Magnetic Seizure Therapy in the treatment of Depression

A Randomised Controlled Trial of Magnetic Seizure Therapy (MST) compared to Electroconvulsive Therapy (ECT) for the treatment of depression

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Main Messages

- We compared the effects of a new type of depression treatment, Magnetic Seizure Therapy (MST), to Electroconvulsive Therapy (ECT) in a group of participants diagnosed with treatment resistant depression.

- All of the participants showed a significant improvement in their mood over the course of the 4 week treatment trial, irrespective of whether they received ECT or MST.

- 38% of patients who completed the trial experienced either a partial or complete clinical response to the treatment.

- Cognitive side effects, i.e. problems with memory and attention, are often reported following ECT. Therefore, we also investigated the effects of ECT and MST on cognition.

- Before and after the course of treatment we asked participants a series of questions about their past (i.e. where did you go on your last holiday). Those participants who had MST were able to retain more information (82%), compared to those who had ECT (72%); although this was not a significant difference.

- The participants who underwent MST showed significantly improved performances on cognitive tests of psychomotor speed, immediate verbal memory, and executive functioning. They also showed near significant improvements on attention, associate learning, delayed verbal memory and working memory. There was no reduction in cognitive performance across any of the tasks in the MST group.
• The participants who underwent ECT largely exhibited non-significant reductions in performances across the cognitive tasks. They did show a significantly reduced performance on a test of psychomotor speed, and a near significant reduction on a test of executive functioning.
Executive Summary

Electroconvulsive therapy (ECT) remains the only established treatment for the large group of patients with depression who do not get benefit from other treatments (i.e. medication and talk therapy). ECT is commonly used but has substantial problems including the occurrence of cognitive side effects (i.e. difficulty with things such as memory and attention), which are often highly distressing for patients. The development of a new treatment with similar antidepressant effects as ECT but which minimises the cognitive side effects would have great clinical value. This project aimed to investigate one highly promising possibility: Magnetic Seizure Therapy (MST). MST involves replacing the electrical stimulation used in ECT with a magnetic stimulus.

The study involved a randomized double-blind clinical trial comparing MST directly to ECT. A total of 40 people with moderate to severe treatment resistant depression participated in the trial. Participants underwent a treatment course of between 9 and 15 treatments receiving either MST or ECT. We investigated the effect of treatment on participant’s depression symptoms and their cognitive functioning. This was a ‘double-blind’ trial, meaning that neither the participants nor the researchers conducting the assessments of depression and cognition knew which condition they were in.

Overall we found MST to be as effective as ECT in reducing depression symptoms. We found no cognitive side effects following MST, while ECT was found to produce mild cognitive side effects in the current study. While MST was shown to be effective in improving mood, the overall response rate of the trial was low.

We believe there are a number of improvements which can be made to the way in which MST is delivered that may significantly improve the response rate. Therefore, we are now conducting a clinical trial comparing an ‘optimised’ form of MST with the standard approach as was used in this study.
Report

Context

The primary aim of this research study was to compare the clinical response between MST and ECT in patients with moderate to severe depression. We also wanted to see whether MST was associated with the cognitive side effects that are often reported in ECT. In order to do this we additionally compared the changes in cognition from pre to post treatment in both MST and ECT.

Depression is a common clinical problem that affects between 15-20% of the Australian population. There are a significant group of patients with depression, up to 30%, who continue to experience highly distressing and disabling symptoms despite standard treatments such as antidepressant medication and/or talk therapy. For these patients there are only very few treatment options. In Australia, electro convulsive therapy (ECT) is the most effective and established treatment for these patients and is widely used in most psychiatric treatment settings in Australia. For example in the 2011-2012 reporting period, 18,803 ECT treatments were reported to the chief psychiatrist’s office in Victoria involving 1688 patients.

Even though ECT is used often it can have substantial problems including the common occurrence of cognitive side effects, such side effects are highly distressing for patients. The most cognitive side effects reported with ECT relate to memory (both memory for the past and the ability to form new memories) and disorientation immediately following treatment. The development of a new treatment which is as effective in treating depression as ECT is but which does not have these cognitive side effects would have great clinical value. A highly promising possibility is magnetic seizure therapy (MST), which was the focus of this research study.
Like ECT, MST involves the induction of a seizure; however in MST the seizure is induced through the use of magnetic stimulation rather than direct electrical current as occurs with ECT. This ensures a more focused seizure onset in the brain. By avoiding the use of direct electrical current and inducing a more focal seizure onset it was predicted that MST would result in an improvement in depression symptoms without the cognitive side effects seen with ECT. Patient studies of MST began in 2000, with approximately 40 patients undergoing the early form of MST between 2000 and 2006. These studies strongly suggested that MST had a much lower rate of cognitive side effects and patients recovered orientation much more rapidly that with ECT. Since these early studies the technology used to produce MST has advanced, and in 2008 a MST device was developed that was able to stimulate at a higher strength. This meant that MST was able to be delivered at a higher intensity that was equivalent to that of ECT, i.e. a number of times above the threshold required to induce a seizure. This type of MST is known as 100Hz MST.

There are only a handful of these devices in use worldwide, and in 2009 we began the first Australian investigation of 100Hz MST for the treatment of depression. This was a preliminary study, where 13 patients with depression received open label MST. We found that 38% of patients (5) met anti-depressant response criteria following the MST treatment, with a further 23% (3) achieving a partial anti-depressant response. There was no evidence of any impairment of orientation, memory, or other elements of cognition after MST treatment. There have now been a handful of trials of 100Hz MST worldwide, with the initial findings showing a more rapid recovery of orientation than traditionally seen with ECT, and a similar antidepressant response rate. The next step in this research was to undertake a head-to-head trial of MST versus ECT in order to provide a direct comparison between the two treatments. This is what we did in the current research study.
In summary, depression is an extremely common clinical problem affecting between 15-20% of the Australian population. It is less well recognised that 30% of patients with depression fail to respond to treatment. ECT remains the only established therapy for these patients. It is commonly used but has substantial problems including the occurrence of cognitive side effects that are often highly distressing for patients. The development of a new treatment with similar efficacy but which minimises these side effects would have great clinical value. Therefore, the aim of the current study was to compare the clinical and cognitive effects between MST and ECT in patients with moderate to severe depression.

**Implications**

Although we saw significant reductions in depression scores in patients overall, the percentage of patients that achieved either a partial or complete clinical response was low (38%). However, there was no difference in clinical response between ECT and MST. Additionally, MST did not produce any of the cognitive side effects seen with ECT. The next stage in this research, which we are currently planning, is to advance the way in which MST is delivered in order to produce higher response rates.

If MST can be shown to be possible of delivering response rates as high as those traditionally seen with ECT (i.e. around 60%) \(^6\), but with fewer side effects we anticipate that it could be rapidly adopted in clinical practice. All of the facilities are available for the provision of MST in every substantive mental health service in the country (in current ECT suites / facilities); all that would be required would be the replacement of the ECT machine with MST equipment for seizure induction. Therefore, it is envisioned that it could rapidly replace ECT in clinical practice throughout Australia and indeed internationally with substantial ongoing benefits to patients. This would be due to the greater tolerability of the procedure and potential acceptability to patients. The extremely rapid rate of recovery of post procedure orientation compared to ECT seen in the initial pilot studies, also suggests that MST would be a much more realistic outpatient treatment, as patients would not require
lengthy periods of observation post procedure which is usually the case with ECT. This would make a form of convulsive treatment potentially much more available to patients, reduce currently overburdened psychiatric hospital bed use and decrease health care costs.

**Approach**

**Design**

Full details of the methods and design of the study are included on the Australian New Zealand Clinical Trials Registry (ANZCTR: ANZCTRN12611000054910). The study was approved by the Alfred Health Human Research Ethics Committee and the Monash University Human Research Ethics Committee.

This was a randomised double-blind clinical trial with 2 treatment arms. This means that participants were randomly allocated to receive either a treatment course of MST or ECT. Participants and raters did not know which type of treatment was being received. The trial was based at the Alfred Hospital in Melbourne and was conducted by researchers at the Monash Alfred Psychiatry Research Centre (MAPrc). MAPrc is a clinical research centre focussed the development of new treatment approaches for patients with severe mental illness.

**Participants**

To be included in the trial participants were required to meet the following criteria:

- Have a DSM-IV diagnosis of a major depressive episode
- Be referred for or an outpatient course of ECT at the Alfred Hospital
- Be between the ages of 18-75 years
- Be experiencing an episode of at least moderate to severe depression (i.e. have a HAMD score of $>20$)
- Demonstrate that they are able to give informed consent
- Be considered sufficiently well to undergo general anaesthesia
• Not have an unstable medical condition, or neurological disorder
• Not be currently pregnant or lactating.
• Not have a cardiac pacemaker, cochlear implant or other implanted electronic or metallic devices.
• Not have any other significant mental illnesses diagnosis.

Participants were taken off anticonvulsant medications prior to treatment but remained on their antidepressant medication if it was deemed clinically appropriate to do so. A total of 40 participants were randomised into the study. The baseline demographics are provided in Table 1.

### Table 1. Baseline Demographics

<table>
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<th>Mean</th>
<th>Standard Deviation</th>
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<tr>
<td>Age</td>
<td>45.93</td>
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<td></td>
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<td></td>
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<td>Time since diagnosis (years)</td>
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<td>Number of antidepressant medications trialled</td>
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<td>Length of current illness (years)</td>
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<td>Baseline Depression Score (HAMD)</td>
<td>26.58</td>
<td>5.06</td>
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</table>

Of the 40 participants randomised 37 patients completed the trial. Of the three patients who withdrew 2 did so prior to the commencement of treatment (due to improvement in mood, difficulties with time commitment), the third withdrew following their first three treatments (difficulties with time commitment).

**Interventions: MST and ECT**

Stimulation was provided three times a week on Monday, Wednesday and Friday for a minimum of 3 and a maximum of 4 weeks. Propofol and succinylcholine was used for anaesthetic induction and muscle relaxation. The patient’s brain activity during the seizure was monitored throughout using electroencephalography (EEG).
MST Treatment Procedure

The MST coil used was a bilateral dual cone coil (See Figure One).

Figure 1: MST Set Up

All patients initially underwent a dose titration procedure to establish the intensity of stimulation needed to induce a seizure. Single simulation trains at 100% machine output were applied at 100 Hz at progressively increasing durations (commencing at 2 seconds and increasing each time by 2 seconds). Treatment sessions were then provided at the participants seizure threshold + 4 seconds (i.e. if the seizure threshold was 2 seconds, treatment was provided for 6 seconds).

ECT Treatment

ECT was given with a standard clinical ECT machine – Thymatron DGX. ECT treatment was be based on the seizure threshold which was determined at the first ECT session. In the majority of subjects we used right unilateral ECT at three times seizure threshold. Dose
increases during ECT treatment were determined by an independent psychiatrist rater who reviewed each seizure and received general information regarding clinical response from treating staff.

**Outcome Measures**

**Clinical**

Demographic variables and potential co-variates were recorded at baseline following a clinical interview. Diagnosis was assessed with the SCID (DSM IV). Primary clinical rating outcome measure was the Hamilton Depression Rating scale (HAMD).

**Cognitive**

All patients were assessed in regards to their cognitive function prior to and at the end of treatment. This included assessments of their memory for past events (Autobiographical Memory Interview), their ability to form new verbal and visual memories (Rey Verbal Auditory Learning Test, Verbal Paired Associates, Logical Memory, Brief Visual spatial Memory Test and Rey Complex Figure Test). We also looked at their attention, information processed and speed of thought (Digit Span, Digit Symbol Coding, and Trail Making Test). Finally, we also looked at executive function (Stroop, Verbal Fluency).

**Analysis of Clinical Outcomes**

The primary analysis was conducted on HAMD scores, and secondary analysis on cognitive scores from baseline to end of treatment. The primary analysis will compare the change in HAMD scores over time between the two groups, as well as looking at response rates between the groups (defined as a 50% reduction in HAMD scores). Multivariate analysis was performed using repeat measures, with a two-sided p value of 0.05 considered statistically significant.
Plans for Dissemination

The results of this research study will be disseminated in a number of ways. Articles for peer reviewed journals are currently being prepared. Results will also be presented in the form of conference presentation(s) as well as presentations to appropriate public forums. Our research group is of the belief that it is our responsibility to also disseminate research results to the general public: to this end appropriate media releases will be prepared and information provided through our Web site and publications of Monash University and the Alfred Hospital. In addition, we provided a specific report to each patient who participated in the study as well as an overall summary of the study results.

Results

There were no differences in the baseline demographics between the participants allocated to MST or ECT (See Table 2). Of the 37 patients who completed the trial 18 received MST and 19 received ECT.

Table 2. Baseline Demographics as a function of treatment group

<table>
<thead>
<tr>
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<th>MST Mean ± SD</th>
<th>ECT Mean ± SD</th>
<th>Sig</th>
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<tbody>
<tr>
<td>Age</td>
<td>44.76 ± 14.93</td>
<td>47.21 ± 16.13</td>
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<tr>
<td>Female/Male</td>
<td>9/12</td>
<td>13/6</td>
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<tr>
<td>Time since diagnosis (years)</td>
<td>21.74 ± 14.58</td>
<td>27.56 ± 14.39</td>
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<td>Number of antidepressant medications trialled</td>
<td>4.47 ± 3.28</td>
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<tr>
<td>Length of current illness (years)</td>
<td>10.57 ± 10.59</td>
<td>16.66 ± 17.67</td>
<td>ns</td>
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<tr>
<td>Baseline Depression Score (HAMD)</td>
<td>26.47 ± 5.23</td>
<td>26.68 ± 4.91</td>
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</tr>
</tbody>
</table>

Clinical Outcomes

Overall, all of the participants showed a significant improvement in their mood over the course of the trial, irrespective of whether they received ECT or MST (See Figure 2).
With respect to clinical response rates, 38% of patients who completed the trial experienced either a partial (n= 10) or complete clinical response (n=4) to the treatment. Again, the response rates did not significantly differ between the MST and ECT groups.

**Cognitive Outcomes**

On the assessment of memory for the past, participants who had MST were able to retain more information following treatment (82%) compared to those who have ECT (72%) – although the difference was not significant. See Figure 3.

*Figure 2. Change in HAMD score over time by treatment group.*

*Figure 3. Mean percent memory retention following treatment by treatment group. Error bars show standard error of the mean.*
Participants who underwent MST also showed significantly improved performances on cognitive tests of information processing speed, immediate verbal memory, and executive functioning. They also showed near significant improvements on attention, associate learning, delayed verbal memory and working memory. There was no reduction in cognitive performance across any of the tasks in the MST group. Figures 4 – 6 below show the significant results only.

**Figure 4.** Mean performance from baseline to endpoint on task of information processing speed (Digit Symbol Coding) in the MST group. A higher score indicates improved performance. Error bars show standard error of the mean.

**Figure 5.** Mean performance from baseline to endpoint on task of immediate verbal memory (Story Memory – immediate recall) in the MST group. A higher score indicates improved performance. Error bars show standard error of the mean.
The participants who underwent ECT largely exhibited non-significant reductions in performances across the cognitive tasks. They did show a significantly reduced performance on a test of information processing speed, and a near significant reduction on a test of executive functioning. Figure 7 below shows the significant result only.
Further research

Over recent years we have conducted several initial MST studies, all of which have received funding from beyondblue. In the current study we compared MST and ECT in a direct head to head randomised double blind trial. As described in this report the results of this study suggest that MST may well have similar efficacy to ECT without cognitive side effects. The next stage of this program of research will investigate optimised forms of MST in order to investigate whether it is possible to obtain higher clinical response rates than those reported with standard MST to date. We are currently planning a trial which will address this question, and we will compare an optimised way of delivering MST (lower intensity of stimulation for a longer period of time) to the standard MST approach as was used in this study.

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