Health Policy Advisory Committee on Technology

Technology Brief

Transcranial magnetic resonance-guided focused ultrasound and deep brain stimulation for refractory depression

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AHTA
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emerging health technology

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Summary of findings

Two technologies for treatment of refractory depression were considered in this Brief: transcranial magnetic resonance-guided focused ultrasound (tcMRg FUS) and deep brain stimulation (DBS). No reports on human studies on the use of tcMRg FUS for the treatment of refractory depression were identified, though ClinicalTrials.gov indicates that trials are underway. While deep brain stimulation (DBS) is an established technology for a number of neurological motor conditions, psychiatric applications are currently prohibited in several jurisdictions throughout Australia, and the use of the technology overseas to treat refractory depression is considered experimental/investigational. A small number of inconclusive, low level studies on DBS for depression were identified in the peer reviewed literature. Only one small randomised controlled trial of DBS for depression, claiming to be the first such trial, was identified. The trial failed to show any differences in treatment effectiveness between DBS and sham stimulation. A total of 71 serious adverse events related to DBS, including worsening depression, suicidal ideation, suicide attempt, implant site infection, and lead revision for reasons including but not limited to infection, were observed among nearly three quarters of study participants.

HealthPACT Advice

There is a real need for an effective treatment for refractory depression with up to one third of diagnosed patients not responding to standard medication and psychological therapy. Although DBS is an established technology for other neurological conditions, published studies indicate the use of DBS for refractory depression is associated with high rates of serious adverse events. As such, HealthPACT does not support public investment in DBS for refractory depression in clinical practice at this time, and recommends no further review of the evidence is warranted.

The evidence base for tcMRg FUS for the treatment of refractory depression is immature, however initial studies on a very small number of humans published since the completion of this brief have reported improvements in depressive and obsessive/compulsive disorder symptoms. Given the ongoing research and the evolving evidence base on tcMRg FUS, HealthPACT recommends that this technology be reassessed in 24 months.

Technology, Company and Licensing

Register ID	**WP245**
Technology name	**Treatments for refractory depression including deep brain stimulation and transcranial magnetic resonance imaging-guided focused ultrasound**
Patient indication	**Refractory depression**

Description of the technology

Deep brain stimulation (DBS) is a neuromodulatory technique which has been widely researched and is established for the treatment of a range of neurological conditions. Neuromodulation is either non-invasive or invasive, depending on the method by which the brain is stimulated.[1] Non-invasive options include electroconvulsive therapy (ECT), transcranial magnetic stimulation and transcranial direct current stimulation. These are beyond the scope of this Brief and are not further discussed. Invasive options include vagal nerve stimulation and *deep brain stimulation*; neither of these technologies are limited to the treatment of depression, but DBS for indications other than depression are also beyond the scope of this Brief. The efficacy and safety of DBS in treating neurological disorders of movement (e.g. Parkinson disease, essential tremor, dystonia), combined with its advantages over traditional ablative neurosurgical procedures (e.g. reversibility, easy modification of stimulation parameters), have more recently led to applications of DBS for the treatment of psychiatric disorders, including major depressive disorder that is unresponsive to pharmacotherapy and other established treatments.[a1]

Deep brain stimulation utilises a neurosurgical procedure to implant intracranial electrodes in a specific region of the brain. The electrodes are connected to a programmable, implantable pulse generator (IPG) in the patient's chest wall. The procedure to place the implantable components makes DBS is the most invasive therapy of all currently available neuromodulation approaches. Post-implantation, stimulation is always on and in most cases continues indefinitely. Periodically, stimulation parameters are adjusted with the aim of maintaining the therapeutic benefit.[1, 2]

The exact mechanism by which DBS operates is still debated. The early theory that DBS simply induces a reversible inhibitory lesion has been superseded by data indicating that DBS produces both immediate and long-term, target-specific effects on the pattern and rate of neuronal firing. In depression, DBS has been used to target nodes within dysregulated mood circuits that perpetuate the depressed state. The most common target area has been

[a] Simplified definitions of major depression, sometimes called major depressive disorder, clinical depression, unipolar depression or simply "depression", are available from www.beyondblue.org.au. Clinical depression may be described as mild, moderate or severe; melancholic or psychotic. The blanket term "depression" is subsequently used throughout this Overview to indicate a *clinical diagnosis* of depression/depressive disorder for purposes of consistency and convenience.

the subgenual cingulate cortex (SCC), although the ventral caudate/striatum, nucleus accumbens and inferior thalamic peduncle have also been investigated.[1]

Treatment of refractory depression using transcranial magnetic resonance imaging-guided focused ultrasound (tcMRg FUS) is a novel area of research; available literature is sparse, no human clinical trials of this technology for the indication of interest were identified, and recent reviews by several authors suggest only animal and cadaver research has been published to date.[3-5]

The application of tcMRg FUS for depression targets specific areas of brain tissue for ablation via rapid temperature rises.[3] While ablative surgical procedures have been used to treat refractory psychiatric disease for more than 70 years, and procedures have changed dramatically over time, the central premise is equally applicable now to tcMRg FUS: disruption of the limbic pathways connecting frontal and subcortical structures. The most common ablative procedures for depression are cingulotomy and anterior capsulotomy. Both the anterior cingulate and anterior limb of the internal capsule are within current "treatment envelopes" for tcMRg FUS. For patients experiencing inadequate response to conventional psychiatric treatment, or those who cannot tolerate other approaches, tcMRg FUS may provide a treatment alternative. It is conceived that real-time guidance using magnetic resonance imaging and the ability to re-treat recurrence non-invasively are among the advantages offered by tcMRg FUS over conventional ablative surgery.[4]

tcMRg FUS typically utilises a hemispherical helmet-like array of 1,024 transducer elements that can focus ultrasound through the skull to the mid brain. All components, inclusive of transducer, electronic driver, cooled degassed water system, and workstations, are integrated into an MRI scanner. Prior to the procedure, the patient's skull is analysed with a CT scan to obtain information about skull thickness and to determine the patient-specific phase aberration corrections necessary for each element of the array. Sonications of the target tissue volume proceed and are incrementally increased in acoustic power until an ablation temperature reaches 56–62°C.[3]

Company or developer

DBS, widely diffused internationally and within Australia, is offered by several companies, notably St Jude Medical, Medtronic and Boston Scientific. One company, ExAblate by Insightec (INSIGHTEC, Tirat Carmel, Israel), was identified that offers the tcMRg FUS technology, and its use is currently limited.; Supersonic Imagine (Aixplorer, Provence, France) is developing a tcMRg FUS system, but to date this company has only presented data on brain tissue ablation working with cadavers.[6]

Reason for assessment

The technology would be applicable to a large proportion of the Australian/New Zealand population and may therefore represent a considerable clinical and cost impact to the jurisdictions.

Stage of development in Australia

DBS is an established treatment for neurological disorders in Australia, but using this technology to treat mental illness, including depression, is largely the preserve of international practice.[b] In most Australian states, the use of DBS to treat psychiatric/mental illness is defined as a form of psychosurgery. As such, the therapy comes under the governance of state-based mental health legislation, and in New South Wales and the Northern Territory, DBS for the treatment of psychiatric disorders/mental illness is banned.[c] In some jurisdictions DBS for the treatment of several neurological motor disorders, namely Parkinson's disease, Gilles de la Tourette syndrome, and chronic tic disorder, is legal. For example, in NSW, amendments to the state Mental Health Act 2007 allow DBS to be used for the disorders named above.[d] In Victoria, DBS for the treatment of mental illness is legal but heavily regulated, subject to approval by the Victorian Mental Health Tribunal, which stipulates the patient must demonstrate capability of consent and psychosurgery may only be used as a treatment of last resort.[e]

The use of tcMRg FUS as a potential treatment for depression is a newly emerging, still experimental technology (animal and cadaver studies have been performed internationally) that is yet to diffuse within the Australian healthcare system.

Licensing, reimbursement and other approval

DBS is approved for the treatment of neurological movement disorders in several world regions, including North America, Europe and Asia. DBS was FDA-approved for the treatment of obsessive compulsive disorder (OCD) in 2009,[f] however the FDA has not approved its use for the treatment of depression. Despite several examples of international research on DBS for this indication, it would appear that interest for DBS for depression has dwindled from companies offering the technology since the BROADEN trial (sponsored by St Jude Medical) was terminated early due to futility.[g]

No evidence was identified which suggested that tcMRg FUS is approved for the treatment of depression, however, the ExAblate system which uses this technology has been CE approved for thalamotomy and pallidotomy for essential tremor, tremor dominant Parkinson's Disease and neuropathic pain in Europe.

Australian Therapeutic Goods Administration approval

St Jude Medical, Boston Scientific and Medtronic Australia all have multiple listings for DBS; none of the ARTG public summary documents accessible online cited depression as an

[b] There is some evidence to suggest that Australian research is occurring, but no evidence of the technology's diffusion into clinical practice for the relevant indication was identified.
[c] NSW Mental Health Act 2007 – Section 83; NT Mental Health and Related Service Act 2016 – Section 58.
[d] NSW Mental Health Regulation 2013 – Regulation 10.
[e] VIC Mental Health Act 2014 – Section 400.
[f] See the FDA website.
[g] An article featured in Scientific American online provides a succinct lay summary.

indication, but did cite OCD and several movement disorders as the clinical indications for the various DBS systems.

ExAblate does not appear to be approved for use in Australia, but contacting INSIGHTEC[h] revealed that the company is partnered with Australian medical and surgical device company, MediGroup EBI[i], for marketing purposes. As such, INSIGHTEC have a presence in Australia, but ExAblate for the treatment of depression remains experimental and the technology's other clinical applications have only been introduced in Europe.

☒	Yes	ARTG number (s): Several listings for all companies offering the technology in Australia, but approval is subject to indications as per public summary documents (not depression)
☐	No	
☐	Not applicable	

Technology type	**Procedure/device**
Technology use	**Therapeutic**

Patient Indication and Setting

Disease description and associated mortality and morbidity

Depression is a common psychiatric illness and up to one third of patients diagnosed with depression do not respond to standard medication and psychological therapy.[7] Refractory depression results in considerable suffering for individuals, and increased burden on families. The economic burden is substantial. Depression costs the Australian community more than $600 million each year in treatment payments, and individuals with treatment-resistant depression contribute a disproportionate amount to the cost. People with depression that does not respond to conventional treatment are frequent users of healthcare services, and treatment costs for refractory depression may be up to 19 times greater than for patients who respond to treatment with medication and psychotherapy.

The management of treatment-resistant depression involves repeatedly trialling medication, different medication combinations, psychotherapy and eventually brain stimulation therapy including transcranial magnetic stimulation and ECT. However, even after ECT, 10 to 20 per cent of patients remain chronically non-responsive. Among those patients who do respond to ECT, relapse is common and many patients develop therapeutic resistance with prolonged use. Currently, these patients have no effective treatment options.[7]

It is difficult to provide accurate estimates of the burden of disease due to depression. Available data, such as those captured through hospital admissions by the Australian

[h] Email sent 28 July 2016; the contact was forwarded to the managing director of MediGroup to respond to Australian enquiries regarding ExAblate.
[i] Brief information about the use of ExAblate is available from the MediGroup website.

Institute of Health and Welfare, and data on the population living with mental health problems from the Australian Bureau of Statistics/Department of Health (DoH) are incompletely stratified according to diagnosis and have not been recently updated.[8]

In 2013, the DoH estimated[j] that between two and three per cent of Australians (about 600,000 people[k]) have a 'severe' mental disorder, according to diagnosis, intensity and duration of symptoms, and the degree of disability.[9] People diagnosed with psychotic disorders represent approximately one third of all people with severe mental disorders, while the other two thirds are people with severe and disabling forms of depression and anxiety. Another four to six per cent of the population (about 1 million people) have a moderate disorder and between nine and twelve per cent (about 2 million people) have a mild disorder, but there is a lack of accurate information about the proportion of these patients that have a diagnosis of 'depression'.

Mental and behavioural disorders, such as depression, anxiety, and drug use are significant drivers of disability and morbidity.[10] The 2010 Global Burden of Disease study reported on the health impact due to disease and injury that does not improve through current treatments, rehabilitative and preventative efforts of the health system and society. In 2010, mental and behavioural disorders were estimated to be responsible for 12.9 per cent of the total burden of disease in Australia, collectively placing these conditions as the third largest cause of health loss after cancer and cardiovascular disease.[10]

In terms of the number of years of 'healthy' life lost due to living with a disability, mental and behavioural disorders contributed to 22.3 per cent of the non-fatal burden of disease in Australia in 2010.[10]

In 2011, mental disorders were responsible for 754 Australian deaths (excluding suicide and dementia) with most deaths due to substance abuse, notably alcohol abuse, a behaviour for which depression can play a major role.[11]

Among Aboriginal and Torres Strait Islander (ATSI) Australians, data suggest that levels of psychological distress among this population is two times higher than observed among the non-ATSI population, and ATSI women reported these levels of stress more frequently than men. While it is even harder to determine how common depression is among ATSI Australians than the non-ATSI population (given differences in cultural understandings around depression and mental illness) the available data on higher levels of psychological trauma experienced by ATSI people suggest that they are likely to be highly vulnerable to developing depression.[12]

As in Australia, depression is very common in New Zealand (NZ). In the 2011/2012 NZ Health Survey, 14.3 per cent of NZ adults (more than half a million people) had been diagnosed with depression during their lives. Rates were significantly higher in women than in men:

[j] Data for the period 1993-2011.
[k] Based on the total Australian population at time of reporting.

17.9 per cent of women had been diagnosed with depression at some time in their lives, compared to 10.4 per cent of men. Among all women with depression, the highest proportion was observed among women aged 35 to 44 years (21%).

For New Zealanders, anxiety and depressive disorders account for 5.3 per cent of all health loss, second only to health loss following coronary heart disease (9.3%) among men, and the leading cause of health loss in women (7%).

Antidepressants were prescribed to more than 400,000 NZ patients during the 2012-2013 financial year, representing more than a 20 per cent increase over the last five years (348,300 patients received prescriptions in 2008). It is important to note that the NZ population has also been growing during this time, and that antidepressants are also used for other conditions other than depression, such as anxiety, pain, and sleep disorders.[13]

Speciality	**Mental health**
Technology setting	**Specialist hospital**

Impact

Alternative and/or complementary technology

Additive and substitution: Technologies can be used as a substitute in some cases, but may be used in combination with current technologies in other instances.

Current technology

Pharmacotherapy is the mainstay for treating clinical depression, but not all patients respond. Various forms of psychotherapy may be used as complementary interventions, but benefits are highly variable depending on severity of depression, patient compliance, and the psychotherapy chosen. The use of ECT is relatively rare in Australian clinical practice as it is not usually considered until pharmacological treatment options are exhausted.

Diffusion of technology in Australia

DBS is diffused as a treatment for neurological disorders of movement, largely within the private sector, but use of this technology for depression is prohibited in several states/territories, meaning that the diffusion of the technology for this purpose has not occurred. The high cost of DBS, potentially including high out-of-pocket costs for patients, is a factor which has presumably limited the use of DBS for any indication occurring outside the private health system. Given the total cost of treatment, conceivably amounting to $50,000 or more[l], once ongoing maintenance, surgical and anaesthetist costs are added to the fees shown in Table 1, it is unlikely that many patients considered suitable for DBS would be able to afford it without health insurance. Notably, the Prostheses List payments

[l] See The Conversation, 22 May 2013.

are indicative of amounts that are paid by private insurers under requirements of federal law and may not actually cover hardware costs in entirety.

As noted previously tcMRg FUS, specifically for depression, is an experimental technology and has not diffused into Australian clinical practice. Indeed the technology is also in its infancy internationally.

International utilisation

Country	Level of Use		
	Trials underway or completed	Limited use	Widely diffused
Worldwide (DBS)	✓		
Europe (tcMRg FUS)	No evidence of human use for treatment of depression		

Cost infrastructure and economic consequences

As noted above, the pricing of DBS systems, the surgical expertise required to implant the componentry and the ongoing maintenance collectively contribute to high treatment costs.

In Australia, the pricing of all technology used for any form of DBS is governed by the Prostheses List Advisory Committee. This includes all implantable devices, associated external componentry and kits comprising equipment essential for the surgical placement of leads and implantable pulse generators (IPGs). The pricing is largely uniform across companies, reflecting the intended purpose of each component. DBS systems produced by several companies are listed as "no-gap" prostheses on the Prostheses List.[14] This means that each product is listed with a single benefit, and assuming that conditions for an insured patient are met, health insurers are legally required to pay this benefit. This is in contrast to gap-permitted prostheses which have minimum and maximum benefits listed. For these prostheses, private health insurers are required to pay at least the minimum benefit.[m] Table 1 shows a breakdown of costs for the DBS technology offered by St Jude Medical. The full Prostheses List (Part A)[14] should be referred to for the costings of DBS systems offered by other manufacturers. Costings do not include fees for professional services rendered by the treating doctor(s), anaesthetist or hospital fees. Relevant item numbers for the Medicare Benefits Schedule (MBS) include: 40862, 40858, 40854, and 40852.[n]

[m] In cases where the treating doctor considers that a gap-permitted prosthesis is the most clinically suited option for a patient, the doctor should disclose appropriate clinical and financial information, allowing the patient to give fully informed consent prior to any procedure. Guidelines are available at www.health.gov.au/internet/main/publishing.nsf/Content/69F6A026037D6093CA257BF0001B5EDA/$File/ifc_guidelines.pdf

[n] MBS online: http://www.mbsonline.gov.au/.

Table 1 Cost break-down and total cost for implantables and accessory componentry used for the Libra/Libra XP system and Brio system (St Jude Medical Australia Pty Ltd) for deep brain stimulation[14]

Part billing code	Description of part	Size	Price
Implantable pulse generator – primary cell non-rechargeable			
SJ197	Libra System 6608 – IPG for DBS, 8 channel	NS	$9,050
SJ206	Libra XP 6644 – dual channel IPG for DBS, dual 4 channel	76 mm x 58 mm x 14 mm	$15,060
Rechargeable pulse generator			
SJ202	Brio DBS 6788 - IPG for DBS, dual 4 channel	29 g, 17 cc	$19,150
Patient programmer			
SJ204	Brio DBS Patient Controller 6856 for DBS	One size only	$1400
Recharger			
SJ351	Brio LE Charging System 6722 for Brio DBS device	One size only	$1,975
Leads			
SJ148	Libra DBS System - Leads 6142 – 6149; Leads 6142 – 6145, 1.5mm electrode and space 1.5mm; 6146 – 6149, 1.5mm electrode and 0.5mm space	25 – 40cm	$4,150
Lead extension			
SJ234	IS-1 Pocket adaptor	25 cm and 50 cm	$2,100
SJ350	8-Channel Adapter	10 cm and 60 cm	$2,100
SJ373	Extension lead for DBS	50 – 90 cm	$2,100
Microtargeting electrodes			
SJ198	Microtargeting monopolar and bipolar electrodes	100 – 300 mm	$1,500
Accessories			
SJ199	Guardian Cranial Burr Hole Cover System	14 – 17 mm outer diameter	$550.00

DBS = deep brain stimulation; IPG = implantable pulse generator; NS = not specified
Costings do not include fees for professional services rendered by the treating doctor(s), anaesthetist or hospital fees.
Prices shown are in Australian dollars.

The Australian contact for INSIGHTEC (MediGroup EBI) provided all cost information for their tcMRg FUS system, ExAblate, and estimates of treatment costs.[o] MediGroup EBI also provided the opinion that any discussion on the cost of ExAblate should be contextualised by a comparison alongside DBS, which they consider to be an alternative technology for the same patient indication. Their advice that DBS costs $55,000 – $70,000 per patient is roughly in keeping with the estimates of cost noted above and summing the relevant individual components listed in Table 1, which amounts to approximately $50,000 per patient. It should be kept in mind that tcMRg FUS is a commercial competitor with DBS, and therefore the possibility of an overestimated price for DBS cannot be ruled out due to the potential for a financial conflict of interest. On MedGroup's admission, the costs they provide for DBS are approximate and appear to be based on a working knowledge of the Prostheses List.

[o] Email correspondence received 8 August 2016.

Based on the quoted figure of per patient cost for DBS, the 10 year cost of treating a hypothetical 100 patients per year is $55-70 million. It was suggested by MediGroup that costs to set up an operating room for complicated neurosurgery, including stereotactic navigation, frame and computer, lights, anaesthesia machines, the operating table, sterile instruments, device specific programmers, and ward and intensive care unit beds would be between $6-8 million for the 10-year period, but notably, a large part of this cost could not be attributable as direct costs solely for DBS, given that a range of procedures would be performed with the same equipment and infrastructure.

By comparison, MediGroup costed ExAblate at $15-20 million for a 10-year period for 100 patients per year. ExAblate involves a half day outpatient procedure. Consumables are costed at $5,000 per patient per procedure. The procedure, including clinician time and administrative costs was quoted at $5-$10,000 per patient, i.e. consumable cost plus ongoing patient cost equates to $10-15 million over ten years. Capital set-up requires a support shielded MRI, and MediGroup claimed that this is likely to be lower than the costs associated with setting up a neurosurgical operating room and associated peri-operative services. The ExAblate unit with the required frequency set up ranges between US$2.2 and US$2.8 million (depending on whether high frequency alone is used or medium and high frequency are intended to be used). The MRI set-up is estimated between US$1.2 and US$1.4 million. These costs approximate between A$4.5 and A$5.6 million.

Ethical, cultural, access or religious considerations

Continuing to withhold active treatment from trial patients allocated to sham DBS in the context of worsening symptoms presents an ethical dilemma, particularly in light of the last resort nature of treatments like DBS for refractory depression. In the vast majority of cases, patients will have exhausted all other treatment options, and withholding a potentially beneficial treatment when no suitable or effective alternative is available (especially for long periods) is difficult to justify from an ethical perspective. In depth guidance on ethical issues surrounding the use of DBS for psychiatric conditions is readily available.[15]

Evidence and Policy

Safety and effectiveness

A search of the literature revealed a dearth of evidence regarding tcMRg FUS for the treatment of depression. To date, only animal studies and experiments on cadavers have been published.

Conversely, DBS is an established technology for a number of neurological conditions. While the potential for using this technology for the treatment of refractory depression is a more recent development, searching the literature identified a number of systematic reviews/meta-analyses of studies which investigated DBS for this indication. Included studies in the identified systematic reviews were only of small sample size, none used

randomisation, and it would appear that most of the studies included in the reviews were non-comparative. In addition to the systematic reviews, one recently published, *small* randomised controlled study (RCT) was identified and included here.

Dougherty et al[16] conducted an RCT (level II intervention evidence) in which 30 participants who met criteria for major depressive disorder (MDD) as per the Diagnostic Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV) were randomised (permuted blocks of 2 and 4) to receive DBS or sham stimulation. Patients were blind to their assigned treatment. Efficacy of treatment was measured at 16 weeks follow-up, using a comparison of the active treatment and control group mean change and percentage improvement in the Montgomery-Asberg Depression Rating Scale (MADRS) from baseline.[p] No differences in these outcomes were observed between the groups.

The authors commented that this study was the blinded-treatment phase of a planned open-label trial of 208 MDD patients treated using DBS; not surprisingly and by the authors admission, the blinded-phase was underpowered to detect significant differences in treatment outcomes. In *unblinded* extended follow-up, during which all patients who had received sham treatment had switched to active treatment for ethical reasons,[q] selected data was reported. These non-comparative data indicated that of 26 patients who had received active DBS and remained in the trial at 24 months, only five achieved and held responder status for a period of six months or more, and no subject who met responder status stayed in it continuously for the duration of follow-up. Response was defined as a 50 per cent improvement on MADRS from baseline. The mean percentage decrease (indicating an improvement) in MADRS at 24 months was approximately 40 per cent from baseline, while the proportion of patients who were considered to be responders at 24 months was in the range of 20 to 25 per cent (graphical data). A total of 71 serious adverse events related to DBS, including worsening depression, suicidal ideation, suicide attempt, implant site infection, and lead revision for reasons including but not limited to infection, were observed among nearly three quarters of study participants.[16]

In summary, during the randomised 16-week trial period, there was inadequate power to detect a true difference between active and sham treatment. During extended follow-up which provided non-comparative evidence (the equivalent of level IV intervention evidence), it is evident that the majority of patients, all of whom received active treatment, did not experience a sustained response to DBS, and of those that did, the observed mean change in MADRS was consistent with an improvement from “severely” depressed to “moderately” depressed. No information on the clinical impact of this improvement was provided. While DBS is considered a last-line treatment, given the serious safety concerns, this study does not provide enough evidence to make an informed decision about the place

[p] MADRS interpretation: 0-6, normal; 7-19, mild depression; 20-34, moderate depression; >34, severe depression.
[q] Continuing to withhold active treatment from trial patients allocated to sham DBS in the context of worsening symptoms presents an ethical dilemma, as noted above. See “Ethical, cultural and religious considerations”.

of DBS in clinical practice. The study was funded by Medtronic and several of the authors disclosed financial relationships with various companies, including but not limited to the pharmaceutical and device industries.[16]

Other than the level II evidence identified and discussed above, the remaining body of evidence was limited to systematic reviews of open label trials providing non-comparative data (level IV intervention evidence).[17-19]

Naesstrom et al (2016)[18] conducted a systematic review which included nine case series (level IV intervention evidence) in which DBS was used to treat MDD[r]. Two of the studies included in the systematic review were case reports and the results are not considered here. Of the seven remaining studies, all were small case series (≤21 patients). The systematic review did not provide a quality appraisal of the included studies. Results of the included studies were reported individually (no meta-analysis) and are summarised in Table 2. The authors concluded that DBS may show promise for the treatment of MDD but that randomised controlled data are lacking and confidence in the findings is limited due to the small sample sizes of included studies, noting that DBS for indications other than OCD remains "purely experimental".

[r]A systematic review is rated according to the highest level applicable to any included studies; however, given that Naesstrom et al included mostly case series in their systematic review, it should not be interpreted the same way as a level II systematic review including only RCTs. The majority of evidence making up the Naesstrom review is actually level IV evidence, and as such, should be interpreted accordingly.

Table 2 Studies of deep brain stimulation for major depressive disorder included in Naesstrom et al's SR[18]

Study	n	Target	Complications* (n events)	Comments/Results
Lozano et al 2008[20]	20	Subcallosal cingulate gyrus	1 seizure; 4 infections; 5 perioperative pain	Case series. DBS used open-label. 11 patients had 50% reduction in HDRS at 1 year from baseline; 7 patients were 1 point or less from remission
Malone et al 2009[21]	15	Ventral internal capsule/ventral striatum	2 hardware complications; stimulation-induced reversible effects of hypomania in 1 bipolar patient	Case series. DBS used open-label. 1 patient with bipolar disorder; 6 patients in remission within 1 year
Bewernick et al 2010[22]	10	Not reported	3 pain; 2 paraesthesia; 1 lead dislodgement; stimulation-induced reversible effects included hypomania, psychotic symptoms and anxiety	Case series. DBS used open-label. 5 patients had 50% reduction in HDRS; 3 patients achieved remission
Holtzheimer et al 2012[23]	17	Subcallosal cingulate gyrus	1 infection; 3 hardware complications; stimulation-induced reversible effects included anxiety, gait and hand/arm weakness	Case series. DBS used open-label.; 7 patients with bipolar disorder; 10 patients were in remission after 2 years active stimulation
Lozano et al 2012[24]	21	Subcallosal cingulate gyrus	1 infection, 2 hardware complications	Case series. DBS used open-label. 57% of patients had a 50% reduction in symptoms at 1 month, while 48% and 29% experienced a 50% reduction at 6 and 12 months, respectively
Puigdemont et al 2012[25]	8	Subcallosal cingulate gyrus	3 pain at location of subdermal cable; 2 headaches	Case series. DBS used open-label. 4 patients in remission after 1 year
Schlaepfer et al 2013[26]	7	Medial forebrain bundle	1 intracerebral haemorrhage; 2 infections; 1 hardware complication; stimulation	Case series. DBS used open-label. 6 patients fulfilled response criteria; at day 7 following onset of stimulation, all patients had a reduction of >50% in MADRS At last observation, from 3 to 6 months, 6 patients were responders of whom 4 were remitters

HDRS = Hamilton Depression Rating Scale (scores from 0 to 7 are considered normal; scores >20 indicate moderate, severe, or very severe depression; MADRS = Montgomery-Asberg Depression Rating Scale (0-6, normal; 7-19, mild depression; 20-34, moderate depression; >34, severe depression).
*All complications were considered to be minor in terms of health impact

A systematic review by Morishita and colleagues (2014)[17] included at total of 22 case series (level IV intervention evidence) investigating the use of DBS for refractory MDD. Although this systematic review was published prior to the review by Naesstrom et al,[18] it identified approximately nine times the number of studies for potential inclusion (n=473 versus n=54) and finally included an additional 13 of these studies in the review. The search strategy reported by Morishita et al included a more extensive list of search terms, but both systematic reviews had similar inclusion criteria, suggesting that the search terms used by Naesstrom et al were inadequate to identify all available relevant literature at the time of searching. However, the 13 studies unique to Morishita et al provided results that were not dissimilar to those of Naesstrom et al, and based on the available evidence, Morishita et al

also concluded that DBS for depression remains experimental and further accumulation of data is warranted to determine whether the technology is effective for refractory depression.[17]

A third systematic review by Nanganoori et al (2013)[19] (level IV intervention evidence) included a meta-analyses of six studies which provided outcomes using disease-specific standardised measures. All six studies were identified and included in the systematic reviews previously mentioned. Pooled data showed a statistically significant improvement in depression, based on inputs derived from baseline and post-DBS depression scores reported in the original studies (standardised mean difference 2.47 [95%CI 1.9, 3.0]). It should be noted that the total number of patients among the six studies included in the meta-analysis was small (n=48), and all included studies were non-comparative. The authors did not comment on the clinical significance of their findings.[19]

Economic evaluation

None identified.

Ongoing research

A search of ClinicalTrials.gov identified six relevant trials of DBS for depression that are currently recruiting patients (NCT01798407; NCT02046330; NCT01973478; NCT00367003; NCT01983904; NCT01984710). Two relevant trials of tcMRg FUS were identified (NCT02685488; NCT02348411).

Two relevant trials of DBS were identified on the Australian and New Zealand Clinical Trials Registry (ACTRN12611000889954; ACTRN12613000412730), however no trials of tcMRg FUS were identified.

Other issues

Besides the funding of trials by manufacturers and financial conflicts of interests disclosed by a number of authors involved in writing the studies identified for inclusion, no further issues were identified.

Number of studies included

All evidence included for assessment in this Technology Brief has been assessed according to the revised NHMRC levels of evidence. A document summarising these levels may be accessed via the HealthPACT web site.

Total number of studies: 4

Total number of Level II studies: 1

Total number of Level IV studies: 3

Search criteria to be used (MeSH terms)

MeSH terms

Depression; Depressive Disorder; Depressive Disorder, Treatment Resistant; Deep Brain Stimulation; Ultrasonography

Text terms

Depression; deep brain stimulation; DBS; neuromodulation; ultrasound; transcranial focused ultrasound; psychosurgery; neurosurgery; electric stimulation therapy

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