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Purpose

The Royal Australian and New Zealand College of Psychiatrists (RANZCP) has developed this clinical memorandum to inform psychiatrists who are interested in using Deep Brain Stimulation (DBS) as a treatment for psychiatric disorders.

Key messages

- Clinical trials into the use of Deep Brain Stimulation (DBS) to treat psychiatric disorders such as depression, obsessive-compulsive disorder, substance use disorders, and anorexia are occurring internationally, including within Australia.
- Although overall the existing literature shows promise for DBS in the treatment of psychiatric disorders, it is still an emerging treatment and requires a stronger clinical evidence base of randomised control trials (RCTs) to develop a substantial body of evidence to identify and support its efficacy.
- DBS has potential application as a treatment for appropriately selected patients. For severe, treatment-refractory OCD, there is a small but consistent evidence base to support the use of DBS when all other conventional therapies have been trialled. When used in this way patients should be provided with information on the considerable limits of the evidence base and treatment should not be provided without the collection of outcome data through a clinical trial or registry.
- DBS should only be used at specialised centres or hospitals where there is an experienced multidisciplinary team involved in work-up, implantation, and follow up and also where frameworks are in place to provide careful clinical governance and ensure appropriate fully informed consent.
- Long-term outcomes for all patients treated with DBS should be published in the scientific literature to ensure a comprehensive record of all cases is available for evaluation.
- Access to appropriately approved and regulated clinical trials evaluating the use of DBS should be available to carefully selected patients regardless of geography. Legislative reform is required to ensure uniform access to DBS for psychiatric disorders in all Australian states, territories and New Zealand

Background

DBS is an established treatment for movement disorders such as Parkinson's disease, essential tremor and dystonia, and has also been used in the control of motor and vocal tics associated with severe and medically-intractable Tourette's syndrome. [1]

In Australia the Therapeutic Goods Administration (TGA) has approved devices for DBS implantation. DBS implantation and postoperative device adjustment is eligible for reimbursement

under the Medicare Benefits Schedule (MBS) for the treatment of movement disorders but not for other neurological or psychiatric disorders. As the use of DBS in the treatment of psychiatric disorders is emerging, it is currently only available in speciality clinics or hospitals under research settings. In New Zealand devices are approved by the New Zealand Medicines and Medical Devices Safety Authority and the National Deep Brain Stimulation Committee oversees DBS administration including patient eligibility, but presently the treatment is provided only for people with movement disorders.

Most Australian and New Zealand Mental Health Acts allow for DBS, subject to appropriate consent procedures, psychiatrist recommendation, and review board oversight, although the use of DBS to treat mental illness is currently prohibited in New South Wales and the Northern Territory. [2] There is no scientific or legal rationale for states banning the use of DBS in psychiatric disorders but allowing unrestricted use in neurological disorders. This prohibition limits patients' equality of access to health care, unduly restricts research into DBS as a potential treatment option for psychiatric disorders, and complicates the treatment of people who travel interstate to receive DBS and need ongoing care and monitoring. [3]

What is Deep Brain Stimulation?

DBS is a neurosurgical procedure in which electrodes are implanted into specific regions of the brain to provide targeted stimulation of neurons and their connections in order to alleviate the symptoms of the disorder being treated. No ablative lesions are made in the brain. DBS is reversible and can be adjusted postoperatively in the outpatient clinic.

In DBS, once the electrodes have been implanted, they generate continuous electrical stimulation through a pulse generator, which is usually implanted in the upper chest under the collarbone and connected to the electrodes under the skin by cables (leads). This is a two-stage procedure, with electrodes implanted in the brain in stage one, and the impulse generator implanted in stage two under general anaesthetic. Some centres combine both stages into one procedure. The impulse generator is also referred to as a 'brain pacemaker' and has a battery life of up to 15 years for those with externally rechargeable batteries. [4] It should be noted that stimulation amplitudes in DBS for psychiatric disorders are typically higher than those employed in DBS for movement disorders. This limits the lifespan of a non-rechargeable pulse generator to 12-18 months. Given that, if beneficial, ongoing stimulation is likely to be necessary for the remainder of the patient's life, rechargeable devices are preferred.

After the patient has recovered from surgery, the impulse generator is turned on and various stimulation parameters (including amplitude, pulse width and frequency) are adjusted to treat the symptoms of the disorder. The level of stimulation is individualised to the clinical requirements of each patient and the disorder being treated. Programming of the device may occur on an outpatient basis but sometimes hospitalisation is required to allow for careful monitoring during this time. Due to the large number of treatment parameters (including choice of the electrode contacts to be used), optimising stimulation setting after the operative procedure is often a complex and lengthy process. Contrary to DBS for movement disorders, in some indications and patients, but not all, the response to DBS for psychiatric disorders is often slow to evolve over 6-12 months postoperatively and patients require significant ongoing support during this period.

Evidence of efficacy

Although overall the existing literature shows promise for DBS in the treatment of psychiatric disorders, it is still an emerging treatment and requires a stronger clinical evidence base of randomised control trials to develop a substantial body of evidence to identify and support its efficacy. [5, 6]

There are several issues with assessing the efficacy of DBS. The vast majority of the evidence is from uncontrolled trials which may be subject to a variety of bias. Where RCTs of sham versus real DBS are done most are of the crossover design rather than parallel group. This can potentially introduce complex biases of either positive or negative placebo effects. However, a crossover

design is often preferred in DBS for psychiatric indications for two reasons. First, due to the low number of participants who are sufficiently unwell to qualify for DBS, parallel group trials will be underpowered to detect treatment effects. Second, it is ethically challenging to implant severely unwell participants and delay initiation of treatment for 12-months or more (the typical length of time it takes to accrue a treatment response). In addition, although RCTs are described as being double-blinded, it is possible that patients may become aware of their treatment allocation if they develop side effects to active therapy. Future studies should report on the effectiveness of blinding to treatment condition

A recent systematic review highlights some of the limitations of the available evidence. [7] Out of 71 articles assessing DBS, the quality assessment rated 19 articles as good, 44 as moderate and eight as poor. Only 11 out of 71 articles were RCTs, and 35 were case reports, which meant a randomised control aspect and group level analysis was not present in almost half of the patients included here. Furthermore, only half of the articles reported on more than one time-point, which limits interpretations regarding the duration and pattern of response. Within the bias assessment, there were multiple deviations from the intended protocol, including DBS explants or switch off, and closed-label conditions ending early. It is possible that not all cases of device switch off, explant, or repositioning were captured. Taking account of these limitations, DBS efficacy from the studies that are available are summarised below.

DBS for major depression

In recent years the use of DBS, as applied to various brain regions, has been researched for the treatment of patients with highly refractory depression and research is ongoing within Australia and worldwide. [8, 9] A meta-analysis of 12 studies with 186 unique patients found a significant benefit of active over sham stimulation with no variation in implantation / stimulation site. The largest study included in this analysis included 85 patients and no other study included more than 30. [10] These studies have explored a variety of treatment targets including the ventral striatum / anterior limb of the internal capsule, nucleus accumbens, subgenual anterior cingulate, bed nucleus of the stria terminalis and medial forebrain bundle.

The patients eligible for DBS treatment have generally been diagnosed with chronic and treatment-resistant depression who have not responded to extensive pharmacological and psychotherapy treatments and, with few exceptions, electroconvulsive therapy. The vast majority of investigator-initiated trials have produced promising results with response rates usually around 50% and the persistence of benefits seen in the long term. [11-14] However, two industry sponsored multi-site trials were prematurely terminated when an interim analysis suggested that they were unlikely to show positive results. [15, 16] Whether this reflects a lack of efficacy of the intervention or the inadequacy of the clinical trial designs used, has been debated.

Overall the existing literature shows some promise for DBS in the treatment of depression, including the persistence of clinical benefits in a substantial subpopulation of previously highly treatment refractory patients with depression. However, research into the effectiveness of the treatment is ongoing.

DBS for obsessive-compulsive disorder (OCD)

Research has evaluated the use of DBS in the treatment of adult patients with severe and intractable obsessive-compulsive disorder (OCD). With slight variations, patients eligible for DBS have suffered at least five years from severe OCD, defined by the Yale-Brown Obsessive-Compulsive Scale as a minimum score of 24/40. Treatment refractoriness has involved adequate trials of pharmacotherapy and psychotherapy incorporating exposure and response-prevention. Surgical targets have comprised the anterior limb of the internal capsule, the nucleus accumbens, the bed nucleus of the stria terminalis and the subthalamic nucleus. A total of six randomised, double-blind, sham-controlled studies involving 63 unique participants have been published worldwide including one in an Australian cohort. [7, 17] These studies have shown a statistically-significant benefit of active over sham stimulation with most participants meeting the criteria for response (35% reduction in YBOCS score) after chronic stimulation. A recent meta-analysis of eight studies with 80 patients found a positive effect of therapy. [18] Findings from a further 203 unique open-label cases have also recently been published. [19-28] These studies support efficacy

of this therapy and also contribute to understanding of the brain circuits implicated in refractory OCD that are correlated with treatment response. [29]

In the United States, access to DBS for OCD has been approved through the Food and Drug Administration (FDA) Humanitarian Device Exemption (HDE) program allowing clinical use of the device. The approved indication is for bilateral stimulation of the anterior limb of the internal capsule (AIC), as an adjunct to medications and as an alternative to anterior capsulotomy for treatment of chronic, severe, treatment-resistant OCD in adult patients who have failed at least three selective serotonin reuptake inhibitors (SSRIs). The HDE process involves a review of safety and a consideration that the probable health benefits outweigh the risks of injury or illness from its use. However, it does not indicate that efficacy has been established through large clinical trials. In Europe, DBS for OCD is available via a Conformité Européene (CE) mark in a similar model to the United States. Importantly, these approvals allows access to this treatment (namely, reimbursement) in a group of treatment-refractory OCD patients where other clinical options are essentially non-existent.

Overall, the existing literature shows promise for the use of DBS in the treatment of severe, refractory OCD. It is recognised that the total number of participants who have received DBS for OCD remains low compared to other evidence-based interventions. However, given that DBS for OCD has been trialled with promise in the most unwell, treatment-refractory patients who have not other effective treatment options, the cautious provision of this therapy in highly-specialised centres may be appropriate for some patients. Therefore, whilst more research data should be collected regarding the long-term outcomes of DBS for OCD (including from sham-controlled trials), programs that increase access to patients whilst also permitting ongoing treatment evaluation should be encouraged.

Other

Promising effects of DBS have been reported in small studies and case reports for anorexia nervosa and alcohol and heroin substance use disorders. [30, 31] However, published evidence is very limited and DBS in such conditions is highly experimental. More randomised controlled trials of approaches for these disorders are needed. [32-35]

Clinical indications

Within psychiatry, for most indications, DBS should be considered a treatment that remains under research evaluation. Whilst there is promising initial data to support the efficacy of DBS as a form of treatment for otherwise treatment-refractory psychiatric disorders, there is insufficient evidence at present to support the global use of DBS as a clinical treatment for psychiatric disorders outside of clinical trials.

For severe, treatment-refractory OCD, DBS could be considered a potential treatment if all other treatment avenues have been exhausted, including trials of at least 4 SSRIs at maximum tolerated dose (up to the equivalent of at least 100mg of fluoxetine), one trial of clomipramine at maximum tolerated dose, one augmentation trial with an antipsychotic and one complete trial of exposure-based cognitive behavioural therapy. Where available other treatments with an evidence base supporting efficacy in OCD, such as deep repetitive Transcranial Magnetic Stimulation (rTMS), should also be provided prior to a consideration of a trial of DBS.

DBS use with other treatments

Treatment with DBS can occur in conjunction with psychological therapies or medications. This depends on the care needs and symptom profile of the particular patient. Patients undertaking DBS usually require substantial psychological support, whether responding or not responding to the DBS. The safe use of ECT in patients with implanted DBS electrodes has been described in a very few cases but poses specific risks which must be carefully evaluated on a case-by-case basis. Treatment with ECT when DBS electrodes are present should only be considered after

careful review by experts with specific relevant knowledge, and with detailed discussion of likely risks and benefits during the consent process.

Patient selection and consent for research trials

- As DBS is a surgical procedure, careful screening and selection of candidates is essential and most importantly the procedure should be reserved for patients who have a severe treatment refractory disorder. By most definitions this requires multiple years of illness (e.g. five years) and comprehensive prior therapy with established treatments. Selection and screening for psychiatric indications should in all cases be conducted by a multidisciplinary team that is led by an experienced psychiatrist and includes a specialist functional neurosurgeon, all with appropriate training and expertise in DBS.
- Generally, agreed guidelines exist for patient selection for DBS for movement disorders. Whilst there are no universally accepted guidelines defining ideal DBS candidates for Tourette's syndrome, important factors to consider are age, tic severity and treatment refractoriness. [36] There are no established guidelines for DBS for other neurological or psychiatric disorders, although these are emerging in some areas. [37]
- A review of the literature shows that important factors for the screening and selection of candidates for DBS include the candidate's age (how it relates to the disorder), severity of the disorder, treatment refractoriness, and presence of psychiatric symptoms. If the patient has a history of psychosis or depression, then post-operative, monitoring of these symptoms is essential. [38]
- Due to the complexities of undertaking a DBS procedure, informed patient consent is necessary for patients considering DBS and should be obtained in line with legislation controlling access to the procedure. Patients being treated with DBS should understand that it remains under research evaluation and the consent form they sign should state that. The procedure is not suitable for use as an involuntary intervention.
- Pregnancy is generally an exclusion for DBS trials so there is no available data on safety or adverse effects with only a few case series reported [39-43]. Use of DBS in pregnant women should only be undertaken within a formal research study with ethical review and approval.
- Due to the lack of clinical evidence of the effectiveness or safety of DBS for treating children or adolescents with psychiatric disorders, use in this population should be considered experimental. It is recommended that this age group should not be considered for this treatment at this time except in an ethically approved and appropriately regulated clinical trial. Consideration of the procedure in exceptional circumstances should be via a legally mandated review process (e.g. mental health tribunal).
- Patients should be made clearly aware of the potentially lengthy programming time required postoperatively and DBS should only be provided where this ongoing treatment / support can be provided.

Adverse effects

DBS has generally proven to be safe, with few severe complications in patients. Owing to the complexity of patients undergoing DBS, adverse effects are difficult to define. For example, in a meta-analysis of DBS in depression, 84 participants experienced a total of 131 serious adverse effects, although not all could be directly attributed to the device or surgery, and in a meta-analysis of OCD, one-third of patients experienced significant adverse effects. [44, 45]

In terms of adverse effects, there are mainly two types of concerns associated with DBS, those directly related to the surgical procedure and the implanted device hardware, and those that are a result of the electrical stimulation:

- As with any surgical procedure, there are potential side effects. The adverse effects related to the surgical procedure include haemorrhage (1-2% of procedures), seizure induction (less than 1%: usually in the first 24 hours), infection (2-3%: usually superficial) and other general surgical or anaesthetic complications. [46] With regards to the implanted hardware device, adverse effects include hardware malfunctioning or cables breaking; however, with advances in device technology these effects are likely to become uncommon. Battery depletion within the implantable pulse generator may result in a loss of therapy and rebound of psychiatric symptoms. [47] Patients should be warned about this eventuality and be instructed to check their battery status at regular intervals.
- Research indicates that the side effects of electrical stimulation differ and depend upon which disorder is being treated and which targets of the brain are being stimulated. Adverse events reported include transient psychiatric symptoms, particularly hypomania, increased anxiety, deterioration of mood and suicidal thoughts, which were generally resolved with programming adjustments. [7] Other adverse effects to electrical stimulation also described include: changes in sexual behaviour, weight loss, psychiatric symptoms (e.g. psychosis, depression and hypomania), nausea, vertigo, anxiety, agitation, euphoria, panic, fear and worsening depression. [36]

Due to the 'trial and error' style of searching for optimal stimulation settings, the side effects may be fleeting and reversible via adjustment of the stimulators, or may be stopped by ceasing the stimulation altogether. [46] The aim is to optimise the effect on psychiatric symptoms whilst avoiding stimulation induced side-effects. An advantage of DBS is demonstrated by the fact that altering the stimulation can abolish all stimulation-induced side effects. [33]

DBS administration and the role of the psychiatrist in conducting research trials

- The DBS assessment and treatment process should be conducted by a multidisciplinary team led by a psychiatrist and including a neurosurgeon, both with appropriate training and expertise in DBS, and be located at an appropriate institution (e.g. speciality clinic or hospital) that is experienced in carrying out the procedure. Any investigational use of DBS should occur at an institution following a research protocol approved by a human research ethics committee.
- DBS should only be undertaken in a clinical setting where there is a commitment to support patients in the long term, both in the management of the DBS itself, including through the ongoing programming of the device, and their broader psychosocial needs.
- Long-term outcomes from all cases should be published in the peer-reviewed literature or in a clinical registry, in order to contribute to the evidence base for this therapy.
- The psychiatrist with responsibility for selecting and assessing patient for DBS suitability, and overseeing the DBS treatment process should have appropriate expertise and be approved by the institution for administration of the DBS treatment. There should be continuing professional education to ensure the psychiatrist is kept updated on treatment advances.
- All practitioners who administer DBS should be properly trained in the identification, assessment and early management of unexpected complications from DBS.
- All practitioners who administer DBS should also have appropriate expertise and supervision.

Summary

DBS has demonstrated emerging effectiveness for major depression and OCD, and shows potentially promising application as a treatment including anorexia nervosa and substance use disorder. For all disorders there is a need for a stronger clinical evidence base of randomised control trials to develop a substantial body of evidence to identify and support the efficacy and safety of DBS. This includes consideration of the efficacy and safety of different stimulation targets. The conduct of further clinical trials across all psychiatric disorders as appropriate is supported.

The use of DBS in psychiatric disorders should generally be applied as a treatment in the context of appropriately developed clinical trials, which are approved by human research ethics committees. DBS for severe, treatment-refractory OCD may be appropriate in a clinical setting when all other conventional therapies have been trialled. This should only be provided following adequate trials of established treatments, appropriate secondary review and the provision of informed consent. The processes for patient evaluation and consent should be institutionally reviewed, the outcomes of a DBS treatment program subject to regular audit and all patients entered into a clinical trial or quality registry to collect outcome and safety data.

Access to appropriately approved and regulated clinical trials evaluating the use of DBS should be available to appropriately selected patients regardless of geography. Legislative reform is required to ensure uniform access to DBS for psychiatric disorders in all Australian states, territories and New Zealand.

As the evidence for the use of DBS continues to evolve, this memorandum will be reviewed and revised.

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DISCLAIMER

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