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PULSE

A Monthly Update on Advances in Neuromodulation

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Magnetic Seizure Therapy for Depression Found to Be as Effective as ECT, with Fewer Side Effects

David M Carlson, MD, reviewing Deng Z et al. JAMA Psychiatry 2023 Dec

A large randomized controlled trial of Magnetic Seizure Therapy (MST) vs ECT for major depressive episodes finds similar response and remission rates, with a slightly longer time to remission and fewer physical or cognitive adverse effects.

Electroconvulsive therapy (ECT) is one of the most effective treatments for treatment-resistant depression, but it comes with the potential to experience concerning physical and cognitive side effects. Magnetic Seizure Therapy (MST), a newer therapy, was designed to achieve this antidepressant effect with fewer adverse effects. Thus far, it has shown promise in small trials. This three-site randomized controlled trial compared MST with right unilateral (RUL) ultra-brief pulse ECT – the best tolerated form of ECT currently available – to assess for both

antidepressant effects as well as adverse effects.

Trial participants were adults (mean age 48 ± 14.1 years, 56.2% female) with major depression or bipolar disorder (either I or II) who were referred for ECT to treat a major depressive episode and had a baseline 24-item Hamilton Depression Rating Scale (HDRS24) score of 18 or higher (mean baseline score 31 ± 7.1). Of the 73 patients, 35 were randomized to receive MST at 100Hz frequency and 100% of device power for 10 seconds, and 38 to RUL ultra-brief ECT at six times the seizure threshold. Participants received treatment three times per week, with identical anesthesia protocols in both arms, until they achieved remission or reached a plateau in response.

For the primary depression outcome, the response was defined as a 50% reduction in HDRS-24 and remission criteria of 60% or greater reduction in HDRS-24 with a total score less than 8. Subjective adverse effects, which included physical (headache, nausea, dry mouth, aches, pain) and cognitive (confusion, memory problems), were assessed using the Columbia ECT Subjective Side Effects Schedule, administered in the afternoon of each treatment day. Statistical analysis consisted of repeated-measure linear mixed models for

continuous measures (including HDRS-24 score), t-tests for between-group comparisons of continuous measures at baseline and end of treatment, chi-squared tests for categorical variables, and Kaplan-Meier survival analysis for examining time to remission.

Of the 73 participants randomized, 53 (73%) completed the trial, with no significant difference in completion rates between groups (MST 82.9%, ECT 63.2%). In the 73-person intention-to-treat group, 46.6% achieved response (MST 51.4%; ECT 42.1%), and 31.5% met remission criteria (37.1%; 26.3%); there was no significant difference in response or remission rate between groups. Among the 53 who completed the study, response was achieved in 60.4% (MST 58.6%; ECT 62.5%) and 43.4% remission (MST 44.8%; ECT 41.7%). Notably, ECT led to significantly faster results, with a mean time to remission of 6.7 treatments vs. 9.0 for MST. In both groups, treatment response was maintained at 2-month and 6-month follow-ups, with no significant differences.

There were five serious adverse events – all in the ECT group (3 cases of worsening depression, 1 case of postictal agitation, and one case of large transient increase in blood pressure) – and four minor adverse events in the MST group (2 cases of nausea and vomiting post-treatment, 1 case of foot

pain unrelated to treatment, and 1 case of treatment not being delivered due to a device-related issue that was repaired). ECT patients had significantly higher severity of nausea and muscle pain, confusion and disorientation, and worse recall of autobiographical memories or autobiographical memory specificity, with t-scores ranging from 2.2 to 3.7 (p= 0.002-0.03). Participants regained orientation faster following MST than ECT at both threshold and suprathreshold levels.

> **Impact: This trial, the largest to date comparing MST and ECT, finds comparable efficacy with increased tolerability and fewer adverse effects in MST than in ECT. Notably, ECT response rates in this study are lower than generally observed elsewhere in the literature, and this study was not designed or powered to be a true noninferiority trial (though that trial is currently underway). Future work already underway seeks to verify these findings, and additional work into accelerating the antidepressant effects of MST is of great interest to the field.**

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. Published online December 6, 2023. doi:10.1001/jamapsychiatry.2023.4599

Ketamine Found to be Noninferior to ECT for Treatment-Resistant Depression

Harinee Maiyuran, MD, reviewing Anand A et al.The New England Journal of Medicine 2023 May

This open-label, randomized, noninferiority trial consisting of 403 patients with treatment-resistant depression (TRD) without psychotic features found that, in those receiving intravenous (IV) ketamine, 55.4% responded and 37.9% remitted, compared to 41.2% response and 21.8% remission in those receiving electroconvulsive therapy (ECT), suggesting IV ketamine's robust antidepressant effects are not inferior to those of ECT.

In TRD cases, where multiple first-line antidepressants have failed, two of our more potent treatment options

are ECT and ketamine. Though ECT is effective, its popularity is limited by availability, concerns of cognitive

impairment, and stigma. Ketamine's effectiveness in depression (including TRD) has

been more recently shown, and it works quickly and without the same risk of cognitive impairment. However, its risk of misuse is not easy to overlook, and its potential to alter perceptions and thought processes means it is typically avoided in patients with psychotic symptoms. Given the advantages and disadvantages of both forms of treatment, this study, the ELEctroconvulsive therapy vs. Ketamine in patients with Treatment-resistant Depression (ELEKT-D) study, aimed to assess the noninferiority of ketamine to ECT in treating non-psychotic TRD.

The trial was a prospective, openlabel, randomized, noninferiority trial conducted at five different sites, enrolling outpatients and inpatients aged 21-75 (mean age 46, 51% women, 88% white, 89% outpatient at the time of treatment, 39% with a history of suicide attempts, median duration of current depressive episode 2 years). During the 3-week initial treatment phase, the ketamine group received intravenous ketamine twice weekly, and the ECT group received thrice weekly right unilateral (RUL) ultrabrief pulse ECT. Notably, 39% of patients underwent mid-treatment transition from RUL to bilateral treatment, typically after four sessions of RUL treatment. The primary outcome measure was clinical response rate as defined by QIDS-SR-16 improvement of at least 50%. Secondary outcomes assessed included QIDS remission rates, MADRS response and remission rates, Global SelfEvaluation of Memory (GSE-My) scores, Squire Memory Complaint Questionnaire (SMCQ),

and Hopkins Verbal Learning Test-Revised (HVLT-R, a rater administered memory test). Those who met criteria for response at the end of the initial treatment phase were followed during treatment for the next six months.

Response rates were 55.4% in the ketamine group and 41.2% in the ECT group (difference, 14.2%; 95% confidence interval [CI], 3.9 to 24.2; Farrington–Manning score statistic, 4.64; $P<0.001$ for the noninferiority of ketamine to ECT). Looking at the QIDS-SR-16, 32.3% of the ketamine group experienced remission, compared to 20% of the ECT group. The MADRS similarly showed remission rates of 37.9% and 21.8% for ketamine and ECT, respectively. The ketamine group experienced a lesser burden of cognitive side effects, demonstrated by lower GSE-My scores in the ECT group (3.2 ± 0.1 vs. 4.2 ± 0.1; difference, 1.1 points; 95% CI, 0.9 to 1.2) fewer patient reports or cognitive concerns on the SMCQ (mean between-group difference 9.0, 95% CI 5.1 to 13.0), and a greater decrease in T-score on the delayed-recall part of the HVLT-R in the ECT group compared to the ketamine group (-9.7 ± 1.2 vs. -0.9 ± 1.1; difference, 8.8 points; 95% CI 5.7 to 11.9). It is important to note that during the initial treatment phase, the average seizure duration during ECT treatment was potentially inadequate compared to the broader literature. Regarding other adverse events, dissociation occurred more frequently in the ketamine group, while muscle pain and/or weakness occurred more in the ECT group.

Impact: Immediately after the initial treatment phase, both ketamine and ECT resulted in an improved quality of life. Interestingly, this trial differs from others in that ketamine was noninferior to ECT in terms of response and remission. This trial does show response and remission rates for ECT that appear to be lower than what might be expected based on the broader literature. This may be related to the ECT protocol chosen for the initial treatment phase in conjunction with continuation treatment pursued only in those who demonstrate an initial response, and the conversion to bilateral ECT early in treatment likely contributed to the high burden of adverse cognitive effects observed. Nonetheless, the large sample size of the trial, combined with the favorable outcomes and side effect profile of ketamine, are all highly encouraging for the ongoing use of IV ketamine as a tool for TRD. Future work examining the inpatient setting, older populations, psychotic depression, and bipolar depression would greatly benefit our understanding of IV ketamine's utility. Obstacles to larger-scale implementation of IV ketamine treatments such as logistics, cost, and insurance coverage remain to be overcome as well.

Anand, A., Mathew, S. J., Sanacora, G., Murrough, J. W., Goes, F. S., Altinay, M., Aloysi, A. S., Asghar-Ali, A. A., Barnett, B. S., Chang, L. C., Collins, K. A., Costi, S., Iqbal, S., Jha, M. K., Krishnan, K., Malone, D. A., Nikayin, S., Nissen, S. E., Ostroff, R. B., … Hu, B. (2023). Ketamine versus ECT for Nonpsychotic TreatmentResistant Major Depression. The New England Journal of Medicine. https://doi.org/10.1056/NEJMoa2302399

Combined tDCS and Virtual Reality Reduces PTSD Symptoms

Harinee Maiyuran, MD reviewing Wout-Frank et al. JAMA Psychiatry 2024 Mar 6

In this double-blind, randomized clinical trial, US military veterans with a diagnosis of PTSD received active or sham tDCS treatment during virtual reality (VR) exposure therapy. Active tDCS facilitated habituation to VR and greater improvement in PTSD symptom severity when compared to sham tDCS.

Posttraumatic stress disorder (PTSD) is characterized by intrusive memories, avoidance of reminders, heightened arousal, and cognitive disturbances. It is prevalent among veterans and is often accompanied by other medical and psychiatric issues, substance abuse, and increased suicide risk. Conventional treatments, such as trauma focused cognitive behavioral therapies and selective serotonin reuptake inhibitors fall short, with high dropout rates due to the distressing nature of exposure therapy and only moderate efficacy of medications.

A hypothesis for PTSD's persistence involves impaired fear extinction and retention due to dysfunctional top-down regulation of the amygdala by the ventromedial prefrontal cortex (VMPFC). This dysfunction hinders the learning and recall of safety cues. Transcranial direct current stimulation (tDCS) is currently being explored in the treatment of PTSD, wherein treatment is hypothesized to facilitate safe memory formation and accelerate fear extinction. In the approach used in this study, tDCS was combined with VR exposure therapy. VR provides an immersive, controllable environment for exposure therapy, which can help patients confront and process trauma-related cues more effectively. An initial pilot study showed that combining tDCS with VR led to significant reductions in PTSD symptoms, encouraging further investigation. Could tDCSaugmented VR improve PTSD severity, physiological arousal, and overall functioning?

This study was conducted within the VA Providence Healthcare System, followed the CONSORT guidelines (Consolidated Standards of Reporting Trials). Patients were recruited from April 2018 through May 2023, with 65 participants consented and 54 ultimately included age 18-65. Most pertinent inclusion criteria were chronic PTSD secondary to trauma in warzones, measured by the DSM5. A parallel-group, double-blind design was used, with up to six sessions over ten business days. Active tDCS involved 2mA of electrical stimulation for 25 minutes, while the sham condition provided minimal stimulation. The VR used replicates environments with sensory inputs related to deployment to Iraq or Afghanistan, over 12 VR events. Primary outcomes included the PTSD checklist (PCL-5) and quality of life, assessed at baseline, midpoint (after 3 sessions), end of treatment, and at both 1- and 3- month follow-up. Secondary outcomes included measures of depressive symptoms, clinician assessed PTSD severity, and social and occupational functioning. Skin conductance was also measured to evaluate psychophysiological arousal. The active tDCS plus VR group showed significant reductions in PTSD symptoms over time, with more than a 10-point reduction in symptom severity on the PTSD Checklist for DSM-5 (PCL-5) after three sessions and continuing to one-month post-treatment. The effect size was large at the one-month follow-up but not statistically significant at three months. Depressive symptoms improved in both groups without significant differences between them. Quality of life and social/occupational function improved significantly in the active tDCS group compared to the sham group. Psychophysiological measures indicated greater habituation to VR events in the active tDCS group, with significant reductions in skin conductance reactivity across sessions.

Impact: This study found that combining tDCS with VR therapy for PTSD was more effective than VR therapy alone. Active tDCS facilitated habituation to VR cues, potentially mediating the noted improvements in PTSD symptoms, although depression severity did not improve significantly. Social and occupational functioning improved more notably at the three-month follow-up. Additionally, tDCS+VR was cost effective and thus easy to implement. Several limitations were noted, including high attrition rates during follow-up, the impact of the COVID-19 pandemic on recruitment, and participants' continuation of their prior treatments. VR scenarios were also not individualized to participants. The findings suggest that a brief course of tDCS combined with VR could be beneficial and warrant further research with longer follow-up periods and potentially more personalized VR experiences.

Walther S, Danai Alexaki, Weiss F, et al. Psychomotor Slowing in Psychosis and Inhibitory Repetitive Transcranial Magnetic Stimulation. JAMA psychiatry. Published online February 28, 2024. doi: https://doi.org/10.1001/jamapsychiatry.2024.0026

Electrical Stimulation Aided by Use of Machine Learning Classifiers May Improve Memory Recall in Patients with Traumatic Brain Injury

Lara Tang reviewing Kahana M et al. Brain Stimulation 2023 July 1

This study examined using closed-loop electrical stimulation via implanted intracranial electrodes to aid memory recall in patients with refractory epilepsy and moderate-to-severe traumatic brain injury (TBI). Using machine learning classifiers to predict memory lapses and trigger electrical stimulation of the lateral temporal cortex, the authors found a 19% improvement in memory recall compared to when stimulation was off.

Patients with a history of moderate-to-severe TBI often experience cognitive impairments. Currently, memory training is the primary method of cognitive rehabilitation for these patients, though its efficacy is limited. Closed-loop electrical stimulation, a form of neuromodulation involving the implantation of electrodes in the cortex to detect signals and stimulate in response, has been effectively used to treat patients with refractory epilepsy by identifying areas of neural dysfunction for surgical resection. Its ability to augment cognition with temporal stimulation is an area of great interest in those who receive these implants, and the authors of this study sought to answer if this form of invasive neuromodulation could be used to improve memory impairment in patients with TBI.

Eight participants (seven male, one female, mean age 44.5 ± 11 years) with refractory epilepsy, a history of moderate-to-severe TBI, and who were undergoing seizure monitoring and lesion localization using implanted intracranial electrodes were recruited for this study. All participants performed delayed verbal free recall tasks in which they were asked to encode and recall several lists, each consisting of twelve words. Participants performed these tasks blinded to which portions of a session did (Stim) and did not have stimulation (record-only) to areas within the lateral temporal cortex applied. Behavioral data (e.g., vocalizations) and EEG data collected during initial record-only sessions were used to train a machine learning model to identify participant-specific classifiers (primarily based on neuronal activity) of memory recall success and failure. Then, when the model's classifiers predicted a low probability of recall during the encoding phases of the Stim portions of sessions, 200Hz stimulation with a current density of 0.081-0.099 mA/mm2 (depending on geometry) was applied to the target areas within the lateral temporal cortex for 500 ms. The primary outcome examined between stimulation conditions was recall rate (proportion of total words in the list recalled), which was first normalized based on the average recall rate during record-only sessions. Differences were tested using t-tests comparing recall rates during the stimulation portions to the record-only portions of each session. Hierarchical linear mixed effects model and likelihood-ratio chi-squared tests were used to account for the effect of list position within each session, word position within each list, and stimulation of additional sites patients may have received for other clinical purposes.

Comparing recall rates between stim and record-only, a 19% improvement in recall rates (25.2% stim vs. 21.1% record-only, t=3.36, p=0.012, d=1.18) was observed across the eight participants. In addition to memory improvements at the overall list level, there was a 17.5% improvement in recall at the individual item level for those on lists in the stim condition. Hierarchical models indicated stimulation benefits were specific to the lateral temporal site and occurred for all stim condition lists, regardless of the position within the session or the word order within the list. On an individual level, seven of the eight participants exhibited improved memory on stimulation lists compared to record-only lists.

Impact: This study demonstrated that neuromodulation may be effective in improving memory recall in epileptic patients with a history of TBI. Although this study is limited by its small sample size and narrow outcomes assessments, and chronic implantation of intracranial electrodes is currently primarily limited to the treatment of epilepsy and some neurodegenerative disorders, this research provides support for further development in the use of neuromodulation in patients with acquired brain injuries.

Kahana MJ, Ezzyat Y, Wanda PA, et al. Biomarker-guided neuromodulation aids memory in traumatic brain injury. Brain Stimul. 2023;16(4):1086-1093. doi:10.1016/j.brs.2023.07.002

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)

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