JULY 2023 / ISSUE 29

PULSE

A Monthly Update on Advances in Neuromodulation

Produced by the Neuromodulation Division of the Semel Institute for Neuroscience and Human Behavior, Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA

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A Special Message to Start the Academic Year

This issue we are delighted to announce that Ms. Danielle Hight will be joining our editorial team as an Editorial Assistant. Ms. Hight is a 4th-year Psychobiology student at UCLA, a volunteer with the UCLA Semel Institute Neuromodulation Division, and a review editor for the AI Ethics Journal, an open-access peer-reviewed journal published by the AI Robotics Ethics Society (AIRES) with a focus on the intersection between AI, philosophy, and humanity. We are pleased to bring her editorial skills to PULSE!

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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

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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, open-label, 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 Self-Evaluation 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 Treatment-Resistant Major Depression. The New England Journal of Medicine. https://doi.org/10.1056/NEJMoa2302399

Accelerated rTMS Found to Act Faster than Intranasal Esketamine in Treatment-Resistant Depression

Jo Huang reviewing Pettorruso et al. Brain Stimul 2023 Jun

This multicenter, observational, retrospective study showed that accelerated repetitive transcranial magnetic stimulation (rTMS) appears to have more rapid onset of antidepressant action, greater tolerability, and comparable efficacy compared to intranasal esketamine for use in TRD.

When it comes to the treatment of TRD, rTMS is becoming a more frequently-utilized tool. Interest in accelerating the effects and easing the logistics of a course of rTMS has led to the development of accelerated rTMS (arTMS) protocols, which entail multiple treatment sessions per day over the course of several days, rather than a single daily session spread across nearly two months. These arTMS protocols appear to have comparable efficacy, safety, and tolerability as standard rTMS regimen. Intranasal esketamine (ESK-NS) is another treatment often utilized in similar circumstances; it also has rapid-onset effects and is typically administered two to three times weekly during index treatment. To date, these two treatment protocols have not been directly compared.

This three-site, observational, retrospective study compared arTMS with twice-weekly ESK-NS in terms of effectiveness, onset of action, safety, and tolerability. 59 patients with TRD (32 women, 27 men, mean age 54.61 ± 11.32, 30 arTMS, 29 ESK-NS) who underwent treatment with arTMS or ESK-NS were assessed at baseline (T0), one month (T1), and three months (T2) after starting treatment. The arTMS protocol consisted of 4 daily sessions of 3000 pulses of 10 Hz stimulation at 120% motor threshold (MT) to the left dorsolateral prefrontal cortex (LDLPFC) for a total of 60000 pulses in five days. The ESK-NS protocol followed FDA and European Medicines Agency (EMA) dosing guidelines (between 28 mg and 84 mg per dose) and was administered twice weekly for the first month, once weekly for the second month, and every other week for the third month. Efficacy outcomes were primarily assessed by examining changes in MADRS score from T0 to T1 and T2. Response and remission rates were assessed, as were incidence rates of adverse effects.

At baseline, MADRS scores did not differ between the two groups ($p = 0.307$), although the arTMS group had a longer average duration of current episode than the ESK-NS group (months, 19.57 vs 12.03). Both groups showed a significant decrease of MADRS at T1 (arTMS: $d = 1.709$; ESK-NS: $d = 1.361$, both $p < 0.001$), with a significantly greater reduction in the arTMS group ($p = 0.048$) and a greater response rate (though not remission) in the arTMS group (50% vs. 17.2%, $p=0.008$). At T2, both groups again showed significant MADRS reduction as compared to both T0 and ESK-NS showed significant reduction compared to T1 (arTMS T0 vs. T2: $p < 0.001$, $d = 1.822$; arTMS T1 vs. T2: $p = 0.989$, $d = 0.218$; ESK-NS T0 vs. T2: $p < 0.001$, $d = 2.338$; ESK-NS T1 vs. T2: $p < 0.001$, $d = 1.042$). There were no significant inter-group differences in score reduction or response and remission rates at T2. Indeed, a repeated measures ANCOVA further supported this finding with a significant time-by-protocol interaction effect ($F=3.81$, $p = 0.025$) on MADRS score. Regarding adverse effects, eight patients (26.66%) and 24 patients (82.75%) from the arTMS and ES-NS groups reported side effects, respectively, but no statistical testing of side effect incidence was performed. The most frequent arTMS side effects were transient post-stimulation headache and scalp discomfort at stimulation site, and the most prevalent side effects of ESK-NS were temporary sedation, transient dissociation, transient hypertension, and transient agitation. Neither treatment induced significant adverse events.

Impact: This study showed comparable efficacy of arTMS with ESK-NS in treating TRD in a small-moderate observational sample, with arTMS demonstrating more rapid antidepressant action and a smaller side effect burden without need for the continuation treatment used in the ESK-NS group. The results further establish arTMS as a promising treatment for TRD, warranting future work focused on prospective blinded studies and durability of effects.

Pettorruso M, d'Andrea G, Di Carlo F, De Risio L, Zoratto F, Miuli A, Benatti B, Vismara M, Pompili E, Nicolò G, Niolu C, Siracusano A, Sensi SS, Dell'Osso B, Di Lorenzo G, Martinotti G; ReModula Study Group. Comparing fast-acting interventions for treatment-resistant depression: An explorative study of accelerated HF-rTMS versus intranasal esketamine. Brain Stimul. 2023 Jun 17;16(4):1041-1043. doi: 10.1016/j.brs.2023.06.003. Epub ahead of print. PMID: 37331507.

From the Archives: ECT Is More Effective than rTMS for Treating Psychotic Depression and Equivalent for Non-Psychotic Depression

Lara Tang reviewing Ren et al. Progress in Neuro-Psychopharmacology & Biological Psychiatry 2014 February 18

This systematic review and meta-analysis of 10 studies comparing the efficacy of ECT and TMS is one of the cornerstone publications on the issue. It demonstrates (1) that, while ECT seems more efficacious overall than TMS for TRD, this is potentially mediated by an efficacy gap in psychotic depression and (2) that the modalities appear equivalent in non-psychotic depression.

As previously discussed in Pulse, ECT and rTMS are effective modalities for treating TRD. For many years, ECT was one of the only treatments available for TRD, and it remains in use to this day

because of its high success rate. Although ECT is a relatively low-risk procedure, patients who cannot tolerate anesthesia, seizure induction, or adverse effects on cognitive effects may not be good candidates for this treatment. For such individuals, rTMS is an enticing alternative. This meta-analysis compares the long-term efficacy of these two interventions using treatment response and remission on the observer-rated HAM-D as their primary outcomes, as well as cognitive function and self-rated mood improvements as secondary outcomes.

Ten papers of nine randomized controlled trials comparing the efficacy of ECT and rTMS were ultimately included in this systematic review and meta-analysis of 429 patients with a major depressive episode (including unipolar and bipolar as well as with and without psychotic features). In total, 212 patients were randomized to ECT (mean age 49.8 ± 12.6, 61.8% female; 94.8% unipolar and 5.2% bipolar; 15.6% psychotic depression), and 217 patients (mean age 47.6 ± 12.4, 57.1% female; 93.1% unipolar and 6.9% bipolar; 15.2% psychotic depression) were randomized to rTMS. Data extracted from each study included response to the intervention, defined as having a 50% or more reduction in HAMD scores after the intervention. Remission was also measured using HAMD-based remission criteria specific to each trial.

Cognitive function was characterized based on the individual study, while mental state changes were reported using the Beck Depression Inventory, Brief Psychiatry Rating Scale, and HAMD scores as continuous metrics. Meta-analyses used RevMan 5.2.0 developed by Cochrane Collaboration, while chi-squared tests and I2 were used to analyze the heterogeneity across studies.

Clinical response rates were greater for ECT than both high frequency (HF, i.e., 10 Hz) rTMS and low frequency (LF, i.e., 1 Hz) rTMS. The pooled risk ratio of response for ECT compared to HF rTMS (64.4% vs. 48.7% response, respectively) was 1.41 (95% CI = 1.04-1.90, p=0.03) and to LF rTMS (56.7% and 20.0% response, respectively) was 1.85 (95% CI = 1.18-2.89, p=0.007). The pooled risk ratio of remission for ECT compared to HF rTMS was 1.38 (95% CI = 1.10-1.74, p=0.006), and to LF rTMS was 1.57 (95% CI = 1.01-2.44, p=0.04). The combined remission rate for both rTMS protocols was lower than the ECT group at 32.2% and 53.0%, respectively. Notably, response rates were greater for the ECT group than the HF rTMS group in the presence of psychosis (66.7% and 33.%, respectively) and not statistically different in non-psychotic depression (51.4% and 52.5%, respectively). Examining outcomes as continuous rather than categorical, there was no significant difference in continuous measures of the HAMD between HF rTMS and ECT (mean point difference 2.15 [95% CI = -0.50–4.81, p = 0.11]). However, LF rTMS proved to be significantly more effective than ECT (mean point difference 5.5 [95%CI = 2.64-8.36, p=0.0002]). Performing similar analyses for the BDI and Brief Psychiatric Rating Scale (BPRS), ECT proved to be more effective in improving self-reported mood compared to HF rTMS (BDI: 95% CI = 5.02-15.79, p=0.0002; BPRS: 95% CI = 0.08-5.24, p=0.04), though none compared these continuous outcomes between LF rTMS and ECT. Individuals in the ECT group performed significantly worse on multiple cognitive metrics (related to verbal fluency and delayed recall) compared to individuals in the rTMS group, though all-cause dropout was not significantly different between groups, indicating similar acceptability.

Impact: This meta-analysis demonstrates that, while ECT tends to be superior to rTMS for the treatment of TRD at an aggregate level, this benefit becomes less clear when delineating along psychotic and non-psychotic subtypes and when examining rating scales as continuous rather than categorical. This further supports the notion that rTMS may be an acceptable alternative to ECT in TRD though primarily for those without psychotic features.

Ren, J., Li, H., Palaniyappan, L., Liu, H., Wang, J., Li, C., & Rossini, P. M. (2014). Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: A systematic review and meta-analysis. In Progress in Neuro-Psychopharmacology and Biological Psychiatry (Vol. 51, pp. 181–189). Elsevier Inc. https://doi.org/10.1016/j.pnpbp.2014.02.004

From the Archives: Ketamine as Anesthesia in ECT for Depression May Accelerate Response

Michael K. Leuchter, MD, reviewing Ren et al Journal of Psychiatry Research July 2018

This systematic review and meta-analysis of 16 individual studies examines the effects of ketamine during ECT for TRD and found that while it does not appear to increase response or remission rates resulting from treatment, it seems to accelerate antidepressant response when used as an add-on anesthetic.

ECT remains a tried-and-true treatment for TRD, with robust response rates (generally at least 60%). However, when it was initially developed, it came with a significant side effect burden,

including fractures, cardiovascular effects, and confusion. General anesthesia was implemented as a measure to reduce much of this burden with good effect, and, as such, is now standard practice. Ketamine, one of many anesthetic agents used in ECT, has more recently garnered attention for its independent antidepressant effects. As a result, many have hypothesized that combining ECT with ketamine as the anesthetic agent might result in a synergistic antidepressant effect. The authors of this meta-analysis sought to consolidate the literature on the matter and characterize the impact of ketamine as an anesthetic agent on ECT for depression. The primary outcome assessed was symptom rating scale score reduction as measured by HDRS, MADRS, and/or BDI (based on availability in the study). Secondary outcomes included response and remission rates, as well as incidence rates of adverse events.

The authors identified 16 trials that included 928 patients comparing 12 treatments of ECT with ketamine vs. another anesthetic agent or ketamine plus another agent vs. an agent besides ketamine; the demographics of the aggregate sample were not discussed, though study sample sizes ranged from 16 to 160 and generally included more female than male patients.

Five studies included both unipolar and bipolar depression, and three studies examined exclusively TRD. Ketamine served as an add-on anesthetic in seven studies, was the sole anesthetic in six, and was used as either a solo and/or add-on in three. Of the 16, 14 were used in the initial systematic analysis (852 patients), which found no significant reduction in mean scale score when ketamine was used (standardized mean difference [SMD]=-0.17, 95%CI=-0.39-0.06, p=0.14). This lack of a significant reduction was maintained when restricting to high-quality trials, reliable trials, or larger trials (SMD=-0.12 to -0.17, p=0.23 to 0.49). No significant inter-group differences were observed with response or remission rates. When ketamine was examined as the sole anesthetic during ECT, it was found to have significant and potentially robust antidepressant effects on the 1st ECT session (SMD=−0.85, 95% CI, −1.63 to −0.08, p=0.03) though not any later sessions. Interestingly, when examined as an add-on, it was found not to have effects on the 1st session but did accelerate antidepressant effects until session 6 (SMD=-0.29 to -0.37, p<0.0001 to p=0.008). This impact on symptom reduction following treatment sessions was not present for later sessions. Though adverse events were not statistically assessed, the authors did note that those who received ketamine experienced higher incidence of nausea/vomiting, disorientation, fatigue, headache, sense of fear, transient hypertension, infection, and musculoskeletal pain compared to those who did not receive ketamine. Of the 11 studies that assessed cognition, three found ketamine was associated with fewer cognitive effects than the non-ketamine group, seven found no association between ketamine during ECT and cognitive side effects, and one found verbal fluency was more impaired with ketamine.

Impact: This meta-analysis demonstrates that, while using IV ketamine as an anesthetic agent during ECT may not enhance overall response or remission rates, it certainly has the potential to accelerate response to treatment, which is particularly relevant to the inpatient setting. That said, this analysis is limited by the sample sizes of the underlying studies, and this response acceleration did appear to come with a greater side effect burden. Nevertheless, it is important to keep ketamine in mind as a tool to accelerate treatment response to ECT for depression.

Ren, L., Deng, J., Min, S., Peng, L., & Chen, Q. (2018). Ketamine in electroconvulsive therapy for depressive disorder: A systematic review and meta-analysis. In Journal of Psychiatric Research (Vol. 104, pp. 144–156). Elsevier Ltd. https://doi.org/10.1016/j.jpsychires.2018.07.003

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)
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)
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)