JANUARY 2023 / ISSUE 23

PULSE

A Monthly Update on Advances in Neuromodulation

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Adjunctive D-Cycloserine May Enhance iTBS Outcomes in Patients with MDD

Nicole Wong reviewing Cole et al. JAMA Psychiatry 2022 Oct

An RCT of 50 participants assigned to either iTBS plus placebo or iTBS plus D-cycloserine demonstrated greater clinical response and remission in the adjunctive D-cycloserine group

Intermittent theta-burst stimulation (iTBS) is a noninvasive brain stimulation modality with efficacy in MDD. iTBS is theorized to target synaptic plasticity in selected brain circuits. A potential strategy to improve iTBS outcomes is to target the NMDA receptor, which regulates synaptic plasticity. D-cycloserine is a partial agonist of the NMDA receptor and has been shown to result in greater persistence of iTBS-induced effects than placebo, but no study has examined whether D-cycloserine alters iTBS clinical outcomes.

In this single-site, four-week, double-blind, placebo-controlled RCT, the authors recruited participants aged 18-65 years with a primary

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diagnosis of MDD, a HDRS score ≥18, a Young Mania Rating Scale (YMRS) score ≤8, and normal blood work. Exclusion criteria were D-cycloserine allergy, acute suicidality or potential harm to others, psychosis, substance use disorder within the past three months, benzodiazepine use, seizures, pacemaker or metallic implant, unstable medical condition, pregnancy or lactation, history of nonresponse to rTMS or ECT, and initiation of psychotherapy within 3 months of enrollment or during the trial. Participants were randomly assigned 1:1 to either iTBS plus placebo or iTBS plus 100 mg of D-cycloserine for the first 2 weeks followed by iTBS without an adjunct treatment for weeks 3 and 4. iTBS treatment was targeted to the left DLPFC and consisted of 600 pulses of iTBS delivered at 80% of resting motor threshold. Participants received treatments Monday through Friday for a total of 20 treatments. Outcomes included the MADRS, CGI, 7-item Generalized Anxiety Disorder (GAD-7), QIDS-Self Report (SR), Snaith Hamilton Pleasure Scale (SHAPS), visual analog scale (VAS), and World Health Organization Quality of Life (WHOQOL-BREF) administered at baseline, 2 weeks, and 4 weeks.

Fifty participants were randomized and included in the final intention to treat sample (mean age 40.8 ± 13.4 years; 31 females [62%]). Demographic and baseline clinical values were not significantly different between groups and the participants in the final sample presented with moderate-severe depression. Blinding integrity was preserved, as there was no significant difference between groups in accurately predicting whether they received adjunctive D-cycloserine or not. The iTBS plus D-cycloserine group demonstrated a greater decrease in depressive symptoms on the MADRS from baseline to 4 weeks relative to placebo (placebo = -10.20 +/- 7.79; D-cycloserine = 16.16 +/- 6.99; p = 0.007; Hedge's g=0.99 [95% CI: 0.34-1.62]). The iTBS plus D-cycloserine group also demonstrated greater rates of clinical remission at 4 weeks (placebo = 4.2%; D-cycloserine = 39.1%; p = 0.01, OR = 14.78 [95% CI 1.68-129.52]), improvements from baseline to 4 weeks on the CGI-severity scale (z=3.24, p=0.001), GAD-7 (chi-squared=6.67, p=0.04), and VAS scale measuring overall well-being (chi-squared=7.94, p=0.02). Notably, there were no significant between-group differences on the QIDS-SR or on anhedonia as measured by the SHAPS. Rates of clinical remission did not separate at 2 weeks (iTBS plus placebo: 4.2% vs. iTBS plus D-cycloserine: 17.4%) but were statistically significantly different at 4 weeks (iTBS plus placebo: 4.2% vs. iTBS plus D-cycloserine 39.1%; OR: 14.78; 95% CI: 1.68-129.52, p = 0.01). There were no serious adverse events during the study.

Impact: This single-site, double-blind, placebo-controlled, randomized clinical trial suggested that noninvasive neuromodulation treatment outcomes, such as with iTBS, can be enhanced by mechanistically informed adjuncts, like D-cycloserine, a NMDA receptor partial agonist. It is interesting to note that iTBS was administered at subthreshold intensity (80% MT) as opposed to the more common suprathreshold intensity (120% MT). It is possible that use of an NMDA partial agonist potentiated the efficacy of subthreshold stimulation, and future studies should examine the interaction between intensity and pharmacologic augmentation. If larger multicenter studies demonstrate similar findings, D-cycloserine and other mechanistically informed adjuncts may be used to increase treatment response in TMS.

Cole J, Sohn MN, Harris AD, Bray SL, Patten SB, McGirr A. Efficacy of Adjunctive D-Cycloserine to Intermittent Theta-Burst Stimulation for Major Depressive Disorder: A Randomized Clinical Trial. JAMA Psychiatry. 2022 Dec 1;79(12):1153-1161. doi: 10.1001/jamapsychiatry.2022.3255.

High-Frequency rTMS Improves Depression and Insomnia More than Sham when Combined with Agomelatine

Collin M Price, MD reviewing Pu et al. J Affect Disord 2022 Nov

A randomized, sham-controlled trial of HFL rTMS combined with open-label administration of agomelatine in patients with untreated mild-moderate depression and insomnia revealed a significantly greater improvement in the active rTMS group on depression and insomnia scales and polysomnography. These changes were accompanied by significant changes in serum markers of neural plasticity.

Insomnia and depression are closely related disorders, with sleep disturbance frequently present in depression, and insomnia a significant risk factor for developing depression. Agomelatine, an antidepressant that stimulates melatonin and inhibits serotonin 2C receptors, can improve mood and sleep, and the antidepressant effects of rTMS can lead to sleep improvements. In this study, the authors sought to examine the combined effects of agomelatine and rTMS on depression and sleep parameters, using sham rTMS to isolate the contribution of active rTMS.

Eighty-two patients completed a prospective, eight-week, open-label (agomelatine) and randomized sham-controlled (rTMS) trial. Patients were recruited from inpatient and outpatient settings if they were aged ≥18 years, right handed, and experiencing both: 1) mild-to-moderate depression as characterized by a HAM-D score between 7-23, and 2) "non-organic insomnia" characterized by a Pittsburgh Sleep Index (PSQI) score >7. Patients were excluded if they had psychiatric or sleep disorders not meeting these criteria; contraindications to either of the interventions; were lactating, pregnant, or "willing to conceive" women; or had taken any psychiatric medications within the preceding 2 weeks. Participants were withdrawn if they started any psychiatric medications during the trial. All participants received agomelatine for eight weeks at doses ranging from 25-75 mg daily, and half of the patients (n=42) were randomized to receive HFL rTMS while the other half (n=40) received sham rTMS. rTMS was delivered as five sessions per week for four weeks of 10-Hz rTMS delivered at 120% MT to the left DLPFC. Outcomes included the HAM-D (assessed at baseline and after weeks 1, 2, 4, and 8), the PSQI (assessed at baseline and after weeks 4 and 8), and polysomnography (assessed at baseline and after week 8). Blood samples were taken at baseline and after week 8 to measure serum norepinephrine (NE), 5-hydroxytrypatmine, brain-derived neurotrophic factor (BDNF), and melatonin. The primary outcome was between-group difference on the PSQI, and response was defined as reduction of PSQI by >50%.

There were no significant differences between the active and sham rTMS groups with respect to demographic or clinical measures, dosage of agomelatine, baseline polysomnography, or serum measures. Active rTMS yielded a response rate on the PSQI of 78.5% compared to 52.5% in the sham group ($p = 0.013$). The active rTMS group had significantly lower HAM-D scores after weeks 2, 4, and 8, with a significant group x time interaction ($p < 0.05$). PSQI scores similarly favored active rTMS after weeks 4 and 8, with a significant group x time interaction ($p < 0.01$). Polysomnography revealed that post-treatment total sleep time, sleep efficiency, and N3 percentage were all significantly higher in the active rTMS group compared to sham ($p < 0.05$) and post-treatment sleep latency, awakening time, micro-awakening times, and N1 percentage were all significantly lower in the active group compared to sham ($p < 0.01$). Serum analyses revealed significantly higher post-treatment NE and BDNF in the active group compared to sham, with a significant group x time interaction in serum BDNF ($p < 0.05$). Adverse reactions to treatment were rare, mild, and time limited.

Impact: This randomized, sham-controlled trial of HFL rTMS combined with open-label agomelatine revealed that the addition of active rTMS yielded significantly greater improvements in sleep quality and mood compared to sham, as well as significant increases in serum NE and BDNF. A lack of pharmacologic placebo limits interpretation of these results. Because both groups of subjects received agomelatine, it is unclear how much the active medication contributed to outcome; it is possible that rTMS alone may have accounted for most or all of the effect. Other limitations of this study include a small sample size, a short follow-up period, and the exclusion of participants taking psychotropic medications. The lack of availability of agomelatine in the United States limits generalizability.

Pu Z, Hou Q, Yan H, Lin Y, Guo Z. Efficacy of repetitive transcranial magnetic stimulation and agomelatine on sleep quality and biomarkers of adult patients with mild to moderate depressive disorder. J Affect Disord. 2023 Feb 15;323:55-61. doi: 10.1016/j.jad.2022.11.062. Epub 2022 Nov 23. PMID: 36435397.

Electroconvulsive Therapy May Be a Viable Treatment for Obsessive-Compulsive Disorder

David Lee reviewing Li et al. Frontiers in Psychiatry 2022 Nov

This limited retrospective study suggests that ECT may have efficacy for the treatment of OCD, though this efficacy is limited in the presence of other psychiatric comorbidities.

Obsessive-compulsive disorder (OCD), a complex and debilitating mental illness characterized by uncontrollable intrusive thoughts and compulsive behaviors, has a lifetime prevalence of 2.3%, and a 12-month prevalence of 1.2% in adult populations. The efficacy of current first-line treatments for OCD (medications and cognitive behavioral therapy) is variable, with 40-60% of those treated reporting unsatisfactory benefit. In cases of treatment-refractory OCD, deep brain stimulation can be considered, however, its practicality is limited by invasiveness and cost. On the other hand, electroconvulsive therapy (ECT), a much less invasive technique, is often used in severe or treatment-refractory cases of depression and schizophrenia, though it is not typically a treatment for OCD. However, prior case reports and observational studies reported a

response rate of roughly 60% for ECT in patients with OCD, prompting this retrospective analysis to further investigate the response of OCD to ECT.

The authors included 21 patients (11 men; mean age 27 years) who met criteria for OCD and received ECT at West China Hospital of Sichuan University between 2009 and 2020. Baseline clinical and demographic data were reported including age of OCD onset, education level, comorbid psychiatric conditions (depression and psychotic disorders), general treatment history (whether they had failed "adequate dose and time" of SSRIs, which was not defined or discussed in the paper), and number of ECT sessions. ECT was administered bitemporally in all cases with 3 sessions per week (average of 7 ± 2 sessions per patient); the authors did not comment on other ECT stimulus parameters. Clinical response to ECT was defined by a Clinical Global Impressions-Improvement scale score of 1-2 at the end of treatment (CGI-I; observer-rated 1-7 Likert scale where 7=very much worse, 4=no change, and 1=very much improved). No OCD-specific measures or measures of clinical response beyond the CGI-I were assessed in this study. The authors compared responder and non-responder groups using t-tests for continuous variables, and Chi-squared test for categorical variables.

Of the 21 patients, 12 had no other comorbid psychiatric conditions, and 15 were reported to have "adequate" SSRI trials prior to ECT administration. Subjects received on average seven ECT treatments, and 11 subjects experienced side effects (five with headache, five with amnesia, and one with muscle soreness). Twelve patients responded to ECT (57%), while the other nine did not. Statistically-significant differences were observed between responders and non-responders in comorbidity pattern (7/9 with comorbidity in non-responders, 2/12 in responders, $p<0.05$) only; no other differences were noted between groups.

Impact: This small-scale retrospective study suggests that the ECT may have some efficacy in patients with OCD, though comorbid psychiatric conditions limit this efficacy. Significant limitations of this study include the small sample size, retrospective nature, and lack of measures specific to OCD such as the Yale Brown Obsessive-Compulsive Scale. Future work examining larger populations in a randomized control design utilizing OCD-specific metrics will be crucial in better determining the efficacy of ECT for patients with OCD.

Li K, Long J, Deng W, Cheng B, Wang J. Electroconvulsive therapy for obsessive-compulsive disorder: A retrospective study. Frontiers in Psychiatry. 2022 Nov 9:2544.

Borderline Personality Disorder Associated with Increased Risk of Relapse of Depression in Patients Treated with Electroconvulsive Therapy

Norman Spivak reviewing Hein et al. Psychiatry Res 2022 Aug

BPD is a risk factor for relapse of depression within six months in patients who are either partial or complete responders to ECT.

ECT is one of the most effective treatments for unipolar or bipolar depression, with a response rate of about 74%, compared to pharmacological treatment with a response rate of only about 49%. However, while effective, there is a high relapse rate (65%) after ECT for depression. Borderline personality disorder (BPD), characterized by unstable relationships and sense-of-self, impulsivity, and fear of abandonment, is frequently comorbid with depression and can complicate the illness course. In this retrospective chart review, the authors sought to measure the impact of BPD on depression relapse after ECT.

Data from 109 patients with MDD or bipolar depression (62.4% female, 63.3% ≥ 50 years of age) who either partially or completely responded to ECT were extracted from the chart. Prior to ECT, all patients had been evaluated with the Mini International Neuropsychiatric Interview and a BPD screening instrument. ECT was delivered bitemporally with a brief pulse (0.5 ms) three times per week for 6-18 sessions, depending on clinical response. Outcomes were assessed using the HDRS, with response defined as >60% reduction in HDRS scores and either 1) a score <10 (full response) or 2) a score < 16 (partial response). Relapse was defined as the presence of one or more of the following: depressive relapse with HDRS ≥ 16 (maintained for ≥ 1 week) and a mean increase of at least 10 points since post ECT interview; rehospitalization; new treatment with ECT; or suicidal behaviors. A Chi-square test was used to compare categorical data, and survival (time without relapse) was plotted using the Kaplan-Meier method and then compared using a log-rank test. A Cox regression was used to examine the likelihood of relapse within 6 months with respect to BPD status.

The authors do not comment on any potential differences between BPD and non-BPD groups in terms of baseline characteristics or ECT parameters. Within 3 months after ECT, 50% of patients with comorbid BPD relapsed, a significantly greater proportion than the 19.5% of patients without BPD who relapsed ($p = 0.003$). At 6 months, this difference was even more significant, with 72.7% of BPD patients having relapsed and only 28.7% of non-BPD patients having relapsed ($p < 0.001$). The multivariate Cox regression analysis yields a hazard ratio of 4.14 after adjusting for age, gender, and mood stabilizer after ECT ($p < 0.001$).

Impact: This retrospective analysis of data from hospitalized depressed patients who responded to ECT indicates that patients with comorbid BPD were at a significantly greater risk of depression relapse. Generalizability of these findings are limited by the single-site design and limited information presented on ECT treatment courses received by BPD and non-BPD patients. Future studies should be performed prospectively to confirm the association suggested here, and such studies should also examine any effects of ECT on BPD symptoms. Such confirmation could direct efforts to screen and closely monitor patients at increased risk of depression relapse after ECT.

Hein M, Mungo A, Loas G. Risk of relapse within 6 months associated with borderline personality disorder in major depressed individuals treated with electroconvulsive therapy. Psychiatry Res. 2022;314:114650. doi:10.1016/j.psychres.2022.114650

Abbrevations

cTBS (continuous theta burst stimulation)
DBS (deep brain stimulation)
dTMS (deep transcranial magnetic stimulation)
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)
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)

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)

ADHD (attention-deficit/hyperactivity disorder)
AUD (alcohol use disorder)
GAD (generalized anxiety disorder)
MDD (major depressive disorder)
OCD (obsessive compulsive 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)
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)
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)
OFC (orbitofrontal cortex)
SMA (supplementary motor area)