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PULSE

A Monthly Update on Advances in Neuromodulation

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Large Naturalistic Registry Study Demonstrates High Efficacy of TMS for MDD

Collin M. Price, MD reviewing Sackheim et al., J Affect Disorder 2020 Dec 1

This large-scale registry-based study in primarily community settings using TMS for MDD demonstrated greater antidepressant effects than earlier clinical trials, with better results in women and those who received a larger number of pulses.

Since the first clinical trials using transcranial magnetic stimulation (TMS) to treat major depressive disorder (MDD) began two decades ago, TMS has grown into a major subfield in psychiatry. Although most medical interventions demonstrate superior outcomes in clinical trials compared to community settings, the authors of this study asked whether a large community sample of patients receiving TMS for MDD would show similar efficacy to prior clinical trials.

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Data was collected from the NeuroStar Advanced Therapy System Clinical Outcomes Registry, which had deidentified patient data from 103 sites (97% private practice) using the NeuroStar TMS Therapy System, with 95% of patients treated between May, 2016 and October, 2019. An intention to treat (ITT) sample of 5,010 patients was generated by selecting adult patients with a primary diagnosis of MDD, no comorbidity other than an anxiety disorder, a baseline PHQ-9 ≥ 10, and at least one PHQ-9 score after the start of treatment. Researchers selected for the acute phase of treatment by including data from the first treatment until a period of at least 7 days without treatment. A subset of the ITT sample, Completers, was generated by excluding patients who were PHQ-9 non-responders and received fewer than 20 TMS sessions, or who did not have a PHQ-9 score from within ± 4 days of the final acute-phase treatment. All patients received at least one course of 10 Hz rTMS to the left DLPFC. Primary outcomes were response (≥50% improvement) and remission (score ≤4) on the PHQ-9, while Clinical Global Impression – Severity (CGI-S) scores were analyzed for a subset of patients.

The population was comprised of roughly 66% women, with an average age of 50 years. Response rates for the PHQ-9 ranged from 58-61% in the ITT sample, and 65-69% in the Completers sample, while remission rates ranged from 28-31% and 32-36%, respectively. Response and remission rates were consistently higher using the CGI-S, ranging from 69-79% and 47-58% in the ITT sample and 75-83% and 53-62% in the Completers sample. Female gender and a higher number of pulses were associated with improved outcomes via regression analysis, while higher baseline PHQ-9 and CGI-S scores were associated with worse outcomes. Age and motor threshold level had no consistent association with outcome scores, though the gender difference favoring females was largest among patients 50 years of age and older.

Impact: This registry-based, observational, naturalistic study demonstrated that the real-world efficacy of TMS is as good or greater than what was demonstrated in the original clinical trials. Although open-label and performed in a non-academic population with unclear comorbidities, the large sample size and the fact that most patients likely met criteria for treatment-resistant depression (based on insurance coverage policies) suggests these findings are robust. The authors rightfully call for further studies comparing TMS to medications as a first line option for treatment-naïve patients with depression, given its efficacy and favorable safety profile.

Sackeim HA, Aaronson ST, Carpenter LL, et al. Clinical outcomes in a large registry of patients with major depressive disorder treated with Transcranial Magnetic Stimulation. J Affect Disord. 2020;277:65-74.

Antidepressants Boost Improvements from rTMS in Patients with Severe Enduring Anorexia Nervosa

Shawna Chan, MD reviewing Dalton B et al. J Eat Disord. 2021 Jan 28

In this exploratory post-hoc analysis, concurrent antidepressant treatment during rTMS treatment of severe enduring anorexia nervosa was associated with improvement of eating disorder symptoms but not mood symptoms.

Nearly one-third of patients with anorexia nervosa (AN) have severe, enduring disease. Previous work showed that repetitive transcranial magnetic stimulation (rTMS) to the dorsolateral prefrontal cortex (DLPFC) may lead to small improvements in body-mass index (BMI) and eating disorder (ED) symptoms, as well as moderate-to-large improvements in mood symptoms. Can concomitant use of antidepressant medication enhance the efficacy of rTMS for the treatment of anorexia nervosa?

Investigators analyzed a subset of 26 female patients who underwent real rTMS in a double-blind, randomized, sham-controlled clinical feasibility trial (the TIARA study) evaluating rTMS for treatment of severe enduring anorexia nervosa. Participants received 20 sessions of once daily real or sham high-frequency rTMS to the left DLPFC over 20 consecutive weekdays. Real rTMS was delivered at 10 Hz with goal intensity of 110% motor threshold with 1000 pulses over each 20-minute session. Clinical measures were assessed at baseline, 1-week after completion of treatment, and 4-month follow-up; outcomes included BMI, Eating Disorder Examination Questionnaire (EDE-Q), and Depression Anxiety Stress Scales (DASS-21). Participants were unblinded at the 4-month follow-up assessment, and those who completed sham treatment could elect to receive real rTMS with an identical protocol as above, including repeat baseline, post-treatment, and follow-up clinical assessments.

Sixteen (61.53%) participants had concurrent antidepressant (SSRI, SNRI, MAOi, TCA, bupropion) use while receiving DLPFC-rTMS. At 1-week post-treatment, the rTMS + antidepressant group had slightly greater improvements in ED symptoms (EDE-Q Global d=0.40), while the rTMS alone group had greater improvements in BMI (d=0.22). At

4-month follow-up, the rTMS + antidepressant group had significant improvements in ED symptoms (EDE-Q Global d=1.10) and modest improvements in BMI (d=-0.20) and mood symptoms (DASS-21 Total d=0.13). Of note, participants in the concurrent antidepressant group had more severe ED symptoms at baseline as measured by ED symptom recovery rate (EDE-Q Global Score <1 SD above community mean), with 3/16 (18.75%) participants achieving ED symptom recovery at post-treatment, and 6/15 (40%) at follow-up. Meanwhile, 3/10 (30%) participants in the rTMS alone group were already in ED symptom recovery at baseline, with 1/7 (14.29%) participants achieving ED symptom recovery at post-treatment, and 2/7 (28.57%) participants at follow-up.

Impact: Concurrent antidepressant use with rTMS yielded more robust improvement of core domains of AN pathology compared to rTMS alone, though with minimal improvement of mood symptoms. This finding is particularly striking given that antidepressants are reported to have little effect on ED symptoms. These preliminary results should be interpreted with caution given the exploratory design, small sample size, lack of standardization across dosages and types of antidepressant medications used, and baseline ED-symptom differences between treatment groups.

Dalton B, McClelland J, Bartholdy S, Kekic M, Campbell IC, Schmidt U. A preliminary exploration of the effect of concurrent antidepressant medication on responses to high-frequency repetitive transcranial magnetic stimulation (rTMS) in severe, enduring anorexia nervosa. J Eat Disord. 2021;9(1):16. Published 2021 Jan 28. doi:10.1186/s40337-021-00370-3.

Limitations of Concurrent Mindfulness-Based Cognitive Therapy during TMS Treatment Sessions

Michael K. Leuchter, MD reviewing Cavallero et al. Frontiers in Psychology 2021 Aug 17

In this open-label study, investigators examined the use of concurrent Mindfulness-Based Cognitive Therapy (MBCT) and rTMS treatment for MDD. They found that audio recording-guided MBCT during rTMS sessions was feasible but difficult for patients to tolerate, suggesting that independent or sequential implementation of MBCT and TMS may be better than concurrent implementation.

In the use of repetitive Transcranial Magnetic Stimulation (rTMS) for Major Depressive Disorder (MDD), once the patient is in the chair and the button is pressed, what does the patient do next? Prior work has established that rTMS is more efficacious when patients are also engaged in therapy, and some preliminary work has demonstrated success in combining TMS with exposure therapy for PTSD. Could the use of mindfulness-based audio recordings during rTMS sessions provide an efficient way to take advantage of these therapeutic effects?

Researchers performed an open-label multi-site study of 27 patients starting rTMS for MDD. Patients underwent rTMS with either 10 Hz stimulation to the left dorsolateral prefrontal cortex (DLPFC; n=16) at one study site or 1 Hz stimulation to the right DLPFC followed by 20 Hz stimulation to the left DLPFC (n=11) at the other site. During TMS sessions, patients listened to a series of audio recordings guiding them through Mindfulness-Based Cognitive Therapy (MBCT) exercises. Measures included the Inventory of Depression Symptomatology (IDS-SR), the Patient Health Questionnaire (PHQ9), five other questionnaires examining mindfulness and perceived stress, and a tolerability self-report questionnaire.

Of the 27 patients in the intent-to-treat sample, 10 (37%) withdrew and 17 (63%) completed the study. Reasons for withdrawing included anxiety (n=3) and dislike of the intervention (n=2). Patients completed an average of 35 ± 7.7 TMS treatments, with an average of 18 ± 8.6 sessions including MBCT. Patients reported moderate difficulty (5.4 ± 3.2 on a 0-10 scale, with 10 being the most difficult) meditating during TMS sessions, and 71% of patients reported at least one day during which they did not meditate during their TMS session. Fourteen patients (52%) reported meditating outside of TMS, and 16 (59%) reported an intent to continue meditation after the study. In terms of symptomatic outcomes, patients demonstrated significant improvement in IDS-SR (Pre: 42.4 ± 11.7; Post: 17.42±11.46, $p<0.000001$), PHQ9 (Pre: 17.1 ± 5.8; Post: 5.9 ± 5.2, $p<0.000001$), and all other questionnaire scores (all $p<0.05$).

Impact: This small, open-label study demonstrated the feasibility of concurrent MBCT and rTMS for MDD. Although patients demonstrated significant symptomatic improvement, the authors identified a large number of roadblocks to acceptability, as evidenced by the high dropout rates. Further studies examining a sequential approach or other forms of therapeutic intervention are warranted.

Cavallero F, Gold MC, Tirrell E, et al. Audio-Guided Mindfulness Meditation During Transcranial Magnetic Stimulation Sessions for the Treatment of Major Depressive Disorder: A Pilot Feasibility Study. Front Psychol. 2021;12(August):1-10. doi:10.3389/fpsyg.2021.678911

Focused Ultrasound Capsulotomy as a Potential Treatment for MDD and OCD

Michael K. Leuchter, MD reviewing Davidson B. et al. Molecular Psychiatry 2020 Apr 14

In this pilot study, investigators showed magnetic resonance-guided focused ultrasound (MRgFUS) anterior capsulotomies were effective in the treatment of MDD and OCD, with pre-treatment fMRI predicting response.

Up to a third of those with major depressive disorder (MDD) or obsessive compulsive disorder (OCD) are labeled as treatment-resistant, and patients who do not respond to guideline-based pharmacotherapy or other noninvasive approaches may consider surgical options. Anterior capsulotomy is a well-established neurosurgical procedure for severe cases of MDD and OCD and involves lesion formation in the anterior limb of the internal capsule. Though typically performed using radiofrequency ablation (RFA) or stereotactic radiosurgery/radiation (SRS), these modalities can have significant adverse effects. Magnetic resonance-guided focused ultrasound (MRgFUS) is a novel ablative neurosurgical technique. Is MRgFUS anterior capsulotomy a safe and effective alternative to RFA and SRS?

Investigators performed a prospective open-label pilot study of MRgFUS anterior capsulotomy for treatment-resistant MDD and OCD. Fifty subjects were screened (20 OCD and 30 MDD), with 16 subjects meeting inclusion criteria and ultimately 12 technically successful treatments (6 MDD, 6 OCD). The primary outcome examined was adverse events resulting in hospital admission/readmission or unanticipated treatment. Neuropsychiatric symptoms were also followed using multiple questionnaires and standardized neurological and psychiatric exams up to 1 year after treatment. Neuropsychological tests were performed at baseline, 6 months, and 12 months, while structural MRI, fMRI, and FDG-PET scans were obtained preoperatively and post-operatively on day 1 (MRI only) and at 6 months. After baseline testing, patients underwent anterior capsulotomy guided by a 3T MRI, targeting the most ventral aspect of the bilateral anterior limbs of the internal capsule.

No serious adverse events were reported, while seven nonserious adverse events were reported; the most common were post-procedure headache and scalp swelling at the site of device mounting. Three subjects reported mental slowing after the procedure but demonstrated no objective evidence on neuropsychiatric testing, whereas some patients demonstrated improvement on cognitive testing. No subjects attempted suicide during the trial or follow-up period. Four out of 6 (66%) subjects with OCD met response criteria on the Yale-Brown Obsessive Compulsive Scale (>35% improvement). In those with MDD, 2 out of 6 (33%) met response criteria on the Hamilton Depression Rating Scale (>50% improvement).

Structural MRI with fiber tract analysis verified the presence of the lesions within the anterior capsule, generally targeting fibers connecting the ventromedial/orbitofrontal cortex with the medial-temporal lobes, thalamus, and ventral striatum. Functional MRI data showed that, compared to non-responders, responders had higher connectivity between basal ganglia sites and cortex. These differences in connectivity were no longer observed at 6 months. FDG-PET imaging showed decreased metabolism at 6 months in the bilateral middle temporal gyri, pre/post-central gyri, right middle frontal gyrus, and posterior cingulate.

Impact: This small, open-label study demonstrated the feasibility and safety of MRgFUS anterior capsulotomy in the treatment of intractable MDD and OCD, and noted symptomatic improvement in some patients. Given the severity of disease in this population, these results compare favorably to medications and TMS in the treatment of severe OCD, while response rates may be better with TMS (40-50%) in severe MDD. Future studies directly comparing treatment options in patients with intractable disease are warranted.

Davidson B, Hamani C, Rabin JS, et al. Magnetic resonance-guided focused ultrasound capsulotomy for refractory obsessive compulsive disorder and major depressive disorder: clinical and imaging results from two phase I trials. Mol Psychiatry. 2020;25(9):1946-1957. doi:10.1038/s41380-020-0737-1