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PULSE

A Monthly Update on Advances in Neuromodulation

Baseline levels of Glutamate, Glutamine, and N-acetyl aspartate may predict the outcomes of repetitive transcranial magnetic stimulation in patients with major depressive disorder.

Miguel Serrano-Illan, MD, PhD, reviewing Gonsalves et al. Transl Psychiatry 2024 Jan 6

This prospective study utilized proton magnetic resonance spectroscopy to examine the predictive role of glutamate (Glu), glutamine (Gln), and total N-acetyl aspartate (tNAA) on treatment outcomes of repetitive transcranial magnetic stimulation (tTMS) in major depressive disorder (MDD) patients.

Repetitive transcranial stimulation (rTMS) to the left dorsolateral prefrontal cortex (DLPFC) is an established treatment for Major Depressive Disorder (MDD). Predicting response to rTMS is crucial for

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optimizing treatment efficacy and resource allocation, guiding further treatment towards suitable alternatives when necessary. Biomarkers linked to depression have been posited as a potential way to examine and predict rTMS treatment response. In this prospective study, the author analyzed how changes in relevant metabolites may impact rTMS treatment response in a small cohort of MDD patients.

A cohort of 25 participants (14 female; mean age 38±14.57 years) with a primary diagnosis of MDD and a history of resistance or intolerance to standard antidepressant treatment underwent a 6-week course of daily (5x/week) rTMS, followed by a 3-week taper of 2 sessions per week. The study utilized proton magnetic resonance spectroscopy to measure Glu, Gln, and tNAA levels in the right dorsal anterior cingulate cortex before 10 Hz rTMS treatment to the left DLPFC. MDD severity and symptoms were assessed using the

Inventory of Depression Symptomatology Self-Report (IDS-SR) to evaluate treatment response, defined as a >50% change in IDS-SR scores post-treatment. Generalized linear and logistic regression models were applied to analyze the relationship between metabolites and treatment outcomes while controlling for age and sex, though not ethnicity, highlighting one limitation of this study as the homogeneity of the sample (96% Caucasian).

Overall, IDS-SR scores were classified as "severe" at baseline (Mean=43.20; SD=6.22), decreasing by 46.35% at the end of the study. Thirteen participants were identified as treatment responders (averaging 72.23% improvement in symptoms), while 12 were categorized as non-responders (average improvement of 18.32%) based on the criteria, previously described. Participants with a lower baseline level of glutamate (average of 8.24 institutional units in the responder group vs. 9.33 in the non-responder group) and glycine exhibited

greater improvement in mood and cognition symptoms post-rTMS treatment (p<0.001). Similarly, individuals with lower tNAA levels (6.95 in responders vs 11.71 in non-responders) exhibited substantial and statistically significant improvement (p=0.007), suggesting a role for these metabolites in predicting treatment response.

Impact: This study provides valuable insights into the potential use of neurochemical markers to enhance treatment efficacy in MDD, supporting a personalized medicine approach in rTMS therapy selection. Further research is warranted to explore the reproducibility and reliability of metabolic biomarkers to predict rTMS treatment response for TRD as well as to better understand the biochemical underpinnings of the findings.

Gonsalves, M. A., White, T. L., Barredo, J., DeMayo, M. M., DeLuca, E., Harris, A. D., & Carpenter, L. L. (2024). Cortical glutamate, Glx, and total N-acetylaspartate: potential biomarkers of repetitive transcranial magnetic stimulation treatment response and outcomes in major depression. Translational psychiatry, 14(1), 5. https://doi.org/10.1038/s41398-023-02715-9

rTMS and Aripiprazole Augmentation Likely More Effective Than Switching in Antidepressant Nonresponders

Michael K. Leuchter, MD, reviewing Papakostas et al. Molecular Psychiatry 2024 Jan.

In this multi-site open-label randomized trial, 278 participants who failed to respond to antidepressant treatment for MDD were randomized to receive aripiprazole augmentation, rTMS augmentation, or switch to an SNRI. Both rTMS and aripiprazole augmentation demonstrated greater improvement on self-rated scales, while rTMS alone demonstrated greater improvement on the MADRS clinician rating scale. The three arms demonstrated no significant differences in overall response and remission rates, though trends suggest rTMS may confer additional benefit.

All psychiatric providers develop their own set of treatment "algorithms" for depression. Refined over the years, the idea of the "best," next step in treatment after a medication failure is a hotly debated issue. Despite its widespread use, rTMS is quite young compared to ECT, lacking clarity as to where it falls within this algorithm. Furthermore, compounding factors

such as insurance coverage, accessibility, training, and patient beliefs are also at play. Therefore, it is important to do our best to scientifically ask the clinical question of "when should I prescribe rTMS instead of another medication?" The authors here add an important contribution toward answering that question.

This open-label eight-week multi-site trial randomized 278 participants (mean age 45.6 ± 15.3, 74.3% white, 70.5% female, n=235 completed, goal enrollment n=639) who failed at least two antidepressants in their current MDE (mean # failed adequate trials 2.85 ±1.0) in a 1:1:1 fashion to either aripiprazole augmentation

(n=92 randomized, n=83 completed), switch to venlafaxine or duloxetine (n=98 randomized, n=91 completed), or augmentation with rTMS (n=70 randomized, n=61 completed). Participants completed a self-rated depression questionnaire (SDQ) and were rated on the MADRS at baseline and weeks 1, 2, 3, 4, 6, and 8 by a blinded rater. The primary outcome examined was change in MADRS score from baseline to week 8. Of note, proper statistical correction required a threshold of p=0.025 in this study. For MADRS and SDQ point changes, mixed-effects repeated measures models were used, while logistic regression was used for the categorical outcomes of response and remission rates. It is crucial to note the analyses only compared aripiprazole or rTMS augmentation to switching to a SNRI; this study did not statistically compare rTMS and aripiprazole augmentation to each other.

On the primary outcome of change in MADRS score, the treatment group demonstrated a roughly 13 point reduction (though the precise stated reduction varied during different analyses for unclear reasons), the aripiprazole group a roughly 14.9-point reduction (group-by-treatment effect vs. switch p=0.708), and the rTMS group a 17.4-point reduction (group-by-treatment effect vs. switch p=0.015). However, group assignment alone did not demonstrate differences in MADRS score. On the SDQ, differences were seen based on group assignment favoring augmentation over switch (aripiprazole vs switch p=0.003, rTMS vs switch p=0.031), but no differences in group-by-treatment were observed (aripiprazole vs switch p=0.17, rTMS vs switch p=0.832). MADRS response and remission rates did not differ between aripiprazole vs switch or rTMS vs switch, though rTMS demonstrated a potential benefit with number needed to treat of 7 and p=0.038.

Impact: This open-label study, designed to compare two augmentation strategies to switching antidepressant agents, indicates that rTMS appears superior to switching to a SNRI as a third antidepressant agent, and aripiprazole may demonstrate this superiority as well. While this is valuable information, it is important to note the open-label nature of treatment in this study, the lack of comparison between augmentation strategies, the short eight-week duration (limiting the full efficacy of switching), and the falling short of recruitment goals (underpowering the study for its goals). Nonetheless, this study provides valuable information, and future work comparing multiple augmentation strategies in a larger randomized study would be a significant contribution to the field.

Papakostas GI, Trivedi MH, Shelton RC, et al. Comparative effectiveness research trial for antidepressant incomplete and non-responders with treatment resistant depression (ASCERTAIN-TRD) a randomized clinical trial. Mol Psychiatry. Published online March 7, 2024. doi:10.1038/s41380-024-02468-x

Peripheral Magnetic Stimulation Shows Promising Evidence for Neuropathic Pain Treatment

Angela Broida, PhD, LCSW, reviewing Dana et al., Pain Practice 2023 Dec.

In this systematic review and meta-analysis, authors highlight the limited yet promising evidence supporting the use of peripheral magnetic stimulation (PMS) for neuropathic pain. Given the lack of accessible, safe and effective treatment options for individuals suffering from neuropathic pain, the need for further advancements in neuromodulatory interventions is great. Overall, PMS may be a viable option for further treatment, requiring further exploration in both quality and quantity.

Chronic pain, particularly neuropathic pain conditions, remains a significant challenge in clinical practice. With few treatment options, and even fewer with significant efficacy and tolerability, neuromodulation offers increasing promise. PMS confers apparent analgesia via low-intensity magnetic stimulation of peripheral nerves in a convenient, in-home treatment approach, reducing the economic and physical burden of many pain treatments.

This systematic review and meta-analysis followed PRISMA guidelines and involved a comprehensive database search including MEDLINE, EMBASE, Cochrane CENTRAL, CINHAL, Web of Science and ProQuest up to July 2023. The review included studies on adults with chronic peripheral neuropathic pain treated with PMS, encompassing study designs such as RCTs, observational studies and case reports. Four reviewers independently screened and selected studies with consults resolved through discussion or senior author adjudication. Pain outcomes were analyzed both qualitatively and quantitatively, with a meta-analysis performed using a random effects model for studies reporting data at various time intervals. Statistical analyses included the Mantel-Haenszel method for dichotomous data and heterogeneity assessment. In this comprehensive review, 13 studies

met criteria for inclusion, comprising 15 RCTs, 5 case series, 2 case reports, and 1 non-randomized trial assessing the effectiveness of PMS for neuropathic pain. The included studies covered various neuropathic conditions and were conducted across several countries, devices, and treatment protocols. PMS devices varied from round, racetrack, or figure-of-eight coils, diamagnetic pumps, magnetic mattresses, and wearable devices. PMS treatment protocols showed a range in magnetic field intensity (0.1 to 1500 mT), frequency (1Hz to 1MHz), duration (5 min to 240 min), and treatment course (1 day to 1 year). Seven RCTs showed high risk of bias, particularly due to the lack of a sham arm, and the overall quality of all trials was deemed to be low. Significant reductions in pain were observed in some conditions, with variable results. Notably, PMS was shown to decrease pain in diabetic peripheral neuropathy and carpal tunnel syndrome, although there still was inconsistent efficacy across studies and with other conditions. Given mixed outcomes and methodological limitations, further research is needed to better address the efficacy of PMS in treating neuropathic pain.

Impact: This systematic review underscores the potential impact of PMS on the field of pain management, and more specifically clinical care contexts where treatments are often limited and accompanied by undesirable side effects. By evaluating the effectiveness of PMS across pain conditions, the study addressed some gaps in pain treatment accessibility and efficacy. Findings suggest that PMS can offer a non-invasive, low-risk alternative to traditional therapies and potentially on the reliance on medication wrought with treatment-limiting side effects. Despite some trials showing no significant difference compared to sham, notable improvements in pain and functional outcomes in others indicate PMS may be a promising pain management strategy with the potential to improve quality of life for many.

Dana E, Tran C, Osokin E, Westwood D, Moayedi M, Sabhaya P, et al. Peripheral magnetic stimulation for chronic peripheral neuropathic pain: A systematic review and meta-analysis. Pain Pract. 2024; 24: 647–658. https://doi.org/10.1111/papr.13332

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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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