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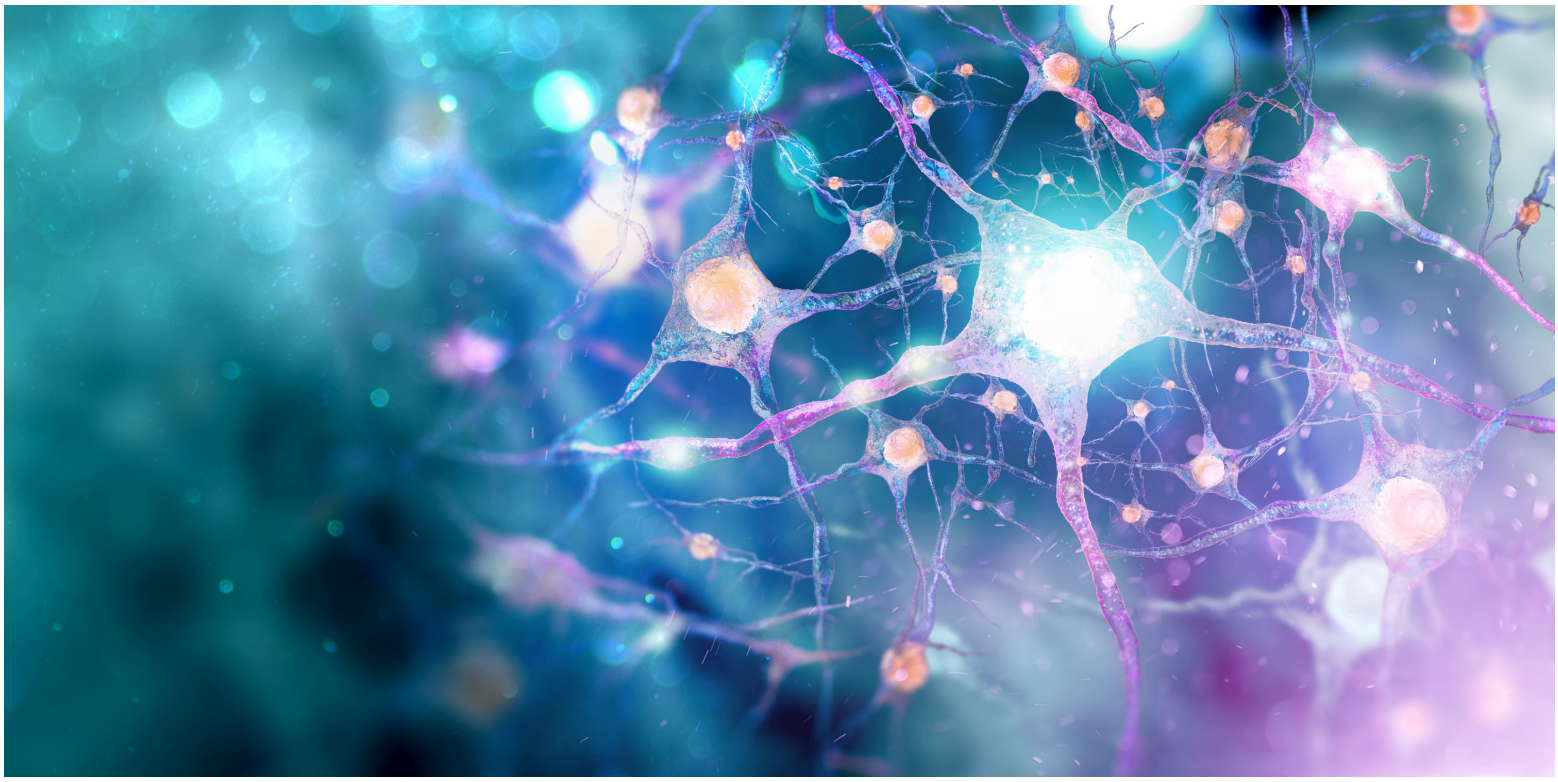
PULSE

A Monthly Update on Advances in Neuromodulation



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EMERGING TMS PARADIGMS FOR TREATMENT OF MAJOR DEPRESSIVE DISORDER

Andrew K Corse, MD reviewing Cheng et al. Major Depressive Disorder 2021

This review describes promising new repetitive transcranial magnetic stimulation (rTMS) paradigms.

A recent meta-analysis reported an average response rate of only 29.3% for patients receiving conventional high frequency (10Hz) rTMS. The pressing need to improve response and remission rates has led to the development of several new paradigms. This article reviews newer rTMS treatment paradigms, including theta burst stimulation (TBS), prolonged iTBS, accelerated and intensive TBS paradigms, synchronized TMS, magnetic seizure therapy, and concomitant therapies intended to enhance rTMS treatment response.

IN THIS ISSUE:

TBS is a patterned form of magnetic pulses typically delivered in 3-pulse 50-Hz bursts every 200ms to the left dorsolateral prefrontal cortex (DLPFC). The standard, FDA-approved TBS treatment protocol delivers 600 pulses of intermittent theta burst stimulation (iTBS) during a 3 minute session. A newer paradigm, prolonged iTBS (piTBS), delivers 1800 pulses over a 9 minute session. Both paradigms offer significant time and cost savings compared to the standard, 37.5 minute 10 Hz protocol. The conventional 3 minute iTBS protocol has proved non-inferior to standard, 10 Hz rTMS in head-to-head comparisons, with response rates of 49% and 47%, respectively. While piTBS has not been directly compared to standard rTMS, in one randomized controlled trial, response rates of 46% were observed after 2 weeks of piTBS therapy, suggesting 2 weeks of piTBS may have similar efficacy as 4-6 weeks of standard iTBS or standard rTMS.

TBS protocols applying burst frequencies other than 50 Hz are another promising development. TBS-20 Hz (bursts comprised of pulses delivered at 20 Hz) has demonstrated very promising results in early, uncontrolled trials. A retrospective chart review reported that 83% of patients responded and 72% remitted while undergoing a course of TBS-20 Hz. Randomized, controlled trials are warranted to further investigate this approach.

Accelerated rTMS protocols (aTMS) deliver several rTMS or TBS sessions in a single day in order to compress an entire treatment course into a matter of days. These approaches have been investigated with the goal of minimizing burden to patients and speeding time to recovery. While some individual trials are promising and demonstrate similar efficacy of aTMS compared to standard rTMS or TBS, in multiple meta-analyses, aTMS has not demonstrated superior efficacy to sham. However, studies to date have been limited by small sample sizes and heterogeneous treatment protocols. Further work is needed to determine the optimal dosing strategy and intersession interval in order to improve the efficacy of aTMS protocols.

Synchronized TMS (sTMS) employs rotating spherical neodymium magnets placed along the midline of the scalp to deliver sinusoidal waveform stimulation synchronized to an individual's alpha EEG frequency. Frontal alpha power is thought to be associated with depressive symptomatology and antidepressant response. In one recent study, alpha-synchronized rTMS over the left DLPFC could reduce resting alpha activity, but non-alpha-synchronized rTMS could not. However, sTMS was not more effective than sham in a recent network meta-analysis.

Magnetic seizure therapy (MST) applies high-frequency (e.g. 100 Hz) pulsed magnetic fields, typically to the vertex, with the aim of inducing a generalized seizure. Compared to electroconvulsive therapy (ECT), MST provides more focal and superficial stimulation, and may therefore cause fewer cognitive side effects. One recent systematic review showed similar antidepressant response between MST and ECT. More research is needed to determine the efficacy of MST compared to ECT and to better elucidate the cognitive side effect profile.

Combining other therapeutic modalities (medication, bright light therapy, and psychotherapy) with rTMS treatment is another emerging paradigm. Concomitant antidepressant medication use during rTMS is associated with a better clinical response. In a small case series, simultaneous bright light therapy and rTMS yielded a 100% response rate. In an open-label study, psychotherapy administered simultaneously with rTMS led to a response rate of 66%.

Impact: While TMS is clearly effective in the treatment of MDD, there is a pressing need to improve its antidepressant efficacy. Novel TMS protocols are an active area of research. Emerging paradigms have the potential to increase response and remission rates while minimizing the burdens of TMS treatment. With multiple TMS paradigms clinically available, it is critically important to identify predictors of response to inform selection of the optimal stimulation protocol.

Cheng CM., Li CT., Tsai SJ. (2021) Current Updates on Newer Forms of Transcranial Magnetic Stimulation in Major Depression. In: Kim YK. (eds) Major Depressive Disorder. Advances in Experimental Medicine and Biology, vol 1305. Springer, Singapore. doi: 10.1007/978-981-33-6044-0_18

TMS FOR THE TREATMENT OF DEPRESSION IN ADOLESCENTS

Emily Wood, MD, PhD reviewing Hett et al. J Affect Disord 2021 Jan 1

This systematic review examined the literature to date on TMS treatment of depression in adolescents. No sham-controlled studies were located, but open-label studies indicate that TMS is safe and may be effective for depression in adolescents.

Depression in adolescents has become increasingly prevalent over the past decade. Depression is a leading cause of disability in this age group, and it is associated with negative health outcomes later in life. The mainstays of treatment are medications, particularly selective serotonin reuptake inhibitors, and psychotherapy, including cognitive-behavioral therapy. However, medications have significant side effects and are linked to an increased risk of suicidal ideation, particularly in the adolescent population. Repetitive transcranial magnetic stimulation (rTMS) is a treatment option for

adults that avoids the side effects of medications, and is FDA approved for the treatment of major depressive disorder. What is the state of the evidence regarding the use of TMS for the treatment of depression in adolescents?

The authors conducted the first systematic review of TMS for the treatment of major depressive disorder in adolescents with the goal of establishing the safety and efficacy of rTMS treatment for adolescent depression. The authors conducted a comprehensive search following PRISMA guidelines. Included studies were published between 2000-2020, published in English, and employed an rTMS intervention to treat depression with mean age of subjects between 12-25 years old. Ultimately, 14 studies meeting inclusion criteria were included in this review. The authors rated the quality of included studies and assessed risk of bias.

Of the included studies, eight were open-label studies (n=142 subjects) and the remaining six studies were post-hoc analyses or follow-up studies from the same open-label trial data sets. No controlled studies were able to be located. Most studies included adolescents with a diagnosis of treatment-resistant depression, usually defined as having failed at least one medication trial. In all but one study, participants were receiving concomitant medication and/or psychotherapy. Most studies employed high-frequency rTMS, while one study used both high and low frequency rTMS and another study employed theta-burst stimulation. Only two trials delivered up to 30 sessions, with most studies administering 10-20 treatment sessions. The most common outcomes were validated depression rating scales, such as the Hamilton Depression Rating Scale (HDRS) or the Children's Depression Rating Scale-Revised (CDRS-R). Included studies were of poor to fair quality, with a high risk of bias, due largely to the lack of a control group and, in some studies, high attrition rates.

All 14 included studies reported at least some beneficial effect of rTMS. Five studies reported statistically significant reductions in HDRS scores after rTMS. In one study, the response rate was 56%; in another study, over three-quarters of participants met criteria for at least a partial response. In the theta-burst study, after 10 sessions, there was a significant reduction in depressive symptoms, and 24% of patients met criteria for response. The largest included study compared rTMS outcomes for adolescents (n=42) to outcomes for adults (total sample n=117) and found that the adolescent group had a greater reduction in HDRS scores compared to adults, although this may be due to lower baseline severity of depression in the adolescent group. Finally, in one study, 59% of adolescents demonstrated reduction in suicidal ideation following rTMS treatment. Based on the included studies, the most rTMS protocol most commonly associated with clinical benefit was high frequency (10 Hz) rTMS (4 second train, 26 second inter-train interval) delivered at 120% of motor threshold.

Regarding safety, commonly reported side effects included headaches, scalp pain, dizziness, and fatigue. Several participants experienced deterioration of their mental health and increased suicidal ideation was reported in multiple studies. Due to the lack of a control group, it is difficult to determine if this was due to rTMS treatment. No included study reported occurrence of seizure in any participant (though there are case reports of seizures in this age group). Four studies investigated effects of rTMS on cognitive functioning; no negative outcomes were reported. One small follow-up study (n=8) examined cognitive functioning 3 years after rTMS treatment, and found no deterioration of cognitive functioning.

Impact: All available open-label studies to date indicate that rTMS treatment may reduce depressive symptoms in adolescents. High-frequency (10 Hz) rTMS treatment appears most promising thus far. Side effects have been mostly mild and no seizures have been reported in multi-subject trials. Randomized controlled trials are needed to confirm these findings. Of note, the authors reported 8 currently ongoing trials of rTMS in this population, including several randomized, double-blind, sham controlled trials, which, once completed, may help to more clearly establish the role of rTMS for adolescents in clinical practice.

Hett D, Rogers J, Humpston C, Marwaha S. Repetitive Transcranial Magnetic Stimulation (rTMS) for the Treatment of Depression in Adolescence: A Systematic Review. J Affect Disord. 2021;278:460-469. doi: 10.1016/j.jad.2020.09.058.

CONCOMITANT LORAZEPAM USE NEGATIVELY IMPACTS TMS RESPONSE

Katharine G Marder, MD reviewing Deppe et al. Eur Arch Psychiatry Clin Neurosci 2021 Feb

This retrospective cohort study demonstrated that depressed patients taking lorazepam had lower rates of response to transcranial magnetic stimulation when compared to depressed patients not taking concomitant lorazepam.

The use of repetitive transcranial magnetic stimulation (rTMS) for the treatment of depression is becoming increasingly widespread. Most patients treated with rTMS take psychotropic medication during their rTMS treatment course. Benzodiazepines are commonly prescribed in major depressive disorder (MDD), but accumulating evidence demonstrates reduced rTMS response among patients taking benzodiazepines. Does lorazepam, one of the most commonly prescribed benzodiazepines, reduce the antidepressant effect of rTMS treatment?

Researchers retrospectively analyzed data from a retrospective cohort of patients treated with rTMS between 2002-2017. Included patients were TMS-naïve, were receiving treatment for unipolar or bipolar depression with or without psychotic symptoms, had no serious medical comorbidities, and had completed a Hamilton Depression Rating Scale (HDRS) at the beginning and end of rTMS treatment. In this naturalistic study, patients were treated with different rTMS protocols. Of the 299 included patients, 73 patients took lorazepam, 50 patients took other benzodiazepines or z-drugs, and 176 patients took no benzodiazepines or z-drugs. The authors compared the lorazepam group to the group not taking benzodiazepines or z-drugs, and excluded the group of patients taking other benzodiazepine or z-drugs, as each other benzodiazepine and z-drug was taken by only a small number of patients.

There were no differences in baseline depression severity or TMS treatment parameters between groups. Both groups showed symptom reduction, but response was attenuated in the benzodiazepine group. Patients not taking lorazepam demonstrated an average HDRS-17 score reduction of 36%, compared to an average symptom reduction of only 19% in the lorazepam group. With response defined as a greater than 50% reduction in the HDRS score, 38% of the patients not taking lorazepam responded to rTMS, compared to only 18% of patients in the group taking lorazepam. There was no association between lorazepam dosing (total dose, average daily dose, number of days used, etc.) and treatment outcome.

The therapeutic effects of TMS arise not only from alterations in intra-network activity, but from downstream effects mediated by changes in other, inter-connected networks. GABA A receptors are implicated in mediating this inter-network communication. Increases in cortical GABA signaling have been demonstrated to accompany TMS response. [*For further discussion of cortical GABA signaling and TMS response, see this month's "From the Archives" section.*] Chronic benzodiazepine use may inhibit TMS response by downregulating GABA A receptors.

Impact: Of four retrospective studies examining the effects of concomitant benzodiazepine use on rTMS outcome, this is third study to demonstrate significantly poorer TMS response among patients taking concomitant benzodiazepines. This study adds to the growing evidence that benzodiazepine use impairs TMS response, and raises several important questions for clinical practice. Should patients be recommended to discontinue benzodiazepines for some length of time before TMS? If a patient fails a course of rTMS while taking concomitant benzodiazepines, should a re-trial of rTMS without benzodiazepines be considered? It is increasingly clear that benzodiazepine use during rTMS is problematic, but it is not yet clear how this should inform clinical practice.

Deppe M, Abdelnaim M, Hebel T, et al. Concomitant lorazepam use and antidepressive efficacy of repetitive transcranial magnetic stimulation in a naturalistic setting. Eur Arch Psychiatry Clin Neurosci. 2021;271. doi: 10.1007/s00406-020-01160-9.

FROM THE ARCHIVES: DORSOLATERAL PREFRONTAL GABA CORRELATES WITH TMS RESPONSE IN DEPRESSION

Katharine G Marder, MD reviewing Levitt et al. J Psychiatry Neurosci 2019 Nov 1

This magnetic resonance spectroscopy study measured GABA in the dorsolateral prefrontal cortex before and after a course of TMS. Increases in GABA were observed and the authors found that a greater increase in GABA levels was associated with superior clinical response.

While repetitive transcranial magnetic stimulation (rTMS) is clearly established as an effective treatment for treatment-resistant depression (TRD), its mechanism of action has yet to be elucidated. One promising hypothesis is that rTMS may exert its effects via alterations in γ-aminobutyric acid (GABA) signaling. Patients with depression have decreased plasma and CSF levels of GABA, and GABA dysregulation has been reported in the dorsolateral prefrontal cortex (DLPFC) of depressed patients. Other antidepressant modalities (selective serotonin reuptake inhibitors, electroconvulsive therapy, cognitive behavioral therapy, and ketamine) have been demonstrated to increase cortical

GABA. Previous work has demonstrated increased GABA levels in the anterior cingulate cortex following high frequency rTMS treatment to the left dorsolateral prefrontal cortex (LDLPFC). Does GABA increase at the stimulation site following rTMS, and do changes in GABA expression differ between responders and nonresponders?

This prospective study included 26 patients who underwent GABA magnetic resonance spectroscopy before and after a 6-week course of rTMS treatment for TRD. Twelve participants were taking 1 or more GABA agonists (i.e. benzodiazepines, sedative-hypnotics, or anticonvulsants). TMS sessions delivered 3000 pulses of 10 Hz stimulation to the left DLPFC at 100-120% of motor threshold; after the 15th treatment session, non-responders could receive sequential bilateral treatment involving 1 Hz stimulation at right DLPFC. Clinical outcomes were measured using the Inventory of Depressive Symptoms (IDS-SR30), and clinical response was defined as a greater than 30% reduction in total IDS-SR score. GABA levels were determined using Mescher–Garwood point-resolved spectroscopy (MEGA-PRESS) spectral-editing MRS.

Treatment with rTMS significantly reduced depressive symptoms by an average of 32% and overall, 46% of patients met response criteria. Across the entire sample, there was an average increase of 10% in GABA levels at the left DLPFC following rTMS. The mean increase in GABA levels was significantly greater in the responder subgroup (24% increase in GABA) compared to non-responders (4% increase). Response rates were significantly higher among patients not taking GABA agonists (71% response rate) than among patients taking GABA agonists (17% response rate). There was no significant interaction between use of GABA agonists and increase in cortical GABA.

Levitt JG, Kalender G, O'Neill J, et al. Dorsolateral prefrontal γ-aminobutyric acid in patients with treatment-resistant depression after transcranial magnetic stimulation measured with magnetic resonance spectroscopy. J Psychiatry Neurosci. 2019; 44(6):386-394. doi: 10.1503/jpn.180230.

Impact: Dubin et al. established that rTMS is associated with increased GABA in the anterior cingulate cortex. The present study—the first MRS study to measure the effects of rTMS on GABA at the site of stimulation—demonstrated increased GABA at the site of rTMS stimulation. This indicates that the DLPFC is not merely a conduit to other brain regions, but is itself metabolically affected by rTMS. This study also demonstrated that greater GABA increases were associated with superior clinical response. The use of GABA agonists did not impact GABA levels, but was associated with inferior treatment response, suggesting that GABA agonists may impede the rTMS therapeutic mechanism of action without directly affecting metabolic levels of GABA.

THE FLOW BRAIN STIMULATION HEADSET FOR THE TREATMENT OF DEPRESSION

Katharine G Marder, MD reviewing Borrione et al. Expert Rev Med Devices. 2020 Sep 7

The portable tDCS device developed by Flow Neuroscience (TM) produces similar electric field patterns to established tDCS montages, indicating it is likely to be safe and effective in the treatment of depression.

Transcranial direct current stimulation (tDCS) is an affordable, portable method of neuromodulation that affects synaptic neuroplasticity of targeted brain regions by applying low-intensity, direct electrical current via two or more electrodes placed on the scalp. Multiple recent meta-analyses demonstrate that tDCS is safe and effective in the treatment of depression. A recent pilot study suggested that at-home use of tDCS reduced depressive symptoms with outcomes similar to those achieved when tDCS is applied in a clinical setting.

The Flow device is an easy-to-use, one-size-fits-all, wireless tDCS device that pairs via Bluetooth to the Flow smartphone app. The app offers instructions for applying and using the tDCS device and delivers a CBT intervention for depression during each stimulation session. The device delivers 2 mA of current during a 30 minute session and is intended to be used 5 times per week for the first two weeks, then 2 times per week for the following four weeks. The device is approved for home use in the European Union without a prescription.

The authors of the current review analyzed the intensity of the electric field produced by the Flow device in the dorsolateral prefrontal cortex, the dorsomedial prefrontal cortex, and the anterior cingulate cortex. Three different device positions were modeled to account for human error in placing the device, especially in the setting of home use. The authors compared the electric field patterns produced by the Flow device to those produced by other, established tDCS protocols, such as the F3-F4 and F5-F6 montages, in order to evaluate its treatment efficacy. Electric field modeling for the Flow device was done using SimNIBS (v3.1, Danish Research Center for Magnetic Resonance, Copenhagen, Denmark). Modeling showed that the Flow device produced similar electric field strength to the F3-F4 and F5-F6 montages in almost all analyzed brain regions. This indicates that the device is likely effective, as it produces similar electric field patterns to setups shown to be effective in prior randomized, controlled trials. However, small deviations in device placement produced significant differences in electric field intensity in the dorsomedial prefrontal cortex, which may impact efficacy.

Impact: The Flow device may help to fill an unmet need for safe, easy-to-use, at-home neuromodulation treatment modalities, but adequately powered sham-controlled studies are warranted to confirm its therapeutic efficacy and to establish the efficacy of tDCS combined with a cognitive-behavioral intervention as a self-administered, home-based intervention.

Borrione L, Suen PJC, Razza LB, et al. The Flow brain stimulation headset for the treatment of depression: overview of its safety, efficacy and portable design. Expert Rev Med Devices. 2020; 17(9):867-878. doi: 10.1080/17434440.2020.1813565.