

Transcranial magnetic stimulation-based methods in the treatment of depression

SUMMARY

A substantial proportion of patients fail to respond to standard treatments for depression. Several new methods of stimulating the brain are being developed as alternative interventions for these and other patient groups.

Repetitive transcranial magnetic stimulation is a method of brain stimulation that involves the application of repeated magnetic pulses to directly activate cortical neurones. Several studies show it has antidepressant efficacy.

There are few adverse effects of repetitive transcranial magnetic stimulation. However, the optimal stimulation parameters are not yet fully established.

Introduction

Major depressive disorder is common and disabling with a lifetime prevalence of around 15%.¹ There are a range of psychosocial treatments and drugs for depression. Despite these options, approximately 30% of patients remain unwell with 'treatment-resistant depression' resulting in substantial suffering as well as high treatment costs.² The main established treatment option for patients with treatment-resistant depression is electroconvulsive therapy (ECT) but this has cognitive adverse effects, requires general anaesthesia and has a stigma associated with it.³ This has prompted research into new methods of brain stimulation.

Repetitive transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation (rTMS) has recently been developed as an additional option for treatment-resistant depression. It may also have a role for patients who cannot tolerate other treatments.

rTMS involves the application of a rapidly time variable magnetic field, administered via a coil placed over the scalp, to stimulate brain activity⁴ (see Fig. 1). A high voltage current in the coil generates a focused magnetic field which passes into the brain and induces an electrical field. This induces depolarisation of superficial cortical neurones.⁴ Repeated high frequency stimulation increases brain activity, and

low frequency stimulation decreases it.⁵ rTMS can be applied either directly to nonconvulsively modulate brain activity or to induce a focused seizure (magnetic seizure therapy).

Procedure

rTMS is usually given in a discrete course, most commonly daily for between 15 and 30 consecutive weekdays. Treatment sessions, which can safely be provided to outpatients, take between 30 and 45 minutes and there are no restrictions on what patients are able to do after the treatment. rTMS needs a medical prescription and administration by an appropriately trained healthcare professional who can deal with a seizure if one occurs.⁶ No sedation or anaesthetic is required.

Efficacy in depression

Standard nonconvulsive rTMS has been investigated as a treatment for depression since the mid-1990s. The standard strategy applies repeated high frequency pulses to the left dorsolateral prefrontal cortex. This region of the brain appears to be underactive in the brain scans of depressed patients.^{7,8} There have been more than 30 double-blind placebo-controlled trials of this method and several meta-analyses. One meta-analysis of 30 trials and 1164 patients found a highly significant effect ($p < 0.00001$) of active treatment compared to sham treatment on the

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Fig. 1 Repetitive transcranial magnetic stimulation procedure



average reduction in depression severity scores.⁹ The effect sizes seen with rTMS are similar to those seen with antidepressant drugs,¹⁰ despite many of the trials enrolling patients with treatment-resistant depression. However, it is notable that response rates across the trials are usually less than 50%, and remission rates are often much lower. Very modest response rates were seen in the two large multisite trials conducted to date, one sponsored by a device manufacturer¹⁰ and one independently funded by the US National Institute of Mental Health.¹¹ Both found statistically significant benefits of rTMS over sham treatment. The first of these trials¹⁰ was used to support a successful application to the US Food and Drug Administration which approved the treatment in 2008.

Comparison with ECT (Table 1)

The trials which have compared rTMS to ECT¹²⁻¹⁵ have generally been underpowered to identify between-treatment differences. Their design is often biased towards a likely finding of a benefit of ECT as longer and more flexible courses of ECT, for example including both unilateral and bilateral approaches, were generally provided. Two studies have shown an advantage of ECT, and an advantage of ECT was supported in a recent meta-analysis of six studies.¹⁶ However, none of these rTMS studies included treatment beyond 20 sessions and all used treatment intensities (percentage of maximum machine output) and total numbers of rTMS pulses below what is now generally considered optimal. ECT clearly produces a faster treatment response than rTMS, although accelerated rTMS protocols are showing some promise in rapid symptom improvement.¹⁷

Adverse effects

One of the major benefits of rTMS is its benign adverse effect profile.¹⁸ Some patients find the treatment uncomfortable or experience a transient headache

afterwards, but there are no other major reported adverse effects. rTMS can induce seizures but the risk is extremely low when treatment is applied following standard safety guidelines.¹⁹ The induction of mania is possible in patients with bipolar disorder, but has not been reported in unipolar depression.²⁰

Uncertainties

Standard left-sided rTMS clearly has antidepressant properties but there are a range of issues that remain unresolved. These include the optimal method of administration. Other forms of rTMS such as low frequency stimulation applied to the right dorsolateral prefrontal cortex and bilateral rTMS also have efficacy.²¹ Other uncertainties include the individualisation of treatment parameters and the evaluation of maintenance protocols to limit the problematic issue of depressive relapse. rTMS also appears a useful treatment for patients with relative contraindications to drugs and ECT or when there is a wish to avoid these treatments, such as during pregnancy, but only limited data on such uses are currently available.²²

Magnetic seizure therapy

The therapeutic benefits of ECT may be related to the seizure, rather than the direct electrical current. Researchers are investigating the effects of using rTMS to provoke a seizure. This requires rTMS to be applied at a frequency and intensity beyond that used in standard therapy. As with ECT, a general anaesthetic is required.

Several human trials of magnetic seizure therapy have begun but currently insufficient data are available to confirm its place in treatment. Open-label data and a small comparative trial²³ have suggested that it might have similar efficacy to ECT with fewer cognitive adverse effects, although this conclusion is still very preliminary.

Table 1 Characteristics of repetitive transcranial magnetic stimulation and electroconvulsive therapy

	REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION	ELECTROCONVULSIVE THERAPY
Action	Nonconvulsive	Convulsive
Indications	Treatment-resistant depression Failure to tolerate other treatments for depression Possible first-line treatment based on patient choice	Severe depression Treatment-resistant depression Catatonia Emergency treatment of depression requiring urgent clinical response
Efficacy	Moderately well established Response rates <50%	Well established Response rates >50%
Safety	Low risk of seizure induction No cognitive adverse effects No general anaesthetic	Risks associated with general anaesthesia Memory impairment, possible other cognitive adverse effects

Conclusion

A range of novel brain stimulation technologies are currently under active investigation for the treatment of depression. rTMS has progressed down this developmental path to a point where it is currently entering into clinical practice. However, further research is still required to optimise its application. Its availability in Australia is currently limited by the lack of a Medicare rebate for treatment. Only limited treatment programs subsidised by hospital services and without direct patient charge are

currently accessible in some private and public hospitals. Magnetic seizure therapy is at an earlier stage of development but there are some promising preliminary results. <

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FURTHER READING

Royal Australian and New Zealand College of Psychiatrists. Clinical Memorandum #18. Transcranial magnetic stimulation. 2008 Feb.



SELF-TEST QUESTIONS

True or false?

- Unlike electroconvulsive therapy, repetitive transcranial magnetic stimulation therapy does not require a general anaesthetic.
- Repetitive transcranial magnetic stimulation therapy induces remission in more than 50% of patients with treatment-resistant depression.

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