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NEUROMODULATION (S TAYLOR, SECTION EDITOR)

Magnetic Seizure Therapy: an Evolution of Convulsive Therapy

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Abstract
Purpose of Review Treatment-resistant depression (TRD) affects a significant subset of depressed patients. It is estimated that about 30 % of patients with major depressive disorder do not respond to standard treatments. For these patients, electroconvulsive therapy (ECT) remains the most effective treatment despite being limited by its side effects. Modifications to ECT parameters have suggested that it may be possible to separate the therapeutic effects of convulsive therapy from the production of side effects.
Recent Findings Magnetic seizure therapy (MST), which uses electromagnetic induction to induce a seizure, is an alternative, experimental convulsive treatment for major depression. Seizures induced by MST are more focal than those produced by ECT, thereby offering greater control over the induced electric field. Most importantly, it offers the potential to provide antidepressant effect without cognitive side effects. Recent findings have further shown the effectiveness of MST and compared cognitive and metabolic side effects to ECT.
Summary This article reviews the current literature for clinical studies on MST. While initial results are promising, future work is needed to compare MST efficacy with other antidepressant treatments.

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Introduction

Treatment-resistant depression (TRD) is associated with significant morbidity, mortality, and increased risk for suicide. Despite the progress made with pharmacotherapy and psychotherapy, a significant percentage of patients remain ill [1]. For these patients with treatment-resistant depression, the therapy that has been considered the gold standard, with proven efficacy, is electroconvulsive therapy (ECT) [2–9]. Despite the finding that modifications to ECT parameters such as pulse width, frequency of sessions, and electrode placement have improved the side effect profile of modern ECT treatments, a significant proportion of patients who receive ECT still experience side effects [10]. In most cases, patients undergo multiple other treatments before trying ECT, and ECT is used as a treatment of last resort. Patients who could potentially benefit from ECT decline treatment due to the stigma attached to the procedure and well-documented cognitive side effects. Therefore, there is a need for an alternative therapy that retains the therapeutic efficacy of ECT but offers a better side effect profile.

Magnetic seizure therapy (MST) is being investigated in an effort to find a safe and effective alternative to ECT. MST is the induction of therapeutic seizures under anesthesia by high-dose repetitive transcranial magnetic stimulation (rTMS). Like ECT, MST requires the induction of anesthesia and must be delivered in a hospital setting. Like ECT, MST induces a seizure, but the seizure induced by MST is different. There is greater control over site and extent of stimulation with MST due to the fact that

magnetic fields pass through tissues unimpeded and the induced electric field remains confined to the superficial cortex. This is in contrast to the widespread stimulation of cortical and subcortical regions with ECT due to the high skull impedance which dissipates the ECT current through the scalp and cerebrospinal fluid and limits the control over the induced electric field. The focal stimulation of MST results in the sparing of medial temporal structures, which are implicated in the cognitive side effects of ECT. Focal stimulation may also make it possible to focus the treatment to areas of the brain thought to be associated with antidepressant response such as the dorsolateral prefrontal cortex.

Initial reports of MST treatment in humans was published over a decade ago by Lisanby et al., describing a 20-year-old patient with TRD who received four sessions of MST [11]. Over the past decade, studies have investigated the effectiveness, safety, cognitive effects such as reorientation time, acute memory retrieval, and brain glucose metabolism effects of MST. Available evidence suggests that MST does not appear to cause cognitive impairment although response rates have not reached the high rates of response seen with ECT [12••, 13]. Early MST treatment used pulse frequencies of 40 to 50 Hz. MST devices capable of delivering 100 Hz stimulus have been developed, known as high-dose MST (HD-MST), to improve effectiveness by modifying the stimulus parameters [12••]. Given that MST is still the early phase of clinical testing, the purpose of this review is to synthesize the recent updates on the clinical and cognitive effects of MST (see Table 1).

Cognition

Cognitive adverse effects have limited treatment with ECT and contribute to the stigma associated with its use. Memory impairment can be a distressing symptom for patients, sometimes causing patients to withdraw from treatment. MST has been investigated with several small studies showing antidepressant effects and absence of cognitive adverse effects [14, 15••]. Sparing of the hippocampi due to the focal stimulation of MST is hypothesized to explain why MST does not cause the memory disturbances seen after treatment with ECT. Acute memory retrieval was compared in a study with 20 patients with treatment-resistant depression randomly assigned to treatment with either MST or ECT. Patients in the study were asked to recall words memorized before their treatment. Patients in the MST group performed equally well on treatment days as on control days while patients who had been treated with ECT performed significantly worse on treatment days than on control days. The authors concluded that acute memory disturbances commonly associated with ECT were not seen in patients who received MST [16•].

Orientation

In order to further assess the cognitive effects of MST, one can assess the time taken for patients to regain full awareness and orientation after a treatment session. As they emerge from anesthesia, patients are asked their name, date of birth, age,

Table 1 Latest clinical studies of the effects of magnetic seizure therapy

Year	Author	Sample	Intervention	Outcome
2008	Kirov et al.	• 11 patients with major depressive episode, in context of MDD or schizoaffective disorders	One treatment out of patients' ECT course was substituted with MST	• Mean time to orientation after treatment was 7 min 12 s after MST, compared with 26 min 35 s after ECT treatment.
2011	Kayser et al.	• 20 patients with TRD	Patients randomly assigned to receive complete courses of either MST or ECT.	• Antidepressant response was significant and similar in both treatment arms. • Orientation time was 6 min 5 s quicker after MST compared to after ECT treatment.
2013	Fitzgerald et al.	• 13 patients with MDD; MADRS score >20	100-Hz MST (open label)	• 38.5 % clinical response rate on MADRS.
2013	Hoy et al.	• 10 patients with TRD	100-Hz MST (open label)	• Effect of MST on regional brain glucose metabolism suggests that MST affects regions implicated in the limbic-cortical dysregulation in depression.
2015	Kayser et al.	• 26 patients with TRD	10 patients were part of randomized trial with ECT, 16 patients were in an open-label study.	• 69 % of patients responded to MST as assessed by HAMD28/17. 46.2 % met criteria for remission.
2015	Polster et al.	• 20 patients with TRD	Patients were randomly assigned to receive either MST (10 patients) or ECT (10 patients).	• Delayed recall was disturbed after ECT treatment; acute memory disruption measured by delayed recall was absent after MST.
2016	Sun et al.	• 33 patients with TRD	MST (open label)	• Measures of cortical inhibition in the frontal cortex correlated with changes in suicidal ideation.

the place where they are, and the day of the week. Time to orientation is the time from the end of the seizure to patients being assessed as oriented to four out of the five items. MST treatment has been associated with a quicker reorientation time than following ECT [12••, 17]. In a randomized trial of 20 patients with treatment-resistant depression, patients were randomized to receive complete courses of either MST or ECT. The study showed that there was a significant difference in reorientation times between the two treatment arms. Patients who were treated with MST were reoriented 6 min 5 s quicker than patients who had received treatment with ECT [14]. This result is in line with the shorter reorientation time with MST initially reported by Kirov et al. Eleven patients with major depressive disorder received MST during one session of a regular course or ECT. Patients in the study described that after MST, they felt less confused than after ECT, they remembered details of events that occurred immediately before their treatment, and they were able to continue conversations after MST that they had begun just prior to their treatment [17]. Shorter orientation time favors patients continuing with therapy, because patients who experience severe post-treatment confusion/delirium are at increased risk of discontinuing treatments early.

Suicidal Ideation

Suicidal ideation is a serious, life-threatening symptom which can accompany major depression. In an investigation to identify a biomarker that may be used to indicate remission following MST, 33 patients with TRD were assessed in an open-label clinical trial of MST treatment [18••]. In the study, cortical inhibition measures were assessed with combined transcranial magnetic electroencephalography (TMS-EEG) in the left dorsolateral prefrontal cortex. Cortical inhibition is mediated by GABAergic interneurons which have been implicated in treatment response for depression as well as improvement in suicidal ideation. The study found that measures of cortical inhibition in the frontal cortex correlated with changes in suicidal ideation, and this biomarker has the potential to identify those patients with suicidal ideation who are most likely to benefit from a course of MST.

Response

Antidepressant response of MST has been reported in several studies, with response rates ranging from 40 to 60 % and remission rates ranging from 15 to 30 % [19]. Although MST has been shown to have a safer cognitive profile compared to ECT, its effectiveness compared to ECT remains variable. Stimulation with higher frequency MST, up to 100 Hz—also known as high-dose MST (HD-MST)—has been investigated in an attempt to improve effectiveness. No significant difference in effectiveness of MST and ECT was found in the first comparison study of HD-MST and ECT study [14]. Twenty patients with TRD randomized to HD-MST or ECT were evaluated. Primary outcome was response defined as 50 % reduction of the Montgomery and Asberg Depression Rating Scale (MADRS). No significant difference was found between treatment groups. A limitation of this study is that the investigators used low-dose right unilateral ECT (RUL-ECT), a lower stimulation dose compared to other studies of ECT. A later study investigating the clinical effect of HD-MST reported 38.5 % clinical response rate, substantially lower than the approximately 70 % response rate that can be seen with ECT [12••].

Metabolic Effects

The influence of MST on regional blood glucose metabolism was investigated in a study with 26 patients with TRD who had received MST. Undergoing [^{18}F]-fluorodeoxyglucose positron emission tomography (FDG-PET) scans, 12 patients showed metabolic increase bilaterally in the frontal cortex and metabolic decrease in the left striatum following the completion of a course of MST. The authors reported that close to 70 % of patients responded to MST though half relapsed within 6 months, similar to the relapse rates seen after ECT treatment [20]. In addition to improvements in depressive symptoms as assessed by the Hamilton Depression Rating Scale (HAM-D), responders were also reported to have lowered anxiety and improved quality of life [15••].

A similar study sought to find the changes of glucose metabolism in brain regions that have traditionally been reported as dysfunctional in depression (limbic-cortical dysregulation model). Although a small sample size of ten patients participated in the study, areas of increased glucose metabolism were seen in the basal ganglia, orbitofrontal cortex, medial frontal cortex, and dorsolateral prefrontal cortex. They further discovered there was a differential finding between responders to treatment and non-responders specifically in the ventral anterior cingulate. The authors reported that responders showed an overall decrease in brain metabolism in the ventral anterior cingulate combined with an increase in metabolism in the frontal brain regions. They suggested that these differences may indicate improvement in depression due to balance restoration [1].

Conclusion

Treatment-resistant depression is a burdensome mental illness that is associated with impaired social and physical functioning and increased risk of suicide. Although ECT is regarded as

the most effective treatment for depression, its use is limited by the cognitive side effects as well as the stigma associated with its use. The findings reported suggest that MST has the potential to be an alternative safe, effective, and tolerable intervention for patients with mood disorders, especially for those who have treatment-resistant depression [21–24]. The favorable side effect profile of MST may enhance adherence to a full course of treatment and allow earlier intervention with convulsive therapy in cases of severe depression. While initial work has been promising, further studies with larger sample sizes and age ranges are needed to optimize the stimulation parameters and assess its effectiveness. Furthermore, investigations of the effectiveness of MST on the treatment of other mental disorders compared to the therapeutic spectrum of ECT as well as other brain disorders such as autism would expand the implications of this particular type of therapy.

Compliance with Ethical Standards

Conflict of Interest Dr. Katalin Martits-Chalangari and Alexis Milton declare that they have no conflict of interest. Dr. Mustafa M. Husain declares grant support from NIH, NIMH, NIDA, NINDS, NIA, NARSD, Stanley Medical Foundation, Cyberonics, Neuronetics (past), St. Jude Medical (ANS), MagStim (equip only), Brainsway, NeoSync, Alkermes, Assurex, and Avanir. He reports research consulting for Allergen and AtheaDx.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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