# Editorial

# Repetitive Transcranial Magnetic Stimulation for Depression: State of the Art

Electroconvulsive therapy (ECT) which was introduced in the early 20th century, enjoyed an unsurpassed position among the neuromodulation treatments for mood disorders until recently, but that is being challenged by a newer neuromodulation technique called repetitive transcranial magnetic stimulation (hereafter, rTMS). rTMS utilizes magnetic pulses to influence the excitability and connection strength of the cortical neurons. In this article, we will review relevant research on the efficacy, mechanism of action, procedure, responsibility of treating physician, clinical recommendations, safety, etc., and comment on the future challenges and opportunities.

## EFFICACY OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION IN DEPRESSION

The neuromodulation treatment with rTMS is sought usually after the failure of one or more antidepressant medications with or without a course of psychotherapy. On the clinical line of management, it comes after the use of medications (±psychotherapy) and before planning for ECT. The response rate in major depressive disorder is between 50% and 55% and remission rate between 30% and 35% according to the researchers.[1,2] In a recent systematic review,[3] the number needed to treat was calculated to be 10. However, in comparison with sham treatments, rTMS had small short-term effect on depression which did not continue for longer periods in the follow-up studies.

Comparison studies of rTMS and ECT showed better effectiveness of ECT over rTMS every time and that ECT was cheaper than rTMS in cost.[3,4] rTMS, on the other hand, had higher patient preference and far less adverse effects compared to ECT.[4] A related neuromodulation treatment is the magnetic seizure therapy (MST). MST also uses magnetic pulses, albeit of a higher frequency than rTMS, to stimulate a specific area in the brain with the aim of inducing a seizure. Researchers have found comparable efficacy between MST and ECT in treatment- resistant depression[5] while MST having lower cognitive side effects.[6]

## MECHANISM OF ACTION IN DEPRESSION

Research on rTMS in depression is also providing insights into its mechanism of action. Functionally, high-frequency stimulation of the left prefrontal cortex and low-frequency stimulation of the right prefrontal cortex leading, respectively, to long-term potentiation and long-term depression of the cortical neurons is related to alleviation of depressive symptoms.[7] This is further supported by instances of high-frequency stimulation of left prefrontal cortex worsening symptoms of patients with mania.[8] Newer research with magnetoencephalography suggests that following changes[9] correlate with improvements in depressive symptoms:

1. Increase in gamma (γ) power at the left dorsolateral prefrontal cortex (L-DLPFC)
2. Increase in delta (δ) band connectivity between L-DLPFC and amygdala and between L-DLPFC and pregenual anterior cingulate cortex
3. Decrease in gamma (γ) band connectivity between L-DLPFC and subgenual anterior cingulate cortex.

## PROCEDURES, ROLES AND RESPONSIBILITIES

The interest of clinicians on rTMS is due to its potential use in an office setting without any need for anesthesia or fear of serious adverse effects. Usually, before the actual procedure, patients are asked to remove any magnet-sensitive objects such as chains and credit cards and asked to wear ear plugs as the machine produces loud clicking sounds much like magnetic resonance imaging machine. As the patient is seated on a chair, measurements are made over the scalp to place the coil appropriately.

rTMS is usually administered[10] in five daily treatments over 3–6 weeks with the objective of delivering 20–30 sessions in a course of treatment. Each session with the current standard protocol consists of high frequency (i.e., 10 Hz) rTMS delivering 3000 pulses within a typical duration of 37.5 min at the resting motor threshold of 120 (or >80% RMT). Few drugs that have to be avoided during the treatment are benzodiazepines in high doses (i.e., not more than

lorazepam equivalents of 4 mg/day) and anticonvulsant medications as these might reduce the effect of rTMS.[11]

It is advised that the important role in the delivery of rTMS should be that of the physician, who apart from the device-specific training from the manufacturer, should also obtain additional training through a peer-to-peer training or a Continuous Medical Education program.[1] Every rTMS clinic should have formal procedures for training and maintenance of staff skills. It is also the responsibility of the physician to determine initial RMT (which is the minimum intensity of rTMS pulse needed to produce a motor evoked potential [MEP]) and appropriately identify the coil location for the treatments. Later sessions can be delegated to other staff, which should also be under the physician's supervision.

## CLINICAL RECOMMENDATIONS

The Clinical TMS Society laid out the following recommendations[1] based on its review of available rTMS research in depression.

1. Indicated for adults with major depressive disorders who have failed antidepressant medication in the current episode with moderate to severe drug resistance, moderate to severe illness severity, and recurrent course of illness (with average patient age being 49 years)
2. Recommended as acute treatment for symptom relief; and additional 1–2 weeks of treatment for partial responders or for those who have a history of delayed response with medication in the past episodes (Level 1b evidence)
3. Recommended as subsequent option for patients with documented benefit using a standard rating scale in the past episode (Level 1b evidence)
4. Recommended to be used along with concurrent medication but with appropriate reassessment of patient's motor threshold for any change (Level 2b evidence)
5. Recommended to be used for maintenance (Level 1b evidence) and early relapse treatment (Level 2b evidence) in those who benefit in acute course.

## ADVERSE EFFECTS OF RTMS

Although hailed as safer compared to ECT, rTMS has few adverse effects which might affect patient preference and treatment continuation.[1] Common adverse effects are the transitory headache and shock-like sensation over face and scalp along with the characteristic loud clicking sound associated with the magnetic pulse which may be annoying. Few people may experience vasovagal syncope after the treatment session. More worrisome adverse effect is the rare possibility of seizure which may occur approximately with one in 1000 people or once in 30,000 sessions. Although the risk is small, we should assess for those with a history of seizure or traumatic brain injury before recommending rTMS. Few case reports also suggested the possibility of a switch to manic state.[12,13]

## FUTURE CHALLENGES AND OPPORTUNITIES

The published research presents a promising picture of rTMS in depression management, but the presented evidence received its share of criticism. In this background, we outline few challenges and opportunities:

1. Some researchers are cautious in interpreting the research data[14] as they question the neuronal functional and outcome measure of MEP or RMT. They argue that MEP (and thereby the related RMT) used in most of the research is poorly defined and by itself is a poor and indirect measure of brain changes. They propose the measurement of cortical silent period (CSP) which is the period of suppression of EMG activity from MEP to the return of voluntary muscle activity after application of a suprathreshold stimulus. CSP purportedly is a direct and an easy measure of cortical change
2. Poor quality reporting of research data requires making assumptions while interpretation of the findings[14] and thereby reduces the overall applicability and quality
3. Clinical applicability requires shortening of duration of each session and along with shortening of the overall duration of a course of rTMS treatment. First of these challenges is being addressed through the use of theta (θ) burst stimulation, which simulates the theta neural firing in the normal brain, trying to bring down the session duration from 37.5 min to a bare 3 min. The Toronto Theta Burst rTMS Trial,[2,15] which is an ongoing research project, is comparing the efficacy of standard high-frequency protocol which has 20–30 sessions of 37.5 min and 3000 pulses each with the efficacy of theta burst protocol which has 20–30 sessions of 3 min 9 s and 600 pulses each. Preliminary data suggest that the efficacy of both the protocols is comparable even when the session durations are drastically different. This may help treatment adherence and increase the number of treatment sessions per day per rTMS machine in the clinic
4. It is difficult for the patient to visit the clinic 5 days a week for 4–6 weeks just to get a 3 min or a 37.5 min session. Hence, the challenge is also to reduce the overall treatment course duration to 1–2 weeks

5. Response and remission rates are variable in the available research. If rTMS has to be effective in the clinic, these rates have to be improved upon. There is a great need for the research to find consistent and higher efficacy.

If we can work on the research and clinical application of rTMS (and MST), we can hope for a future with better, affordable, and accessible neuromodulation in our therapeutic armamentarium to help people suffering with depressive disorder.

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