

## **POSITION PAPER**

# **Use of Repetitive Transcranial Magnetic Stimulation in the treatment of major depressive disorder**

### **Introduction**

Repetitive transcranial magnetic stimulation (rTMS) has recently emerged as a therapeutic option in contemporary psychiatric care for the treatment for major depressive disorder (MDD). To date, rTMS has been approved for clinical use in the treatment of MDD in the United States, Canada, Europe (UK), Australia, New Zealand, Japan and South Korea.

rTMS is currently available in Singapore. This position paper seeks to delineate its uses and practice. It is hoped that position papers like this will facilitate discussion on emerging topics without the experimentation and original research normally present in an Academic Paper. The technology involved in TMS keeps evolving and advancing, so for any doctor who wishes to acquire a TMS machine, it is advisable to seek regulatory approval for quality and safety standards.

### **Definition**

rTMS is a noninvasive method of brain stimulation in which briefly pulsed magnetic fields are used to induce electrical currents in a focused manner in the cerebral cortex, thereby depolarizing neurons and resulting in the stimulation or disruption of brain activity[1]. It has been used to treat specific types of major psychiatric disorders, such as MDD, bipolar disorders, post-traumatic stress disorder, schizophrenia; and neurologic diseases such as Parkinson's disease and tinnitus[2].

### **The Technology**

rTMS operates on the principle of electromagnetic induction. The essential feature of rTMS is the use of electricity to generate a rapidly changing electromagnetic field, which readily crosses the scalp and skull and in turn produces electrical impulses in the brain. In contrast to ECT, rTMS does not require anesthesia, it is an outpatient procedure, the stimulation is specific, targeted and does not induce a convulsion[3].

This electromagnetic field is generated when current is passed through a TMS coil placed over the scalp which is usually round or figure-eight (butterfly) in shape. The latter produces more focal field than the circular coil and is widely used to deliver repetitive TMS (rTMS) stimuli.

Repetitive TMS usually refers to the application of TMS for a train of minutes at frequencies above 1 Hertz (Hz) and is commonly used in treatment for MDD. When rTMS is administered in clinical practice, the number of pulse trains per daily session is usually predetermined in accordance with recommended treatment parameters, as are the intertrain interval, the number of daily sessions, the site of stimulation, the type of coil used, and the orientation of the coil relative to the site on the scalp.

In a typical rTMS therapy session, TMS is delivered in trains, lasting several seconds, followed by inter-train intervals. Several trains can be delivered per session and usually

5-6 sessions per week. The intensity of the stimulus is based on the individual motor threshold (the minimal intensity required to produce muscle twitches), and is usually between 90%-120% of this threshold.

### **Clinical indications – Major Depressive Disorder**

MDD continues to be the most commonly studied psychiatric condition in the application of rTMS. Several single center, controlled studies of rTMS have been conducted that have supported the hypothesis that rTMS manifests antidepressant properties when delivered to the left or right dorsolateral prefrontal cortex (DLPFC)[4].

The DLPFC has been the primary area of interest for stimulation for two reasons: First, networks of brain regions including the prefrontal, cingulate, parietal and temporal cortical regions, as well as parts of the striatum, thalamus and hypothalamus, are thought to regulate mood. Second, this region is the most accessible for treatment with rTMS of the areas thought to be important in mood disturbances[5].

### **Efficacy**

Numerous randomized controlled trials have been undertaken to evaluate the efficacy of rTMS therapy in the treatment of MDD. A full review of the studies demonstrating the effectiveness of rTMS is beyond the scope of this paper. The following is a summary of the main conclusions regarding the efficacy of rTMS for the treatment of MDD.

In a large randomized controlled trial sponsored by the National Institute of Mental Health, it was found that a course of active treatment for 3-5 weeks was superior to sham treatment (remission rates were 15% in the active treatment group and 5% in the sham treatment group) and achieved a 30% remission rate in the open label extension. This data demonstrates that daily left prefrontal rTMS for 4-6 weeks was effective in treating MDD with minimal side effects and offers clinicians an alternative treatment for the treatment of this disorder[6].

Further, rTMS has also been demonstrated to be well tolerated and safe enough to be administered in an outpatient setting. In a study of treatment outcomes in clinical practice carried out across forty-two clinical practices in the United States, observations from the sample size of 307 patients diagnosed with MDD receiving rTMS therapy showed response and remission rates consistent with efficacy outcomes seen in research populations. Furthermore the high adherence rate (83%) and minimal adverse events reported during this study underscore the benign safety profile associated with the treatment[7].

A full review of research evaluating the efficacy of rTMS can be accessed through the suggested further reading at the end of this statement.

### **Adverse Effects**

**Local pain/headache, discomfort:** Published research on safety assessment demonstrate that rTMS is a safe and well-tolerated treatment. Potential adverse effects of rTMS therapy include headaches, facial muscle twitching during stimulation and scalp pain. These symptoms are not generally severe and dissipate over the initial week

of treatment. In addition, repeated analysis of cognitive functioning of rTMS patients has not found any enduring negative effects from the procedure. After a session, patients are able to drive home and return to work[8].

**Hearing:** Rapid mechanical deformation of the rTMS treatment coil when it is energized produces an intense-sounding click. The loud click accompanying rTMS may cause transient hearing loss in patients without hearing protection (earplugs). It is important to note that the majority of studies in which hearing protection was used report no change in hearing after rTMS.[2] Therefore, it is recommended that hearing protection be used by all patients and personnel involved in administering rTMS.

**Cognitive changes:** Side effects related to cognition were not noted or were observed to be insignificant in several rTMS studies researched for this paper. In a large multi-center sponsored study examining the effect of rTMS in 325 patients with MDD by using three different tests (Mini Mental State Examination, Buschke selective reminding test and Autobiographical memory interview), no change in cognitive function was observed on any of the measures[2].

**Seizures:** The inadvertent induction of a seizure remains the most significant medical risk associated with the use of rTMS. However, research indicates that with appropriate pretreatment clinical screening, clinical monitoring and attention to treatment given with recommended safety parameters, the overall risks of seizure are very low[2].

### **Transcranial magnetic stimulation during pregnancy**

The treatment of pregnant women with depression is a challenging issue in clinical psychiatry. Limited evidence to date suggests that TMS appears to be a promising treatment option for pregnant women with depression. In the study done by Sayar et al, pregnant patients' depressive symptoms were significantly relieved, and all the newborns were healthy[9].

### **Duration of treatment**

The evidence in the field points towards longer treatment durations. rTMS treatment started out with a duration of 2-3 days before increasing to 1 week to the current state where a full course of rTMS is commonly considered 1 month of treatment (or about 20 sessions). The available evidence seems to suggest that longer durations of treatments (1 month) are likely to be more effective than shorter durations (1 week). Most practitioners would monitor the patient's condition clinically and after 1 month of treatment decide if there is any response. If there is no response it is reasonable to terminate treatment. If there has been some response but not to remission it is reasonable to continue treatment to reach response. Many patients who reach response or remission will require maintenance therapy.

### **Patient Selection**

The screening and selection of appropriate patients is essential and should be conducted by a psychiatrist with appropriate training and expertise in rTMS. Prescribing psychiatrists should be able to undertake screening procedures, including the

assessment of risk factors (i.e. seizure risks) before deciding whether a patient is suitable for rTMS therapy.

Absolute contraindications include the presence of conductive, ferromagnetic or other magnetic sensitive metals implanted in the head or in close proximity to the head such as cochlear implants, brain stimulators or electrodes, aneurysm clips, plates. Cardiac pacemakers are also a contraindication[2].

### **Credentialing and Training**

International consensus to date on training and accreditation of TMS practitioners recognizes that in-depth requirements may vary from country to country. In the preparation and subsequent implementation of rTMS training protocols, the following statements are worth noting:

- (i) In a 2008 consensus conference on TMS safety, it was recommended that institutions that provide rTMS shall ensure that the application of rTMS is carried out by properly trained practitioners. Institutions should have in place a training program that adequately trains practitioners in rTMS principles together with practical knowledge in key areas such as[2]:
  - (a) brain physiology;
  - (b) mechanisms of rTMS;
  - (c) potential risks of rTMS procedure;
  - (d) physiological changes induced by rTMS; and
  - (e) early management of potential acute complications that may arise from rTMS, such as recognizing and management of seizures.
- (ii) Each institution should institute an explicit plan for dealing with seizures, and every member of the rTMS team should be familiar with it.
- (iii) The World Federation of Societies of Biological Psychiatry (WFSBP) in their published rTMS treatment guidelines recommends that:
  - (a) Those who administer rTMS should be trained as “first responders” in order to render appropriate care in the event of seizures;
  - (b) rTMS should be performed in a medical setting with appropriate emergency facilities to manage seizures and their consequences; and
  - (c) Patients should be continuously monitored during the administration of rTMS for signs of epileptic activity or otherwise adverse effects by a trained individual, according to criteria established in the clinical protocol.

### **Assessment and Documentation**

Before the administration of rTMS, a thorough evaluation of the patient’s psychiatric

and medical status is required. Adequate pre-treatment clinical screening for potential seizure risk should be performed.

Informed consent is essential for all patients considering rTMS. Enough information and time should be provided for patients to make an informed decision along with families and caregivers.

The consent process should be undertaken by a psychiatrist or their designated medical personnel with knowledge and expertise in rTMS therapy, and should detail the possible benefits of rTMS, and possible adverse effects.

### **Summary and Recommendations**

When used in accordance with standards and treatment parameters evidenced by research, rTMS is a safe, well-tolerated and effective treatment for MDD with few mild adverse effects. With the growing body of evidence supporting its antidepressant efficacy, TMS may be considered as an alternative treatment option for MDD that can be administered in an outpatient setting in Singapore.

Because it is a medical procedure with a risk of seizure, rTMS for MDD should be performed only in a medical setting under the guidance and supervision of a psychiatrist who is responsible for handling all precautions.

rTMS for mental conditions should only be prescribed by a SMC registered psychiatrist who is well versed in rTMS principles and knowledgeable of all potential side effects associated with the procedure. It is advisable that the psychiatrist who administers the treatment should have completed a minimum of 15 hours of practical training in the safe application of rTMS. We make this recommendation based on the fact that there are training courses (which run about 2 days) in Australia and the USA that prepare psychiatrists to perform rTMS for treatment. The practical training would cover areas such as:

- (i) proper pre-treatment screening protocols;
- (ii) therapeutic protocols (e.g. FDA approved on-label therapeutic procedures and safety protocols);
- (iii) post-treatment monitoring protocols;
- (iv) training in mapping of the position of the DLPFC;
- (v) motor threshold measurement;
- (vi) learning how to position for machine;
- (vii) setting strength and frequency of impulses; and
- (viii) Management of potential acute complications of rTMS.

Continuing clinical research is encouraged to further improve the clinical application of rTMS therapy.

A thorough patient evaluation, including medical history and psychiatric history is necessary to assess a patient's suitability for rTMS therapy and also to screen for potential seizure risk.

The decision to use rTMS would require a detailed informed consent from the patient.

**Contributors:**

**Dr Tor Phern-Chern**  
**Dr Roger Ho Chun Man**  
**Dr Lo Yew Long**  
**Dr Ng Beng Yeong**

**Disclosures:**

**Dr Tor Phern-Chern**  
**Head, Psychological Centre**  
**Singapore Armed Forces (SAF)**

- **He is currently involved in rTMS evaluation and assessment.**

**Dr Roger Ho Chun Man**  
**Assistant Professor & Consultant**  
**Department of Psychological Medicine, NUHS**

- **No Disclosures**

**Dr Lo Yew Long**  
**Head/Senior Consultant**  
**Neurology (SGH Campus)**  
**National Neuroscience Institute (NNI)**

- **He has done research using rTMS in various neurological conditions.**

**Dr Ng Beng Yeong**  
**Head/Senior Consultant**  
**Department of Psychiatry**  
**Singapore General Hospital**

- **He is interested in doing research using rTMS in various psychiatric conditions.**

**Further Reading**

Slotema CW, Blom JD, Hoek HW, Sommer IE. Should we expand the toolbox of psychiatric treatment methods to include repetitive transcranial stimulation (rTMS)? A meta-analysis of the efficacy of rTMS in psychiatric disorders. *J Clin Psychiatry* 2010 71:7, 873-884

Berlim MT, Van den Eynde F, Daskalakis ZJ. Efficacy and acceptability of high frequency repetitive Transcranial magnetic stimulation (rTMS) versus electroconvulsive therapy (ECT) for major depression: a systematic review and meta-analysis of randomized trials. *Depression and Anxiety* 2013 30:614-623

Tranulis CT, Sepehry AA, Galinowski A, Stip E. Should we treat auditory hallucinations with repetitive Transcranial magnetic stimulation? A metaanalysis. *The Canadian Journal of Psychiatry* 2008 53:9, 577-586

Slotema CW, Blom JD, van Lutterveld R, Hoek HW, Sommer IE. Review of the efficacy of transcranial magnetic stimulation for auditory verbal hallucinations. *Biol Psychiatry*. 2014 Jul 15;76(2):101-10

## References

1. Janicak, P.G., et al., *Transcranial magnetic stimulation in the treatment of major depressive disorder: a comprehensive summary of safety experience from acute exposure, extended exposure, and during reintroduction treatment*. Journal of Clinical Psychiatry, 2008. **69**(2): p. 222-232.
2. Rossi, S., et al., *Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research*. Clinical neurophysiology, 2009. **120**(12): p. 2008-2039.
3. George, M.S. and R.M. Post, *Daily left prefrontal repetitive transcranial magnetic stimulation for acute treatment of medication-resistant depression*. American Journal of Psychiatry, 2011. **168**(4): p. 356-364.
4. George, M.S., et al., *Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial*. Archives of General Psychiatry, 2010. **67**(5): p. 507-516.
5. George, M., et al., *Overview of transcranial magnetic stimulation: history, mechanisms, physics, and safety*. Transcranial Magnetic Stimulation in Clinical Psychiatry, 2007: p. 1-38.
6. O'Reardon, J.P., et al., *Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial*. Biological psychiatry, 2007. **62**(11): p. 1208-1216.
7. Carpenter, L.L., et al., *Transcranial magnetic stimulation (TMS) for major depression: a multisite, naturalistic, observational study of acute treatment outcomes in clinical practice*. Depression and anxiety, 2012. **29**(7): p. 587-596.
8. Wassermann, E.M. and S.H. Lisanby, *Therapeutic application of repetitive transcranial magnetic stimulation: a review*. Clinical Neurophysiology, 2001. **112**(8): p. 1367-1377.
9. Sayar, G.H., et al., *Transcranial magnetic stimulation during pregnancy*. Archives of women's mental health, 2013: p. 1-5.