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The Royal Australian and New Zealand College of Psychiatrists (RANZCP) has developed this clinical memorandum to inform psychiatrists who are involved in using DBS as a treatment for psychiatric disorders. 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 worldwide, including within Australia. Although overall the existing literature shows promise for DBS in the treatment of psychiatric disorders, its use 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 (Widge et al., 2016; Barrett, 2017). The RANZCP supports further research and clinical trials into the use of DBS for psychiatric disorders and acknowledges that it has potential application as a treatment for appropriately selected patients.

## Background

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DBS is an established treatment for movement disorders such as Parkinson's disease, tremor and dystonia, and has also been used in the control of movement disorder associated with severe and medically intractable Tourette syndrome (Cannon et al., 2012).

In Australia the Therapeutic Goods Administration has approved devices for DBS. It is eligible for reimbursement under the Medicare Benefits Schedule for the treatment of Parkinson's disease 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 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 (RANZCP, 2017b; RANZCP, 2017a; Loo et al., 2010). In the view of the RANZCP 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.

## What is Deep Brain Stimulation?

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DBS is a neurosurgical procedure in which electrodes are implanted into specific regions of the brain to stimulate neurons in order to alleviate the symptoms of the disorder being treated. It differs from 'psychosurgery' where ablative lesions are made in the brain. It is also reversible and fully adjustable.

In DBS, once the electrodes have been implanted, they receive continuous electrical stimulation by an impulse 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 2 under general anaesthetic. The impulse generator is also referred to as an 'internal neural stimulator' or 'brain pacemaker' (Coenen et al., 2015) and has a battery life of up to 10 years for those with externally rechargeable batteries.

After the patient has recovered from surgery, the impulse generator is turned on and various stimulation parameters (including voltage, pulse width and frequency) are adjusted to receive the optimal response 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, the pulse width, frequency and voltage or current strength), optimising stimulation setting after the operative procedure is often a complex and lengthy process.

## **Evidence of efficacy**

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### *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 (RANZCP, 2015; Bewernick et al., 2017) and research is ongoing within Australia and worldwide. A recent review identified nine unique published studies describing a total of 100 patients (Naesstrom et al., 2016). 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 treatment 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 (Bewernick et al., 2010; Lozano et al., 2012; Merkl et al., 2013; Holtzheimer et al., 2012; Bewernick et al., 2017). However, two industry sponsored multi-site trials were prematurely terminated when an interim analysis suggested that they were unlikely to show positive results (Dougherty et al., 2014; Fayad and Higuchi, 2014). 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)*

Initial research has evaluated the use of DBS in the treatment of patients with severe and intractable obsessive-compulsive disorder (OCD). A total of 18 unique studies have been published worldwide, describing a total of 112 patients (Naesstrom et al., 2016). With slight variations, patients eligible for DBS have suffered at least 5 years from severe OCD, defined by the Yale-Brown Obsessive-Compulsive Scale as a minimum score of 25–28. DBS shows promise for treatment-resistant OCD but the results are limited by the small sample size and insufficient randomised controlled data (Naesstrom et al., 2016). These studies are further limited to adult populations.

In the United States access to DBS for OCD has been approved through the Food and Drug Administration 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. This approval allows access to the treatment 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 OCD but the limited number of research studies suggests that it should also be considered experimental at this time. However any programs that increase access to patients within the boundaries of ongoing treatment evaluation should be encouraged.

### *Other*

Promising effects of DBS have been reported in small studies and case reports for anorexia nervosa (Lipsman et al., 2017), agoraphobia and alcohol and heroin substance use disorders. However, published evidence is very limited and DBS in such conditions is highly experimental. More randomised controlled trials of approaches for these disorders which have only a very emerging evidence base are needed (RANZCP, 2014; Naesstrom et al., 2016; Hutton, 2013; Treasure and Schmidt, 2013).

## **Clinical indications**

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Within psychiatry, at this stage, DBS can only be considered an experimental treatment (Kiseley et al., 2014; Coenen et al., 2015). Whilst there is promising initial data to support the efficacy of DBS as a form of treatment for psychiatric disorders, there is insufficient evidence at present to support the use of DBS as a clinical treatment for psychiatric disorders outside of clinical trials (Fitzgerald and Segrave, 2015).

## **DBS use with other treatments**

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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 (Vila-Rodriguez et al., 2014). 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**

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- 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 resistant 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 syndrome, important factors to consider are age, tic severity and treatment refractoriness (Fraint and Pal, 2015). There are no established guidelines for DBS for other neurological or psychiatric disorders, although these are emerging in some areas (Park et al., 2017).

- 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 (Ashkan et al., 2013).
- 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 is still an experimental treatment and the consent form they sign should state that. The procedure is not suitable for use as an involuntary intervention.
- 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 highly 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 post operatively and DBS should only be provided where this ongoing treatment / support can be provided.

## **Adverse effects**

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- DBS has proven to be safe, with few severe complications in patients with movement disorders; this is also demonstrated in a review of DBS for serious depression and OCD (Naesstrom et al., 2016). 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 (Fitzgerald and Segrave, 2015). With regards to the implanted hardware device, adverse effects include hardware malfunctioning or cables breaking; however, with advances in device technology these affects are likely to become uncommon.
  - 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. A range of side effects to electrical stimulation including: changes in sexual behaviour, weight loss, psychiatric symptoms (e.g. psychosis, depression and hypomania), nausea, vertigo, anxiety, agitation, euphoria, panic, fear and worsening depression have been described (Fraint and Pal, 2015).
- 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 (Fitzgerald and Segrave, 2015). 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 (Naesstrom et al., 2016).

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

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- 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 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.
- 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 personnel who administer DBS should be properly trained in the identification, assessment and early management of unexpected complications from DBS.
- All personnel who administer DBS should also have appropriate expertise and supervision.

## Recommendations

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The RANZCP recommends that:

- The use of DBS in psychiatric disorders should only be applied as a treatment in the context of appropriately developed clinical trials, which are approved by human research ethics committees.
- 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.
- Further clinical trials are required across disorders for which DBS has emerging demonstrated effectiveness, including major depression and OCD, and for disorders for which it shows promising application as a treatment including anorexia nervosa, agoraphobia, and substance use disorder. The conduct of further clinical trials across these disorders plus other psychiatric disorders as appropriate is supported.
- 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.

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This information is intended to provide general guide to practitioners, and should not be relied on as a substitute for proper assessment with respect to the merits of each case and the needs of the patient. The RANZCP endeavours to ensure that information is accurate and current at the time of preparation, but takes no responsibility for matters arising from changed circumstances or information or material that may have become subsequently available.

## REVISION RECORD

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