MARCH 2021 / ISSUE 1

PULSE

A Monthly Update on Advances in Neuromodulation

WELCOME

Neuromodulation is a rapidly evolving field. New approaches and technologies to treat illnesses of the mind, brain, and nervous system are continually emerging. We understand that it can be difficult for busy clinicians to keep up with the literature in this field. We founded *Pulse* to make new and clinically relevant developments in the field of neuromodulation accessible to you and your practice. This free monthly newsletter will highlight key articles on TMS and other neuromodulation techniques, as well as emerging devices and technologies that offer new hope to those suffering with behavioral health and nervous system disorders. To ensure that you continue to receive this monthly newsletter, please subscribe on our website at neuromodulation.UCLA.edu/newsletter.

Produced by the Neuromodulation Division of the Semel Institute at UCLA
Andrew F Leuchter, MD, Editor-in-Chief
Katharine G Marder, MD, Managing Editor

IN THIS ISSUE:

THE SAINT PROTOCOL: ENHANCING EFFICIENCY AND EFFICACY OF TMS FOR DEPRESSION

Collin Price, MD reviewing Cole EJ et al. Am J Psychiatry 2020 Apr 7

In this open-label trial, 90% of participants achieved response within one week using an accelerated, connectivity-guided, high-dose intermittent theta burst (iTBS) treatment protocol.

Intermittent theta-burst stimulation (iTBS), a form of transcranial magnetic stimulation (TMS) which mimics the firing pattern of hippocampal neurons, has become increasingly attractive as a therapy for treatment-resistant depression (TRD). Since FDA approval of the technique in 2018, several incremental improvements have been developed, including performing multiple sessions per day, delivering higher total pulses, and precision targeting of left dorsolateral prefrontal cortex (DLPFC) subunits based on functional connectivity. Could combining these techniques into a single protocol enhance the efficiency and efficacy of iTBS for TRD?

Researchers at Stanford University enrolled 21 patients with treatment-resistant major depressive disorder or bipolar depression into an open-label study of a novel TMS treatment, the Stanford Accelerated Intelligent Neuromodulation Therapy (SAINT) protocol. All participants were treated with one session per hour for a total of 10 sessions each day, for five consecutive days. Each session delivered 1,800 pulses of iTBS at 90% resting motor threshold, for a total of 90,000 pulses over the five-day period. The specific target within the left DLPFC was personalized to each participant based on resting-state functional magnetic resonance imaging (rs-fMRI) connectivity between DLPFC subunits and the subgenual anterior cingulate cortex (sgACC). Participants were required to maintain their antidepressant regimen throughout the study period. The primary outcome was change in Montgomery-Åsberg Depression Rating Scale (MADRS) score; secondary outcomes included response and remission rates. After one week, 90.5% of participants met response criteria (defined by a ≥50% reduction in MADRS), and 86.4% of participants met remission criteria (defined by a MADRS score <11, in an intent-to-treat analysis. The mean number of days to response and remission, based on daily 6-item HAM-D scores, were 2.30 and 2.63 days, respectively. At one-month follow-up, response and remission rates by MADRS were 70% and 60%, respectively. A subgroup of participants (N=6) who had not responded to a prior course of conventional repetitive TMS (rTMS) had a dampened response through day 3 of treatment, but ultimately had similar response and remission rates after one week. Neuropsychological testing performed before and after the SAINT protocol showed no negative side effects and actually demonstrated improvements in cognitive inhibition.

Impact: The accelerated TMS protocol reported here yielded impressive results, with most patients entering remission after only five days of treatment. This is in contrast to the lower remission rates commonly reported with the customary six week course of treatment. The high remission rates in a short period of time, if replicated, would justify the labor-intensive treatment approach that involves fMRI guidance and 10 daily treatments. These initial results should be interpreted with caution because of the open-label design of the trial. The SAINT protocol is currently being examined in a randomized, controlled trial; if the results are similar, this novel treatment protocol may lead to a paradigm shift in the treatment of depression.

Cole EJ, Stimpson KH, Bentzley BS, et al. Stanford Accelerated Intelligent Neuromodulation Therapy for Treatment- Resistant Depression. Am J Psychiatry. 2020;177(8):716-726. https://doi.org/10.1176/appi.ajp.2019.19070720

IMPROVING TMS OUTCOMES FOR EARLY NON-RESPONDERS

Katharine Marder, MD reviewing Lee JC et al. J Affect Disord 2020 Sep 8

Augmenting high-frequency left-sided TMS treatment of depression with other stimulation strategies may improve outcomes in patients lacking an early response.

When transcranial magnetic stimulation (TMS) is used to treat depression, early response (defined as >20% improvement in symptoms by 2 weeks) predicts response later in treatment. When depressed patients do not show an early response to high-frequency left-sided treatment, can response be improved by augmenting with other types of stimulation?

Researchers retrospectively analyzed outcomes of 139 patients receiving TMS treatment for Major Depressive Disorder (MDD). Participants completed the Inventory of Depressive Symptomatology (Self-Report) (IDS-SR) every 5 treatments, and completed 30 treatment sessions. All participants began treatment with standard, high-frequency left-sided (HFL) treatment (3,000 pulses, 10 Hz frequency, 40 pulse trains, 26 second intertrain interval, goal intensity of 120% of motor threshold). Participants who achieved <20% reduction in depressive symptoms by the tenth treatment session could: i) continue with HFL treatment alone, ii) begin bilateral treatment, where HFL treatment was followed by low-frequency stimulation of right DLPFC, or iii) begin theta-burst priming, a strategy that delivers 600 pulses of intermittent theta burst to left DLPFC immediately prior to standard HFL treatment.

Early responders to HFL (participants who showed >20% improvement in IDS-SR score by treatment 10) fared well, as expected (67% reduction in symptoms, 81% response rate). Participants who did not show early response to HFL treatment who continued with HFL treatment for the remainder of their

treatment course showed limited benefit (24% reduction in symptoms, 12% response rate). Non-responders to HFL who received augmentation with low-frequency right treatment demonstrated better outcomes than the HFL-only group on a trend level (32% reduction in symptoms, 19% response rate), while those who received augmentation with theta burst priming showed significantly greater improvement compared to the HFL-only group (43% reduction in symptoms, 41% response rate). It seemed that approximately 10 treatment sessions were needed to determine the clinical benefit of either augmentation strategy.

Impact: Treatment-resistant depression is prevalent and disabling. TMS is an effective treatment strategy for treatment-resistant depression, but even so, there is an urgent clinical need to optimize TMS treatment parameters to improve response and remission rates. This study demonstrates that use of augmentation strategies in early non-responders can improve treatment outcomes. In particular, the addition of 600 pulses of intermittent theta burst priming at left dorsolateral prefrontal cortex immediately prior to standard HFL treatment appeared to be an effective strategy for improving response to TMS.

Lee, JC, Wilson AC, Corlier, J, et al. Strategies for augmentation of high-frequency left-sided repetitive transcranial magnetic stimulation treatment of major depressive disorder. Journal of Affective Disorders. 2020. 277: 964-969. https://doi.org/10.1016/j.jad.2020.09.011.

TMS FOR TREATMENT OF NEGATIVE SYMPTOMS OF SCHIZOPHRENIA

Andrew K Corse, MD reviewing Kumar N et al. Brain Stimulation 2020 Feb 29

In this randomized, double blind, sham-controlled trial, repetitive transcranial magnetic stimulation (rTMS) showed promise in treating the negative symptoms of schizophrenia.

Negative symptoms of schizophrenia are disabling and often treatment-resistant. These symptoms are thought to arise from decreased brain activity in the frontal cortex, as evidenced by hypoperfusion and hypometabolism seen on neuroimaging. TMS has been shown to improve this hypofrontality and to reduce negative symptoms in some cases. Should TMS be offered routinely as adjunctive treatment to pharmacologic interventions for patients with prominent negative symptoms?

Researchers enrolled 100 patients with schizophrenia, with predominantly negative symptoms, in a randomized, sham-controlled, double-blind trial. Over the course of 4 weeks, each patient received 20 sessions of either active rTMS (2000 pulses in 10 trains, 20 Hz, 100% of motor threshold) or sham treatment delivered to the left dorsolateral prefrontal cortex (DLPFC). Outcomes included the Scale for Assessing Negative Symptoms in Schizophrenia (SANS) and the Positive and Negative Syndrome Scale (PANSS). Assessments were conducted at baseline, post-intervention, and monthly for 4 months after completing treatment. Because depression is a common confounder for negative symptoms in schizophrenia, and it is known that depression responds to rTMS over the DLPFC, the Calgary Depression Scale for Schizophrenia (CDSS) was used to exclude patients with depression.

After 20 sessions, total SANS score was significantly reduced from baseline in both active and sham groups; the active group achieved significantly greater reduction in scores than sham (-16.6 and -11.0 respectively, $p<0.01$). There was further improvement in SANS score in both groups during the follow up period; at 4 month follow-up, the active group continued to show significantly larger reductions in SANS score compared to sham (-26.8 and -17.7, respectively, $p<0.01$) . Although the sham group demonstrated notable improvement as well, the benefits in the active group showed clear statistical advantage. The domains of anhedonia ($p<0.01$), alogia ($p<0.01$), and attention impairment ($p=0.01$) in particular showed significant improvement. Total PANSS scores and PANSS negative scales were significantly reduced in the active group compared to the sham group from baseline to 4 months follow up ($p<0.01$) . There were no significant differences in PANSS positive scale.

Impact: Despite advances in the treatment of schizophrenia in recent decades, the negative symptoms of the disease remain challenging to treat, with antipsychotic medications typically yielding greater improvements in positive symptoms than in negative symptoms.This study demonstrates that augmentation with rTMS can significantly and durably reduce negative symptoms of schizophrenia. These findings suggest that off-label rTMS treatment may have a role in the management of schizophrenia. Further high-power, high-quality studies are needed, and may lead to more widespread use of rTMS treatment for schizophrenia and possible consideration for an FDA indication.

Kumar, N, Vishnubhatla, S, Wadhawan, AN et al. A randomized, double blind, sham-controlled trial of repetitive transcranial magnetic stimulation (rTMS) in the treatment of negative symptoms in schizophrenia. Brain Stimulation. 2020; 13(3): 840-849. https://doi.org/10.1016/j.brs.2020.02.016.

FROM THE ARCHIVES: THETA BURST STIMULATION IS NON-INFERIOR TO STANDARD rTMS FOR MAJOR DEPRESSION

Michael K. Leuchter, MD reviewing Blumberger DM et al. The Lancet 2018 June 11

The THREE-D study found that a 3-minute TMS protocol called intermittent Theta Burst Stimulation (iTBS) is non-inferior to the gold standard, 37.5-minute TMS protocol when used for the treatment of depression. This seminal study led to FDA approval of iTBS in 2018 and increased use of iTBS in clinical practice.

Repetitive Transcranial Magnetic Stimulation (rTMS) is well established as a safe and effective treatment for Major Depressive Disorder (MDD). However, with a typical session of 10 Hz rTMS lasting up to 37.5 minutes, and a typical course of treatment involving 36 treatment sessions, the inherent time and cost of TMS treatment pose a significant barrier to its widespread use. A newer treatment protocol, intermittent Theta Burst Stimulation (iTBS), provides stimulation in a pattern mimicking endogenous brain activity and requires only 3 minutes per treatment session. iTBS has demonstrated efficacy for treatment of MDD in sham-controlled studies, but how does it compare to the gold standard, 37.5 minute treatment in a head-to-head study?

Researchers performed a randomized, experimenter-blinded study comparing the efficacy of iTBS and 10 Hz rTMS for treatment-resistant MDD. 414 participants were randomized to receive 20 sessions of either iTBS (600 pulses per session, 3 minutes, 209 subjects) or 10 Hz rTMS (3000 pulses per session, 37.5 minutes, 205 subjects), each delivered to the left dorsolateral prefrontal cortex at an intensity of 120% of motor threshold. Partial responders (those with 30-50% improvement) could receive additional treatment sessions. The primary outcome was the change in 17-item Hamilton Rating Scale for Depression (HRSD-17) score, and secondary outcomes included response rates, remission rates, and change in the 30-item Inventory of Depressive Symptomatology (IDS-30), 16-item Quick Inventory of Depressive Symptomatology (QIDS-SR), and Brief Symptom Inventory-Anxiety Subscale (BSI-A) scores. Mood scores were collected at 1, 4, and 12 weeks after completing treatment.

In the iTBS group, HRSD-17 scores improved from an average of 23.6 at baseline to 13.4 at the end of treatment (43% reduction); improvement was maintained 12 weeks after treatment (average score 13.6). In the 10Hz treatment group, HRSD-17 scores improved from an average of 23.5 at baseline to 13.4 at the end of treatment (43% reduction); improvement was also maintained 12 weeks after treatment (average score 14.1). Statistical testing demonstrated non-inferiority at a 95% confidence level for the primary outcome at all examined timepoints, as well as for all secondary outcome measures except for IDS-30 scores (though these differences faded over time). Response rates were similar between the 10Hz group (47%) and the iTBS group (49%), as were remission rates (27% and 32% respectively). No significant differences in side effects were observed; while three adverse events related to worsening of mood and agitation were observed in the iTBS group and none were observed in the 10 Hz group, there was no clear association between these events and the group assignment.

Impact: The THREE-D study demonstrated that iTBS provided clinical benefits that were similar to the gold standard of 10 Hz rTMS treatment. In both groups, decreases in depressive symptoms were sustained for at least 3 months. Because iTBS requires just 3 minutes per treatment session, instead of the typical 37.5 minutes required for a 10 Hz rTMS session, increased clinical use of iTBS may help expand access to TMS for the treatment of MDD.

Blumberger, DM, Vila-Rodriguez, F, Thorpe, KE, et al. Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. Lancet. 2018; 391: 1683–1692. https://doi.org/10.1016/S0140-6736(18)30295-2.

EFFICACY OF TDCS IN TREATING DEPRESSIVE EPISODES

Bryson C. Lochte, MD reviewing Razza LB et al. Depress Anxiety 2020 Feb 4

In a systematic review and meta-analysis, active tDCS was superior to sham in reducing depressive symptoms, although likely not as effective as some other antidepressant therapies.

Transcranial direct current stimulation (tDCS) aims to modify neuronal excitability and cortical activity by applying weak, direct current via scalp electrodes (including one anode and one or more cathodes). The left dorsolateral prefrontal cortex (DLPFC) is hypoactive in major depressive disorder (MDD). In the treatment of MDD, tDCS applies a current intensity of 0.5-2.5 mA to the left dorsolateral prefrontal cortex for 20-30 minutes daily, over a course of 5 to 20 daily treatment sessions, in order to stimulate the DLPFC and restore normal functioning. The treatment is safe, well-tolerated, and inexpensive, but evidence of efficacy is mixed. Is tDCS truly effective in the treatment of MDD?

Researchers performed a meta-analysis of 23 sham-controlled randomized controlled trials (RCTs) investigating tDCS as a monotherapy or augmentation therapy for a depressive episode associated with MDD, bipolar disorder, or secondary

depression. Most of these studies (57%) showed a low risk of bias. The primary outcome was change in depression rating scale scores at study endpoint. Secondary outcomes were response (>50% improvement), remission (scale specific), and acceptability (dropout) rates. The included studies used different depression scales, e.g. HRDS, MADRS, and BDI, so a pooled SD for each comparison was calculated. Hedges' g was used as the effect size measure because most studies had small sample sizes.

Among all participants (n=1092), endpoint depression scores showed that active tDCS was superior to sham (k = 25, Hedge's g = 0.46, 95% CI: 0.22–0.70). In analysis of secondary outcomes, active tDCS showed superiority over sham for response rates (k=18, 33.3% vs. 16.56%, OR=2.28 [1.52–3.42], NNT=6), as well as remission rates (k=18, 19.12% vs. 9.78%, OR=2.12 [1.42–3.16], NNT= 10.7). There was no significant difference in dropout rates (k=25, 14.05 % vs. 13.77%, OR=1.01 [0.69–1.48]), suggesting equal acceptability. Further analyses (funnel plot and Egger test) were not suggestive of publication bias. Re-analysis using only RCTs with low risk of bias showed similar results, and a cumulative meta-analysis showed stability in effect size for the past 5 years. While no variable (e.g. number of sessions, session duration) was associated with the primary outcome, a subgroup analysis suggested that cathode positioning over F4 may be superior to F8, and that tDCS monotherapy may be more effective than augmentation.

Impact: Many patients suffering from MDD cannot tolerate or fail to benefit from medication, and alternative treatments such as TMS, ketamine, or ECT may be unaffordable or inaccessible. tDCS may provide a safe, affordable, and accessible option for these patients. This meta-analysis, which is the largest and most current to date, shows that tDCS is significantly superior to sham in reducing depressive symptoms. The effect size of tDCS is modest at 0.46 (0.22-0.70), which, despite the absence of head-to-head studies, is likely smaller than that of antidepressants or rTMS. However, tDCS has appealing advantages in terms of tolerability, cost, and ease of use, especially as a maintenance treatment. Further trials could help improve the efficacy of tDCS treatment, perhaps by extending the treatment period or consistently using it to augment to standard medication or psychotherapies.

Razza, LB, Palumbo, P, Moffa, AH, et al. A systematic review and meta-analysis on the effects of transcranial direct current stimulation in depressive episodes. Depression and Anxiety. 2020; 37: 594– 608. https://doi.org/10.1002/da.23004.

SOMRYST: AN APP FOR CHRONIC INSOMNIA

Katharine G Marder, MD reviewing Morin CM. Expert Rev Med Devices. 2020 Dec 17

Approximately 10% of the adult population worldwide suffers from chronic insomnia. Cognitive behavioral therapy for insomnia (CBT-i) is recognized as the first-line treatment for chronic insomnia, with a favorable risk-benefit ratio compared to pharmacological sleep aids. However, due to the limited number of providers, CBT-i remains inaccessible to millions of Americans.

In an attempt to meet this need, consumer applications (apps) providing CBT-i, or otherwise monitoring or enhancing sleep, have become increasingly common. However, most consumer sleep technologies lack clinical validation in controlled trials. Prescription digital therapeutics (PDTs) are software-based disease treatments that are tested for safety and effectiveness in randomized clinical trials (RCTs), authorized by the U.S. Food and Drug Administration (FDA), and ultimately prescribed by licensed healthcare professionals, much like prescription drugs. Somryst (Pear Therapeutics, Inc.) is the first FDA-approved PDT for chronic insomnia.

Somryst is a mobile-adapted, enhanced version of the Sleep Healthy Using the Internet (SHUTi) online CBT-i program. Like face-to-face CBT-i, Somryst and SHUTi emphasize sleep restriction and consolidation, stimulus control, and personalized cognitive restructuring, using a series of six self-guided and interactive modules. Data entered in the included sleep diary are used by an algorithm to tailor sleep restriction therapy. Cognitive restructuring is based on each user's beliefs about sleep. Other interactive content includes video, animations, illustrations, and text, as well as graphical feedback based on symptom reports. As with traditional CBT-i, the major potential adverse effect of Somryst is sleepiness due to sleep restriction. Somryst should be avoided in those who must be particularly alert, such as air traffic controllers, truck drivers, healthcare providers, etc.

Somryst was FDA approved based on two RCTs studying Sleep Healthy Using the Internet. The first, at the University of Virginia, randomized 303 patients to SHUTi or digital patient education control for 9 weeks.

Patients receiving the SHUTi program versus the control had significantly greater improvements in insomnia severity measured by the Insomnia Severity Index (ISI; mean ISI score reduction 7.83 points vs. 2.94 points, p<0.001) and effects were maintained at 6 and 12 months. 52.6% of participants in the SHUTi treatment group demonstrated meaningful response compared with 16.9% of the control group (P < .001).

The second pivotal study, the GoodNight Study, randomized 1149 participants to either SHUTi or a digital, attention-matched depression prevention program as a control. The SHUTi group had significantly greater reductions in insomnia severity (mean ISI reduction 8.63 points vs. 2.85 points, p<0.001), and more participants in the SHUTi group (62.8% vs. 14.0%, P < .001) demonstrated a meaningful response.

A virtual, open-label, naturalistic post-marketing study of Somryst is ongoing. Learn more at https://www.somrysthcp.com.

Morin CM. Profile of Somryst Prescription Digital Therapeutic for Chronic Insomnia: Overview of Safety and Efficacy. Expert Rev Med Devices. 2020;17(12):1239-1248. https://doi.org/10.1080/17434440.2020.1852929