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Is There Evidence for Effectiveness of Transcranial Magnetic Stimulation in the Treatment of Psychiatric Disorders?

ABSTRACT

Transcranial magnetic stimulation (TMS), since its introduction in 1985, has been studied for its efficacy in different psychiatric disorders. It has been touted to be an effective treatment modality for major depression, obsessive compulsive disorder, Tourette syndrome, and in reducing auditory hallucinations in patients with schizophrenia. In this article, the authors outline the research and evidence toward the efficacy of TMS in psychiatry.

INTRODUCTION

Since the introduction of electroconvulsive therapy (ECT) in 1938, it has been shown to be very effective in treatment for major depression. It has also been shown to be effective in the treatment of acute mania and, to a limited extent, chronic schizophrenia. But ECT still remains one of the most controversial modalities of treatment in the entire field of medicine. Its proponents swear by it, while its opponents hate it. The movie “One Flew over Cuckoo’s Nest,” like many other movies before and after,



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portrayed ECT as a very crude and cruel method of treatment, which is sometimes abused as a form of punishment for behavior control. There has been a steady decline in use of ECT in clinical psychiatry settings, and it remains one of the most underutilized treatments. Less than eight percent of American psychiatrists use ECT.¹

The introduction of transcranial magnetic stimulation (TMS) and vagal nerve stimulation (VNS) have rekindled interest in the use of brain stimulation methods for the treatment of psychiatric disorders. TMS enables the clinician to focally stimulate specific areas of the brain noninvasively and painlessly. The efficacy of TMS in the treatment of depression has been extensively studied. TMS has also been shown to have some beneficial effects in the treatment of posttraumatic stress disorder (PTSD) and obsessive compulsive disorder (OCD).²

TMS was introduced in 1985 by Anthony Baker at the University of Sheffield in England.³ It was designed to be a neurodiagnostic tool used to produce an evoked potential in muscle tissue by activating neurons in the motor cortex.³ TMS is based on two basic principles in physics:¹ Ampere's law² and Faraday's principle of electromagnetic induction.⁴

Ampere's law states that the magnetic field in the space around an electric current is proportional to the electric current. According to Faraday's principle of electromagnetic induction, a voltage would be generated across a length of wire if that wire was exposed to a perpendicular magnetic field flux of changing intensity.

The stimulation coil of the TMS instrument consists of multiple wire loops encased in

an insulated material. This is connected to powerful capacitors capable of passing a large electrical current through the coil.³ If a pulse of current is passed through this coil and placed over a person's head, it produces rapidly changing magnetic pulses that penetrate the scalp and skull and reach the brain with minimal attenuation.⁵ When these pulses alternate rapidly enough, a secondary electric current is induced that alters the local electric field in the nerve tissue.⁴ This leads to depolarization of the underlying superficial neurons.⁶ High-intensity current is rapidly turned on and off in the electromagnetic coil using discharges from powerful capacitors.⁶ TMS thus produces brief but very powerful magnetic fields that lead to induction of electric currents in the brain. TMS pulses can be administered repetitively and rhythmically, and this process is called repetitive TMS (rTMS).⁷ This can be further classified as high frequency rTMS if the frequency is greater than 1Hz, whereas if the speed of stimulation is equal or less than 1Hz it is called low frequency rTMS.⁸

MAJOR DEPRESSION

Major depressive disorder has a prevalence of almost seven percent in the general population.⁹ Many effective treatments are available, but as many as 30 percent of these depressed patients do not respond to treatment. Brain stimulation techniques are a possible treatment modality that can be used in these patients with treatment resistant depression. There have been more than 20 randomized, controlled trials investigating the efficacy of rTMS in the treatment of major depression. The most common deficiency noted is the relatively small

sample sizes of these studies. The sample size varied from 6 to 70. Most of the studies used sample sizes less than 20.⁸

George, et al.,¹⁰ studied the efficacies of rTMS in patients with depression in a double-blind crossover design. Twelve patients were given either active rTMS or sham treatment. The study suggested that daily left prefrontal repetitive transcranial magnetic stimulation has antidepressant activity.¹⁰

Klein, et al.,¹¹ in a double-blind, placebo-controlled study assessed the efficacy of slow repetitive TMS (rTMS) in patients with major depression. Seventy patients with major depression were randomly assigned to receive active rTMS or sham rTMS in a double-blind design. It was shown that patients who received active rTMS had a significantly greater improvement in depression scores compared with those who received sham treatment and provided evidence for the short-term efficacy of slow rTMS in patients with recurrent major depression.¹¹

Berman, et al.,¹² in a randomized, double-blind, clinical trial, studied the efficacy of rTMS in treatment resistant major depression. Depressed subjects, who had failed to respond to a median of four treatment trials, were assigned in a randomized, double-blind manner to receive either active or sham rTMS. Adjusted mean decreases in HDRS scores were 14.0 (± 3.7) and 0.2 (± 4.1) points for the active and control groups, respectively ($p < 0.05$). A two-week course of active rTMS resulted in statistically significant but clinically modest reductions of depressive symptoms, as compared to sham rTMS.¹²

Toro, et al.,¹³ studied the efficacy of rTMS in drug-resistant depression. In this

randomized, double-blind study, 40 patients received either active rTMS or sham rTMS to the left prefrontal cortex. The authors of this study concluded that real, but not sham, HF-rTMS was associated with a significant decrease in the Hamilton Depression Rating Scale and that left prefrontal high frequency-rTMS was effectively associated with antidepressant treatment. But the size effect was small.¹³

Toro, et al.,¹⁴ in another published study examined the efficacy of high frequency rTMS as add-on treatment to sertraline in the treatment of major depression. The addition of HF-rTMS did not show any benefit in speeding up or strengthening the therapeutic response to sertraline in major depression.¹⁴

Boutros, et al.,¹⁵ compared active rTMS to sham rTMS in a double-blind controlled trial. Twenty-one treatment-resistant depressed patients were randomized to either active rTMS ($n=12$) or to sham ($n=9$) treatment. Sub-motor-threshold (MT) stimulation (80% MT) was delivered for 10 consecutive work days while still receiving medications. It was shown that sub-threshold rTMS stimulation for two weeks is not significantly superior to sham treatment for treatment-resistant depressed patients.¹⁵

Hoppner, et al.,¹⁶ in a placebo-controlled study compared high frequency rTMS over left versus low frequency rTMS over right prefrontal cortex compared with sham stimulation in patients with major depression. There were no differences in resolution of depressive symptoms between the rTMS procedures. An additional observation made by these authors was that patients with less severe deficits in psychomotor speed and concentration responded more intensively than patients with severe deficits.¹⁶

Herwig, et al.,¹⁷ in a double-blind, randomized, sham-controlled pilot study investigated the efficacy of neuronavigated rTMS, guided according to the prefrontal metabolic state determined by positron emission tomography (PET). The dorsolateral prefrontal cortex (DLPFC) with lower metabolic activity compared to the contralateral hemisphere, as determined from PET scans, was selected to receive the real stimulation. The preliminary examination of the data showed that stimulation of prefrontal cortex with rTMS may not be advantageous irrespective of the metabolic state.¹⁷

Loo, et al.,¹⁸ examined the efficacy and safety of bilateral prefrontal repetitive transcranial magnetic stimulation (rTMS) for treating resistant major depression in a double-blind, placebo-controlled study. Nineteen medication-resistant depressed subjects were randomly assigned to three weeks of active or sham rTMS. Bilateral rTMS did not show any superiority to sham in treating resistant depression.¹⁸

Hansen, et al.,¹⁹ studied the efficacy of rTMS in patients with major depression. Fifteen inpatients were randomized to receive 15 days of active left prefrontal high-frequency rTMS or sham rTMS, as an add-on to conventional antidepressant treatment. More than 50 percent of the patients receiving real rTMS suffered from local discomfort during treatment. Real rTMS did not add to the efficacy of standard antidepressant medication and thus did not confirm the antidepressant effect of left frontal high-frequency rTMS.¹⁹

Couturier²⁰ did a meta-analysis of six studies of the efficacy of rTMS in the treatment of depression. Two of these studies reported a

significant improvement in mood symptoms versus sham group. When combined in the meta-analysis with the other four studies, it was shown that rTMS was no different from sham treatment in major depression.²⁰

Martin, et al.,⁸ in a recent review of 16 trials studying the efficacy of rTMS in major depression for Cochrane Data Base concluded that there is no strong evidence for benefit from using transcranial magnetic stimulation to treat depression, though they did not exclude the possibility of benefit.⁸

OBSESSIVE COMPULSIVE DISORDER

Greenberg, et al.,²¹ investigated whether prefrontal repetitive transcranial magnetic stimulation influenced OCD symptoms. Twelve patients with OCD were randomized to receive rTMS to a right lateral, a left lateral prefrontal, and a midoccipital site, and the patients' symptoms and mood were rated for eight hours afterward. Compulsive urges showed a significant decrease after right lateral prefrontal repetitive transcranial magnetic stimulation. The study concluded that right prefrontal repetitive transcranial magnetic stimulation might affect prefrontal mechanisms involved in obsessive compulsive disorder.²¹

Sachdev, et al.,²² in a randomized trial evaluated the efficacy of rTMS in OCD. Twelve subjects with resistant OCD were allocated randomly to either right or left prefrontal rTMS daily for two weeks. Subjects were shown to have an overall improvement in the obsessions, compulsions, and total scores on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) after two weeks and at one-month follow-up. But this study, due to the lack of a sham



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treatment arm, cannot exclude a placebo response.²²

Alonso, et al.,²³ examined the efficiency of rTMS of the right prefrontal cortex for patients with OCD in a double-blind, placebo-controlled trial. Patients received either real (low frequency) or sham rTMS. The study concluded that low-frequency rTMS of the right prefrontal cortex did not show any significant improvement of OCD and was not significantly different from sham treatment.²³

Martin, et al.,²⁴ in their review of the different studies of rTMS in OCD for Cochrane data Base concluded that there is a lack of evidence for the effect of TMS in the treatment of OCD.²⁴

TOURETTE SYNDROME

Munchau, et al.,²⁵ studied the efficacy of low frequency rTMS in 16 patients with Gilles de la Tourette syndrome (GTS) in a single-blinded, placebo-controlled, crossover trial. The study showed no significant improvement of symptoms as assessed with the Motor Tic, Obsessions and Compulsions, Vocal Tic Evaluation Eurvey.²⁵

POSTTRAUMATIC STRESS DISORDER

Grisaru, et al.,²⁶ investigated the efficacy of slow TMS on PTSD. Ten patients with PTSD

were given one session of slow TMS. TMS was found to be effective in lowering the core symptoms of PTSD: avoidance, anxiety, and somatization. The patients also showed a general clinical improvement as measured by the Clinical Global Impression Scale. But this effect was short and transient.²⁶

Rosenberg, et al.,²⁷ studied the efficacy of left frontal cortex low frequency rTMS in 12 patients with PTSD and comorbid major depression. Seventy-five percent of the patients showed a clinically significant response after rTMS and 50 percent showed sustained response after two months. Improvements were also seen in anxiety, hostility, and insomnia. But the study showed minimal improvement in PTSD symptoms.²⁷

Cohen, et al.,²⁸ studied the efficacy of repetitive transcranial magnetic stimulation (rTMS) of the right prefrontal cortex in patients with posttraumatic stress disorder (PTSD) under double-blind, placebo-controlled conditions. Twenty-four patients with PTSD were randomly assigned to receive rTMS at low frequency (1Hz) or high frequency (10Hz) or sham rTMS in a double-blind design. This double-blind, controlled trial suggested that right dorsolateral

prefrontal rTMS at a frequency of 10Hz has greater therapeutic effect than slow-frequency or sham stimulation in PTSD.²⁸

SCHIZOPHRENIA

Hajak, et al.,²⁹ in a sham-controlled parallel study, treated 20 schizophrenic patients with rTMS of frontal regions. High frequency rTMS led to a significant reduction of negative symptoms and a nonsignificant improvement of depressive symptoms. High frequency rTMS treatment was paradoxically shown to lead to an increase in positive symptoms.²⁹

Fitzgerald, et al.,³⁰ in a randomized sham controlled, double-blind trial, treated 36 patients with treatment-resistant auditory hallucinations with low frequency rTMS (LF-rTMS). Active treatment led to more reduction of loudness than sham treatment, though it did not result in a greater therapeutic effect than sham.³⁰

Saba, et al.,³¹ in a double-blind, sham-controlled study tested the efficacy of rTMS in schizophrenia. Eighteen patients diagnosed with schizophrenia were randomly treated with active or sham rTMS over left temporoparietal cortex. This study failed to show any superiority for active rTMS over sham treatment.³¹

Hoffman, et al.,³² in a double-blind, sham-controlled, parallel design study, treated 50 schizophrenic patients with left temporoparietal cortex low frequency rTMS. Hallucination change score showed more improvement for people who received active rTMS than sham group. The active group also showed a significant decrease in a hallucination frequency.³²

Chibbaro, et al.,³³ investigated the benefits of treating schizophrenic patients with rTMS focused on left temporoparietal cortex in a 16-patient double-blind, sham-controlled study. The patients were treated with low frequency rTMS or sham treatment. This study also showed reduction of frequency of auditory hallucination in patients treated with active rTMS.³³

Sachdev, et al.,³⁴ in a pilot study, treated four patients having stable deficit syndrome of schizophrenia with high frequency rTMS over the left dorsolateral prefrontal cortex

(DLPFC). The patients showed a significant reduction in negative symptoms and improvement in function.³⁴

The different studies which investigated the efficacy of rTMS in patients with schizophrenia did not show any significant clinical benefits. But there were some studies which showed some improvement in the frequency and intensity of auditory hallucinations. The benefit of rTMS in schizophrenia need to be studied with more focused rTMS and larger patient samples.

CONCLUSION

TMS has rekindled interest in the role of brain stimulation in psychiatric disorders. Some of the studies have shown promising but not conclusive evidence for the efficacy of TMS in depression. But TMS has not been shown to be effective in the treatment of obsessive compulsive disorder, posttraumatic disorder, or schizophrenia. The patient

sample size has been a cause of concern in most studies. There has been no multicenter study so far. There is a need to develop further consensus on the following parameters in TMS studies: Shape of coil, coil-cortex distance, motor threshold, low frequency versus high frequency stimulation, and location of the correct point of stimulation for each disorders.

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