180 days; Poisson regression showed similar findings. However, c/mECT was not associated with significant changes in suicidal behavior (HR: 0.91, 95% CI: 0.63-1.27 in the first 180 days after aECT; HR: 0.87, 95% CI: 0.57-1.34 in the second 180 days) compared to aECT-only. In the c/mECT group, hospitalization costs decreased from $70.8 million pre-aECT to $25.9 million in the 180 days after and further to $17.7 million in the subsequent 180 days. While both the aECT-only and c/mECT groups saw cost reductions, total costs in the c/mECT remained higher due to additional ECT expenses.

Impact: This national registry study suggests that continuation/maintenance ECT after an acute course can reduce rehospitalization rates but incurs higher costs due to ongoing sessions, potentially offsetting savings from fewer hospitalizations. Notably, this study was conducted in Denmark, which could potentially reflect increased access to care and earlier intervention. Future studies incorporating socioeconomic data could increase validity of these findings in the United States. Additionally, this study did not report differences in rates of rehospitalization between different psychiatric indications for ECT, which may be a topic of interest for future studies.

Jørgensen A, Gronemann FH, Rozing MP, Jørgensen MB, Osler M. Clinical Outcomes of Continuation and Maintenance Electroconvulsive Therapy. JAMA Psychiatry. 2024;81(12):1207-1214. doi:10.1001/jamapsychiatry.2024.2360

Meta-Analysis Indicates rTMS is Moderately Effective for Treatment-Refractory OCD

Mohamad Shamas, PhD reviewing Steuber ER et al. Biol Psychiatry Cogn Neurosci Neuroimaging 2023 Nov

This meta-analysis highlights the potential of rTMS as a therapeutic option with moderate efficacy for treatment-refractory OCD, with a three-fold increased likelihood of treatment response compared to sham. Greater reductions in depressive symptoms correlated with improved OCD outcomes, though further optimization of treatment protocols is warranted.

OCD is a debilitating condition affecting approximately 2% of the population and it often results in diminished professional and social functioning and overall quality of life. While serotonin reuptake inhibitors (SRIs) and cognitive behavioral therapy (CBT) are effective first-line treatments, 40–60% of patients do not respond to these treatments. rTMS has shown promise as a noninvasive neuromodulation option, prior RCTs have yielded mixed findings. This meta-analysis evaluates the therapeutic effects of rTMS on OCD severity, exploring patient, intervention, and trial design characteristics to identify moderators that optimize treatment outcomes.

This meta-analysis followed PRISMA guidelines and systematically searched major databases for RCTs comparing rTMS to sham treatment for OCD published through December 31, 2022. Studies were included if they compared rTMS with sham treatment in OCD, used psychometrically validated scales, and provided adequate data for effect size calculation. Theta burst stimulation (TBS) studies were excluded due to methodological differences from traditional rTMS protocols. Effect sizes for OCD symptom severity and depression were calculated using Hedges' g, while relative risk (RR) ratios were used to measure treatment response, with results standardized to ensure comparability across studies. A random effects model accounted for variability across trials, with heterogeneity evaluated using forest plots, the Q statistic, and the I^2 statistic. Publication bias was assessed via funnel plots and Egger's test. Moderator analyses explored how various factors influenced treatment outcomes.

A total of 25 RCTs (n = 860) with 28 treatment comparisons showed a moderate therapeutic effect of rTMS on OCD severity compared to sham (g = 0.65, 95% CI = [0.46, 0.84]; $p < 0.001$), with significant heterogeneity (Q27 = 51.41, $p < 0.003$, I2 = 47.48%).rTMS yielded a higher treatment response rate (39.5% vs. 8.8% for sham; RR = 3.15, 95% CI = [2.13, 4.68]; $p < 0.001$). Adjustments for publication bias reduced the effect (trimmed RR = 2.67, 95% CI = [1.76, 4.06]). Depression improvement strongly correlated with OCD symptom reduction, explaining 33% of treatment variance. Session length positively predicted OCD improvement (24% variance explained), while higher session counts showed diminishing returns

(28% variance explained). Factors 3.15, 95% CI = [2.13, 4.68]; p < 0.001). Adjustments for publication bias reduced the effect (trimmed RR = 2.67, 95% CI = [1.76, 4.06]). Depression improvement strongly correlated with OCD symptom reduction, explaining 33% of treatment variance. Session length positively predicted OCD improvement (24% variance explained), while higher session counts showed diminishing returns (28% variance explained). Factors such as age, sex, OCD duration, symptom severity, and pharmacotherapy had no significant impact on rTMS effects. No significant relationships were found between rTMS treatment effects and factors like sample size, trial attrition, sham condition completeness, treatment-refractory status, or risk of bias, with no meaningful differences across different trial designs.

Impact: This meta-analysis provides compelling evidence for the moderate efficacy of rTMS in treating treatment-refractory OCD, particularly in patients with comorbid depression. However, the study is limited by significant heterogeneity, publication bias, and reliance on short-term outcomes, restricting generalizability and insights into long-term efficacy. These findings highlight the need for further research to optimize stimulation protocols and evaluate long-term outcomes.

Steuber ER, McGuire JF. A meta-analysis of transcranial magnetic stimulation in obsessive-compulsive disorder. Biol Psychiatry Cogn Neurosci Neuroimaging. 2023;8(11):1145-1155. doi:10.1016/j.bpsc.2023.06.003

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)