Non-pharmacological biological treatment approaches to difficult-to-treat depression

Summary

- There has been substantial recent interest in novel brain stimulation treatments for difficult-to-treat depression.
- Electroconvulsive therapy (ECT) is a well established, effective treatment for severe depression. ECT's problematic side-effect profile and questions regarding optimal administration methods continue to be investigated.
- Magnetic seizure therapy, although very early in development, shows promise, with potentially similar efficacy to ECT but fewer side effects.
- Vagus nerve stimulation (VNS) and repetitive transcranial magnetic stimulation (rTMS) are clinically available in some countries. Limited research suggests VNS has potentially long-lasting antidepressant effects in a small group of patients. Considerable research supports the efficacy of rTMS. Both techniques require further study of optimal treatment parameters.
- Transcranial direct current stimulation may provide a low-cost antidepressant option if its efficacy is substantiated in larger samples.
- Deep brain stimulation is likely to remain reserved for patients with the most severe and difficult-to-treat depression, requiring further exploration of administration methods and its role in depression therapy.
- New and innovative forms of brain stimulation, including low-intensity ultrasound, low-field magnetic stimulation and epidural stimulation of the cortical surface, are in early stages of exploration and are yet to move into the clinical domain.
- Ongoing work is required to define which brain stimulation treatments are likely to be most useful, and in which patient groups. Clinical service development of brain stimulation treatments will likely be inconsistent and variable.

It is well recognised that depression frequently does not respond to standard pharmaceutical treatment and psychotherapy techniques.[1,2] Non-pharmacological biological treatments have a long history of use in difficult-to-treat psychiatric illnesses such as depression. With increasing recognition of the frequency and impact of difficult-to-treat depression and a variety of technological developments, the past 10 years have seen a dramatic increase in interest in development of novel brain stimulation techniques. Here, I provide an overview of the characteristics and current status of development of non-pharmacological biological treatments for depression (Box).

Electroconvulsive therapy

Electroconvulsive therapy (ECT) is the most widely used and effective non-pharmacological biological treatment for depression and remains the most effective treatment for difficult-to-treat depression. Its use is particularly indicated when a rapid antidepressant response is required, such as in highly suicidal patients.

Although ECT has been in use for well over 50 years and is a commonly applied clinical tool, questions regarding optimal methods of administration remain. Cognitive side effects, especially anterograde and retrograde amnesia, remain problematic, as does the substantial stigma associated with this treatment in the community. Over the past 10 years, slow progress has been made in refining ECT administration techniques, especially focused on trying to achieve maximum therapeutic benefit with minimal cognitive side effects. Studies have tended to confirm that right unilateral ECT at sufficient intensity has similar efficacy to bilateral treatment,[5] although bilateral treatment may result in a more rapid clinical response. Bifrontal stimulation has not proven to be a substantial advance over other more traditional approaches.[5] Considerable focus has also been given to the use of ultra-brief pulse-width stimulation to try to minimise cognitive side effects. Similar efficacy has been reported in some studies,[6,7] although response to ultra-brief treatment may take longer than standard approaches[8] or be somewhat less than the response to bilateral treatment.[9] ECT can be life-saving, especially in urgent clinical situations, and remains a valuable tool for patients with severe depression that does not respond to other therapies.

Repetitive transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation (rTMS) is a novel, non-convulsive brain stimulation technique that involves the repeated application of a time-variable magnetic field to superficial areas of the cortex through a stimulating coil held above the scalp.[10] Magnetic fields applied at sufficient intensity to the brain will induce electrical activity in cortical neurones, including depolarisation. Repeated stimulation of local groups of neurones will result in changes in local cortical activity and the stimulation of distal brain regions through the activation of projecting neurones. High-frequency rTMS (pulses applied at 5–20 Hz) is known to increase local cortical excitability, and low-frequency stimulation (usually 1 Hz) has the opposite effect.[11] In a therapeutic context, rTMS is usually provided in sessions lasting between 20 and 45 minutes, 5 days a week, for 3–6 weeks.

In the initial studies, high-frequency rTMS was applied to the left dorsolateral prefrontal cortex (DLPFC), following observation of this brain region as underactive in patients with depression.[12] Many sham-controlled studies, including two large multisite trials, have investigated the efficacy of this form of stimulation. Several meta-analyses have summarised the results of these trials, with the more recent analyses showing clear positive antidepressant effects. For example, in a meta-analysis involving 30 trials and 1164

Paul B Fitzgerald
MB BS, PhD, FRANZCP, Professor of Psychiatry

Monash Alfred Psychiatry Research Centre, Monash University and Alfred Health, Melbourne, VIC.

paul.fitzgerald@monash.edu

MJA Open 2012; 1 Suppl 4: 48–51
doi: 10.5694/mjao12.10509

patients, there was a highly significant effect of active treatment compared with placebo on the average reduction in depression severity scores ($P < 0.001$).[13] The included trials involved a mixture of patients with treatment-resistant and non-treatment-resistant depression and produced effect sizes (typically moderate) similar to those seen with antidepressant medication.[13] Trials have also compared rTMS with ECT, but substantial inequalities in the treatments provided in these studies (eg, the number of treatment sessions) make interpretation of the results problematic. Both of the two large multisite trials (one independently sponsored and one industry sponsored) showed greater antidepressant effects of active rTMS compared with sham treatment.[14,15] Remission rates (usually defined as a reduction of rating scale scores below a certain low cut-off) were similar to those seen in medication trials with comparable patient populations.

The result of these trials has been the development of clinical rTMS programs in several countries, including the United States, Canada, Germany and Australia. One rTMS device was licensed for depression treatment in the US in 2008 and is now used in over 200 clinical services. The first publicly funded rTMS treatment program in Australia commenced operation in Victoria in early 2012. Despite this clinical progression, substantial questions remain regarding the optimal methods for rTMS application. High-frequency stimulation to the left DLPFC is not the only effective method for rTMS application. There is evidence for the equivalent efficacy of low-frequency stimulation applied to the right DLPFC and interest in the development of bilateral methods of stimulation.[16] Stimulation efficacy may be found to improve with the use of better brain site targeting and possibly with novel, more complex stimulation methods. Research is also required to define the best methods of maintenance rTMS.

Generally speaking, rTMS treatment is safe and well tolerated.[17,18] There is a very low risk of incidental seizure induction, and some patients find the procedure uncomfortable, or it may produce a transient headache. Switch to mania in patients with bipolar disorder is also possible. However, overall rates of treatment adherence are very high and no other major adverse consequences have emerged, despite more than 15 years of clinical trials. rTMS is likely to be a suitable approach for patients in whom one or more medication treatment trials have failed but who do not require a rapid antidepressant response that would justify immediate ECT.

Magnetic seizure therapy

Magnetic seizure therapy (MST) is a technique that combines both rTMS and ECT. During MST, a high-

Characteristics of brain stimulation treatments for depression

	Electroconvulsive therapy	Repetitive transcranial magnetic stimulation	Magnetic seizure therapy	Transcranial direct current stimulation	Vagus nerve stimulation	Deep brain stimulation
Type of intervention	Convulsive	Non-convulsive	Convulsive	Non-convulsive	Surgical	Surgical
Established treatment indications*	Severe depression Difficult-to-treat depression Catatonia Emergency treatment of depression requiring urgent clinical response	Difficult-to-treat depression Failure to tolerate other treatments for depression One failed medication trial (United States[3])			Difficult-to-treat depression (four failed medication trials in US[4])	
Likely or possible treatment indications†			Severe depression Difficult-to-treat depression	Difficult-to-treat depression First-line treatment of depression		Highly difficult-to-treat depression
Efficacy‡	Well established, response rates > 50%	Well established, response rates < 50%	Limited data, response rates > 50%	Limited data suggest response rates < 50%	Moderately well established data, response rates < 50%	Limited data, response rates > 50%
Safety	Risks associated with general anaesthesia Memory impairment, possibly other cognitive side effects	Well tolerated Very low risk of seizure induction No cognitive side effects	Risks associated with general anaesthesia No apparent substantial cognitive side effects	Well tolerated May produce skin irritation, headaches No serious adverse events reported	Moderately well tolerated Voice and throat effects may persist	Implantation-associated risks: seizure, haemorrhage, infection May reversibly produce a range of adverse effects
Status in Australia in 2012§	Widely available in public and private settings	Available in private services in some states; public services developing	Research only (Victoria)	Research only (Victoria, New South Wales)	Research only (New South Wales)	Research only (Victoria)

* In some countries, not necessarily Australia. † Based on completion of adequate trials. ‡ Response rate is usually defined as a 50% or greater reduction of mean total score on a predetermined rating scale, usually the Hamilton Depression Rating Scale, with treatment. § Location of known trials and services indicated. ◆

powered rTMS device is used to induce a seizure as an alternative to the electrical current used in ECT. The procedure is otherwise performed in a similar manner to ECT, involving a general anaesthetic and muscle relaxant.

The potential for MST arose from the observation that it might be possible to dissociate the therapeutic benefits of ECT from its cognitive side effects — specifically, that the benefits might arise through the induced seizure but the side effects from the electrical method of seizure induction. Studies investigating the safety of MST have been conducted for more than 10 years, supporting the notion that magnetic seizure induction does not appear to produce substantial cognitive side effects. Therapeutic studies have been limited until recent years by the power of stimulation devices. Trials using rTMS stimulation at up to 100 Hz are now being conducted, with early data suggesting similar therapeutic efficacy to ECT, with a benign cognitive profile.[19] For example, in the first small randomised comparison, response rates (defined as a 50% reduction in Montgomery–Åsberg Depression Rating Scale scores) were 60% for MST and 40% for ECT.[19]

Substantive clinical trials of MST are required to establish its efficacy. However, it could be relatively rapidly taken up in clinical practice, using established ECT infrastructure, if its benign cognitive profile is matched by substantial therapeutic efficacy.

Transcranial direct current stimulation

Brain activity can also be changed with the application of a very low-voltage electrical current, termed transcranial direct current stimulation (tDCS). This technique was first proposed in the 1950s, but there has been a resurgence of interest in the past 10 years as studies have demonstrated clearly that it has definite biological effects. When a low-amplitude (1–2 mA) direct current is applied to the brain through two surface electrodes placed on the scalp,[20] cortical activity under the anode (positive electrode) is increased due to a shift in membrane polarisation that results in secondary synaptic effects. In contrast, activity under the cathode is reduced.

Observation of these effects led to interest in the use of anodal stimulation applied to the left DLPFC for treating depression. The efficacy of this approach has been assessed in a series of small randomised controlled trials, and the results have recently been summarised in a meta-analysis that included six trials (involving a total of 96 active and 80 sham treatment courses).[21] A positive antidepressant effect was noted across this limited sample. In a recent single-site study with a larger patient sample ($n = 64$), tDCS produced a greater reduction in mean depression rating scale scores than did sham stimulation, although there was no difference in response rates and no patients achieved remission status.[22] Although no large studies have yet been published, the safety profile of tDCS appears promising. The procedure can result in local irritation or headache, but these effects appear to be predominantly transient.[23,24]

tDCS shows promise as an antidepressant treatment but remains in very early stages of development. Its potential applicability is wide, as tDCS machines can be produced at very low cost, offering the possibility of it being made available in less affluent countries.

Vagus nerve stimulation

Vagus nerve stimulation (VNS) is a procedure involving the surgical implantation of a pulse generator (similar to a pacemaker) in the chest, connected to a stimulating electrode attached to the vagus nerve in the neck.[25,26] Stimulation of the vagus nerve results in activation of a variety of subcortical brain structures, which may reduce seizure frequency in refractory epilepsy and also has antidepressant effects.

Following approval of VNS for treating epilepsy, trials investigating its antidepressant activity were conducted. Initial open-label efficacy data were promising, although a multisite randomised trial produced disappointing results, with a very low response rate no different from that for sham stimulation.[27] However, long-term follow-up suggested that a small group of patients do respond to VNS, even if they have a long history of illness and treatment resistance.[27] Response appears to take some time to develop but persists with continued use.[27] The main side effects with VNS include an alteration of voice, neck discomfort, cough and dysphagia.[28]

VNS treatment for depression has been approved in the US since 2005 for patients in whom at least four medication trials have failed, but similar approval has not been granted in Australia and VNS is not commonly used in this country for this indication.

Deep brain stimulation

Deep brain stimulation (DBS) is the most invasive of the modern brain stimulation approaches to the treatment of depression and other difficult-to-treat psychiatric disorders, such as obsessive–compulsive disorder. Like VNS, DBS was developed for a neurological indication — Parkinson disease — where it is relatively widely used. It involves the implantation of a pulse generator connected to two stimulating electrode wires, which are surgically placed in specific brain regions. Four electrodes are located at the ends of the wires. After implantation, a clinician adjusts a variety of stimulation parameters, including voltage, pulse width and frequency, to try to achieve symptom abatement.

DBS trials in depression have focused on two brain regions. The majority of patients have received implantation in the white matter next to the subgenual anterior cingulate cortex, an area of the brain repeatedly identified in brain imaging studies as related to antidepressant response. Response rates to stimulation in patients with highly difficult-to-treat depression have been reported as around or greater than 50%, with persistent benefit over a 3-year follow-up period.[29] Response rates close to 50% have also been seen in small groups of patients who received implantation in the anterior limb of the internal capsule or in the nucleus accumbens at its ventral end. For example, in 15 patients, stimulation of the internal capsule resulted in a 40% response rate at 6 months and a 53% response rate at final follow-up (at a mean of 23.5 ± 14.9 months).[30]

Side effects can arise with the DBS surgical procedure, as well as with the stimulation. The former can include haemorrhage, seizure induction, infection (usually superficial) and other anaesthetic complications, which are fortunately uncommon. Side effects related to stimulation

can include the induction of lowered mood, fear and anxiety.[31] These are reversible — a substantial advantage over the lesional psychosurgical procedures that DBS has mostly replaced.

Considerable attention has been attracted to the use of DBS in recent years but, because of its invasive nature, it is likely to remain reserved for patients with the most severe and difficult-to-treat depression. Although mostly being provided in clinical trials, it has already replaced the use of lesional psychosurgery in most countries where it is being evaluated. Further research is required to define its role and the most effective method of administration.

New and emerging approaches

Several techniques that are yet to move into the clinical domain are in the early stages of exploration as potential ways of modulating brain activity. For example, recent research has demonstrated that low-intensity ultrasound has the capacity to produce neuronal depolarisation, possibly through the mechanical stimulation of ion channels.[32] This potential application of ultrasound differs from the use of high-intensity ultrasound as a means of ablating tissue and involves intensities not associated with tissue damage. Research is also investigating the application of low-field magnetic stimulation, following the observation of mood changes with specific magnetic resonance imaging paradigms[33] and the effects of other forms of cranial electrical stimulation. Stimulation of the cortical surface with epidurally implanted electrodes has also demonstrated some antidepressant potential in very early pilot-stage research.[34]

Conclusions

Non-pharmacological biological approaches, mostly in the form of ECT, have contributed to the management of depression for many years, and there is currently a rapid expansion of potential therapeutic tools in this area. rTMS is increasingly being used in clinical practice, and other treatments such as VNS have been approved for use in some jurisdictions. Other approaches, some with considerable apparent potential to contribute to the clinical management of depression, are in earlier stages of evaluation. As some of these treatments, such as rTMS, require new clinical infrastructure, the development of services is likely to be inconsistent and variable for some time. Ongoing work is required to define which treatments are likely to be most useful, and in which patient groups.

Competing interests: I have received equipment for research from Medtronic, MagVenture A/S and Brainsway. I have undertaken research with funding and equipment from Cervel Neurotech. I am supported by a National Health and Medical Research Council (NHMRC) Practitioner Fellowship and have project research funds from the NHMRC, the Australian Research Council, Alfred Health, *beyondblue* and Monash University.

Provenance: Commissioned by supplement editors; externally peer reviewed.

1 Fava M. Diagnosis and definition of treatment-resistant depression. *Biol Psychiatry* 2003; 53: 649-659.
2 Fava M, Davidson KG. Definition and epidemiology of treatment-resistant depression. *Psychiatr Clin North Am* 1996; 19: 179-200.
3 United States Food and Drug Administration. Guidance for industry and FDA staff – Class II special controls guidance document: repetitive transcranial magnetic stimulation (rTMS) systems. Rockville, Md: FDA, 2011. http://www.fda.gov/MedicalDevices/DeviceRegulationand Guidance/GuidanceDocuments/ucm265269.htm (accessed Jun 2012).
4 United States Food and Drug Administration. VNS Therapy System – P970003s050. Silver Spring, Md: FDA, 2009. http://www.fda.gov/Medical Devices/ProductsandMedicalProcedures/DeviceApprovalsand Clearances/Recently-ApprovedDevices/ucm078532.htm (accessed Jun 2012).
5 Kellner CH, Knapp R, Husain MM, et al. Bifrontal, bitemporal and right unilateral electrode placement in ECT: randomised trial. *Br J Psychiatry* 2010; 196: 226-234.
6 Sackeim HA, Prudic J, Nobler MS, et al. Effects of pulse width and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. *Brain Stimul* 2008; 1: 71-83.
7 Niemantsverdriet L, Birkenhager TK, van den Broek WW. The efficacy of ultrabrief-pulse (0.25 millisecond) versus brief-pulse (0.50 millisecond) bilateral electroconvulsive therapy in major depression. *J ECT* 2011; 27: 55-58.
8 Loo CK, Sainsbury K, Sheehan P, Lyndon B. A comparison of RUL ultrabrief pulse (0.3 ms) ECT and standard RUL ECT. *Int J Neuropsychopharmacol* 2008; 11: 883-890.
9 McCormick LM, Brumm MC, Benede AK, Lewis JL. Relative ineffectiveness of ultrabrief right unilateral versus bilateral electroconvulsive therapy in depression. *J ECT* 2009; 25: 238-242.
10 Barker AT. An introduction to the basic principles of magnetic nerve stimulation. *J Clin Neurophysiol* 1991; 8: 26-37.
11 Fitzgerald PB, Fountain S, Daskalakis ZJ. A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. *Clin Neurophysiol* 2006; 117: 2584-2596.
12 George MS, Ketter TA, Post RM. Prefrontal cortex dysfunction in clinical depression. *Depression* 1994; 2: 59-72.
13 Schutter DJ. Antidepressant efficacy of high-frequency transcranial magnetic stimulation over the left dorsolateral prefrontal cortex in double-blind sham-controlled designs: a meta-analysis. *Psychol Med* 2009; 39: 65-75.
14 O'Reardon JP, Solvason HB, Janicak PG, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biol Psychiatry* 2007; 62: 1208-1216.
15 George MS, Lisanby SH, Avery D, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. *Arch Gen Psychiatry* 2010; 67: 507-516.
16 Fitzgerald PB, Benitez J, de Castella A, et al. A randomized, controlled trial of sequential bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression. *Am J Psychiatry* 2006; 163: 88-94.
17 Machii K, Cohen D, Ramos-Estebanez C, Pascual-Leone A. Safety of rTMS to non-motor cortical areas in healthy participants and patients. *Clin Neurophysiol* 2006; 117: 455-471.
18 Loo CK, McFarquhar TF, Mitchell PB. A review of the safety of repetitive transcranial magnetic stimulation as a clinical treatment for depression. *Int J Neuropsychopharmacol* 2008; 11: 131-147.
19 Kayser S, Bewernick BH, Grubert C, et al. Antidepressant effects, of magnetic seizure therapy and electroconvulsive therapy, in treatment-resistant depression. *J Psychiatr Res* 2011; 45: 569-576.
20 Paulus W. Transcranial direct current stimulation (tDCS). *Suppl Clin Neurophysiol* 2003; 56: 249-254.
21 Kalu UG, Sexton CE, Loo CK, Ebmeier KP. Transcranial direct current stimulation in the treatment of major depression: a meta-analysis. *Psychol Med* 2012; 42: 1791-1800.
22 Loo CK, Alonzo A, Martin D, et al. Transcranial direct current stimulation for depression: 3-week, randomised, sham-controlled trial. *Br J Psychiatry* 2012; 200: 52-59.
23 Brunoni AR, Amadera J, Berbel B, et al. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *Int J Neuropsychopharmacol* 2011; 14: 1133-1145.
24 Poreisz C, Boros K, Antal A, Paulus W. Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. *Brain Res Bull* 2007; 72: 208-214.
25 George MS, Sackeim HA, Marangell LB, et al. Vagus nerve stimulation. A potential therapy for resistant depression? *Psychiatr Clin North Am* 2000; 23: 757-783.
26 Goodnick PJ, Rush AJ, George MS, et al. Vagus nerve stimulation in depression. *Expert Opin Pharmacother* 2001; 2: 1061-1063.
27 Sackeim HA, Brannan SK, Rush AJ, et al. Durability of antidepressant response to vagus nerve stimulation (VNS). *Int J Neuropsychopharmacol* 2007; 10: 817-826.
28 Marangell LB, Rush AJ, George MS, et al. Vagus nerve stimulation (VNS) for major depressive episodes: one year outcomes. *Biol Psychiatry* 2002; 51: 280-287.
29 Kennedy SH, Giacobbe P, Rizvi SJ, et al. Deep brain stimulation for treatment-resistant depression: follow-up after 3 to 6 years. *Am J Psychiatry* 2011; 168: 502-510.
30 Malone DA Jr, Dougherty DD, Rezai AR, et al. Deep brain stimulation of the ventral capsule/ventral striatum for treatment-resistant depression. *Biol Psychiatry* 2009; 65: 267-275.
31 Okun MS, Mann G, Foote KD, et al. Deep brain stimulation in the internal capsule and nucleus accumbens region: responses observed during active and sham programming. *J Neurol Neurosurg Psychiatry* 2007; 78: 310-314.
32 Tyler WJ, Tufail Y, Finsterwald M, et al. Remote excitation of neuronal circuits using low-intensity, low-frequency ultrasound. *PLoS One* 2008; 3: e3511.
33 Rohan M, Parow A, Stoll AL, et al. Low-field magnetic stimulation in bipolar depression using an MRI-based stimulator. *Am J Psychiatry* 2004; 161: 93-98.
34 Nahas Z, Anderson BS, Borckardt J, et al. Bilateral epidural prefrontal cortical stimulation for treatment-resistant depression. *Biol Psychiatry* 2010; 67: 101-109. ❑