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Evidence Check

Deep brain stimulation in mental health

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Deep brain stimulation in mental health:
a review of evidence for clinical efficacy

Contents

1 Executive summary

Background

Deep brain stimulation (DBS) is a procedure that aims to treat neurological or psychiatric disorders through the implantation of stimulating electrodes into specific localised brain regions. These electrodes are implanted during a neurosurgical procedure and subsequently connected to a pulse generator (like a pacemaker) placed in the chest wall, to allow for ongoing electrical stimulation of the relevant brain region.

DBS has been used extensively over the past two decades in the treatment of a number of neurological disorders, most commonly Parkinson's disease. There is increasing interest in the use of DBS as a potential treatment for psychiatric disorders including obsessive compulsive disorder, major depressive disorder and a number of other conditions. In this review, we analyse the evidence for the effectiveness of DBS in psychiatric disorders with the major focus on obsessive compulsive disorder and major depressive disorder as these are the conditions in which the majority of clinical research has happened to date.

Methods

To conduct the review we identified relevant case reports, case series and clinical trials by searching PubMed, Scopus, OVID Medline and Google Scholar using a series of relevant keywords (additional detail contained within Appendix B). We focused on the review of articles where DBS was primarily utilised in the treatment of a psychiatric disorder including obsessive compulsive disorder, major depressive disorder, anorexia nervosa or an addictive disorder. The evidence for the effectiveness of DBS in the treatment of obsessive compulsive disorder and major depressive disorder was reviewed with studies clustered by the site of implantation. In addition, studies were categorised as to whether they were open label or contained some form of randomised or blinded comparison.

Results

The majority of identified manuscripts report small case series or single cases. A limited number of studies in both obsessive compulsive disorder and major depressive disorder have reported some form of randomised or blinded stimulation comparison. In many of these latter studies, patients have undergone DBS implantation and subsequently been randomised to the stimulator being turned on or off in a blinded fashion. Open-label treatment was then provided after the period of blinded stimulation, in which no study exceeded six months. A slightly different approach involved the provision of open-label stimulation followed by a period of time when stimulation was either left on or turned off in a blinded manner. All of these comparative reports have included small samples of subjects (fewer than 20 per study in total) compromising the feasibility of making statistical comparison between outcomes in the comparison phases. The two exceptions to this have been two industry-sponsored studies conducted in the treatment of major depressive disorder. However, both of these studies have been stopped prematurely due to concerns about poor efficacy and details of the clinical outcomes of the patients in these two studies have not been published to date.

Summary of evidence

In regards to the use of DBS in the treatment of obsessive compulsive disorder, the published studies reported a relatively consistent pattern of modest reduction in core obsessive compulsive symptoms with DBS treatment. All promising studies report DBS implantation in the region of the anterior limb of the internal capsule (ALIC), the ventral striatum (VS), or the nucleus accumbens (NA) with a trend towards better responses with more posterior stimulation locations. The benefits arising with DBS appear to persist for substantive periods of time (years) when stimulation remains on and are associated with modest improvements in quality of life and general functioning. However, the effectiveness of this form of stimulation in patients with obsessive compulsive disorder has not yet been demonstrated in adequately powered double-blind comparisons.

In regards to the use of DBS in the treatment of major depressive disorders, a number of small studies – some with short-term blinded stimulation – have reported antidepressant effects when DBS was applied to several diverse brain regions. In these studies, antidepressant effects appear to persist while stimulation remains on but a relapse of depressive symptoms is commonly seen when stimulation is turned off. However, two somewhat larger industry-sponsored studies with double-blind components have failed to demonstrate efficacy of DBS applied to either the anterior limb of the internal capsule or the subgenual anterior cingulate cortex. Therefore, the effects of DBS treatment for depression remain unproven at this time.

There is little substantive evidence at this stage to support the efficacy of DBS for other psychiatric indications, although small case series have suggested possible benefits in anorexia nervosa and addictive disorders.

DBS is associated with a range of procedural and stimulation-related side effects. Procedural side effects occur at a similar rate to those reported when DBS is used for neurological indications. Stimulation-related side effects are potentially diverse, but reversible with alteration of stimulation parameters.

Conclusions

There is insufficient evidence at this point in time to support the use of DBS as a clinical treatment for any psychiatric disorder. Any application of DBS for the treatment of a psychiatric illness should only occur in the context of a formal clinical trial that is approved by a human subject research and ethics committee following National Health and Medical Research Council guidelines. This research should only be conducted by multidisciplinary teams, where a significant commitment can be made to the long-term supervision and follow-up of patients.

Given the experimental status of DBS for psychiatric disorders, it should only be performed on patients who have an intact decision-making capacity and have provided full and informed consent. It is our opinion that the provision of consent and patients' individual suitability for DBS treatment should be reviewed by an independent body prior to commencement of any DBS procedure. This review process should consider the psychiatric appropriateness of the proposed research-based treatment, the neurosurgical expertise of the individual performing the DBS procedure, the quality of the team providing long-term care for the patient and the patient's capacity to provide informed consent to and engage in the treatment process. This review should be of each individual patient undergoing the procedure and be in addition to formal ethics review of the research protocol in which DBS is being performed.

2 Background

Deep brain stimulation

Deep brain stimulation (DBS) is a procedure that involves the implantation of stimulation electrodes in specific, highly localised brain regions with the aim of modifying local and connected brain activity.[1] DBS has been extensively used in neurological disorders such as Parkinson's disease, intractable tremor and dystonia, and is less commonly used or under investigation for other disorders such as epilepsy and Tourette's syndrome.[2-7] The indication for the use of DBS determines the placement of the individual stimulating electrodes. For many indications there are a number of neuroanatomical targets that provide therapeutic relief. For example, three DBS implantation sites have been shown to be clinically efficacious for Parkinson's disease: the globus pallidus, the subthalamic nucleus (STN), and a subdivision of the thalamus referred to as Vim.[3] A fourth site, the pedunculopontine nucleus, is currently under investigation and specific implantation targets tend to be more or less beneficial depending on an individual patient's clinical presentation.

The actual DBS procedure involves several stages. Initially, the stimulating electrodes are inserted during a stereotactic neurosurgical procedure then a pacemaker-like device is connected to these and placed in the chest below the clavicle. Once the patient has recovered from surgery, the stimulator is turned on and various stimulation parameters (including voltage, pulse width and frequency) are adjusted to achieve optimal response of symptoms. Standard stimulating systems have four small electrodes on the end of the stimulation wire and one of the goals of this initial programming period is to identify the optimal stimulating electrode for the patient in question. Once optimal stimulation parameters are set stimulation is essentially ongoing, although changes in these parameters can occur as needed.

The mechanism of action of DBS remains the subject of speculation.[8, 9] Although it was in part developed from a model of the disruption of brain regions (i.e. invasive psychosurgery), it has also been proposed that the high frequency stimulation alters brain activity in a functional way, rather than just disrupting one limited brain region. The effect of stimulation is likely to vary with stimulation frequency; with frequencies in the range of 50–60 Hz associated with stimulatory activity and stimulation at >100 Hz associated with the induction of inhibition.[7] It is possible that chronic stimulation induces adaptive plastic brain responses, such as altered synaptic activity in relevant circuits.[8, 9]
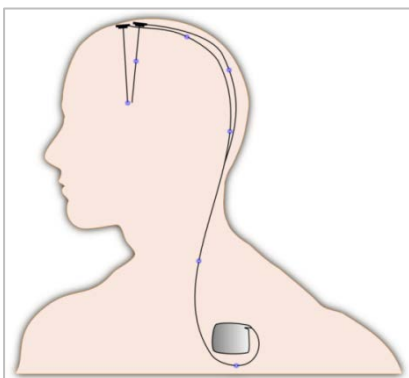

Figure 1: Schematic of implanted deep brain stimulation device

Deep brain stimulation for psychiatric disorders

A number of developments have led to interest in the potential use of DBS for the treatment of psychiatric disorders. First, there is a history of other surgical approaches to the treatment of psychiatric disorders. Historically, neurosurgeries for the treatment of severe psychiatric disorders such as obsessive compulsive disorder (OCD) and depression involved lesioning procedures. A number of such procedures were used, including anterior capsulotomy, subcaudate tractotomy and limbic leucotomy. These aimed to disrupt connections between cortical and subcortical brain regions involved in the proposed symptoms of these disorders.

Second, there has been a consistent demonstration of mood-relevant effects when DBS has been used in the treatment of neurological conditions such as Parkinson's disease. Third, there has been a progressive recognition that psychiatric disorders such as OCD and depression involve disruption of complex brain networks involving multiple dysfunctional brain regions. This view has come to supplant previous ideas about the pathophysiology of these disorders, which were predominantly focused on abnormalities in specific monoamine neurotransmitters. A network understanding of the pathophysiology of disorders, such as OCD and depression, lends itself to the development of therapeutic approaches that target specific nodes in this network or critical white matter pathways responsible for the connections between network notes.

Major depressive disorder and treatment resistance

Major depression is currently the leading cause of non-fatal disability in Australia and the fifth-leading cause worldwide.[10] Depression is an extremely common psychiatric illness, with a 15–20% lifetime prevalence rate globally.[11, 12] Approximately one million Australian adults live with this condition each year [12].

Approximately 30% of these patients do not respond to standard medication and psychological therapies.[13] Treatment-resistant depression results in considerable suffering for individuals, as well as increased burden of care for families. The economic burden is also considerable. Depression costs the Australian community more than $600 million each year in treatment payments, and those with treatment-resistant depression contribute a disproportionate amount to this. They are more frequent users of healthcare services and their treatment costs are up to 19-times greater than those for patients with depression who respond to treatment [14].

The management of treatment-resistant depression includes repeated trials of medication, medication combinations, psychotherapy and forms of brain stimulation (transcranial magnetic stimulation and electroconvulsive therapy. However, there is a significant subgroup of patients (10–20%) who remain chronically non-responsive to treatment. As a result they are disabled and suffer greatly. Even for those patients who respond to the most potent antidepressant electroconvulsive therapy, relapse rates remain high[15] and many patients develop therapeutic 'resistance' over time. These patients currently have no effective treatment options.

Obsessive compulsive disorder and treatment resistance

OCD is a relatively common mental illness with a lifetime prevalence of 2–3%.[16-18] It is characterised by recurrent, intrusive anxious thoughts (obsessions) accompanied by repetitive ritualised behaviours or mental routines (compulsions) that are frequently performed in an effort to reduce distress caused by obsessions. Obsessions and compulsions tend to form around one or more specific themes, such as fear of contamination or an extreme need for order and symmetry. The intrusive, distressing nature of obsessions and the substantial time spent executing compulsive behaviours and rituals can cause substantial impairment in interpersonal relationships, social and occupational functioning and the ability to carry out the basic activities required for daily living.[19, 20] Individuals with persistent or severe OCD report extremely low quality of life and have an elevated risk of attempting suicide, with between 10–27% of patients making an attempt during their lifetime.[21, 22] Co-morbidity with other mental illnesses, most commonly major depression, is high.

Treatment for OCD typically involves pharmacotherapy (e.g. selective serotonin reuptake inhibitors), which is often combined with psychotherapy (e.g. cognitive behavioural therapy). However OCD is a notoriously difficult condition to treat and up to 60% of patients do not obtain adequate benefit with standard treatment approaches.[23-25] Approximately 10% of OCD sufferers remain densely treatment resistant to all known therapies and chronically afflicted with severe symptoms.[26] Compared with psychiatric illness such as depression, there are comparatively few treatments indicated for patients with OCD, leaving those with severe treatment resistant illness with extremely limited therapeutic options and minimal hope for recovery.

3 Analysis of evidence

Deep brain stimulation in major depressive disorder

Potential anatomical targets for DBS applications in depression have been proposed based on: a) extrapolation from sites targeted in lesional psychosurgical procedures, and b) from the results of neuroimaging experiments. The majority of research to date has focused on DBS implantation in the white matter adjacent to the subgenual anterior cingulate (SAC) and on stimulation of the anterior limb of the internal capsule (ALIC) and the associated ventral striatal structures including the nucleus accumbens (NA).

Subgenual anterior cingulate

Research into DBS at the SAC has predominately been driven by Andres Lozano of the University of Toronto (Canada) and Helen Mayberg of Emory University (USA). They have led a series of overlapping clinical trials evaluating the efficacy of this form of DBS in either single site or multisite clinical protocols. They initially published the outcomes of six patients treated in an open-label fashion who were followed for six months. The pair reported a 50% remission rate.[27] Data from the same six patients was included in two reports of a larger sample of 20 patients followed for 12 months[28] or greater than three years.[29] Remission rate of 33% was reported at 12 months and 43% at three years or last follow-up (up to six years). Their most recent report also documented improvements in physical health and social functioning and found that work participation rates had increased from 10% of patient's pre-DBS to 65% at six years, post implantation.[29]

Two further clinical trials have been reported by this group. Holzheimer et al.[30] reported outcomes for 17 patients (10 with major depressive disorder and seven with bipolar affective disorder) who were followed for two years post-surgery. This trail incorporated a sham stimulation lead in phase and a subsequent period of stimulation discontinuation. The latter had to be removed from the protocol due to safety concerns with patients' mental state deteriorating following stimulation discontinuation. The remission rate was 36% at one year and 92% at two-year follow-up. A progressive improvement in social, occupation and psychological functioning was noted, with the average Global Assessment of Functioning scores increased by 44% from baseline at last follow-up. The second clinical trial was conducted in 21 patients across three trial sites in Canada.[31] This was an open-label study with a 12-month follow-up. Response rates were 48% at six months and 29% at 12 months.

Only one publication independent of this group has described the treatment of more than one patient with SAC DBS. In this Spanish study, eight patients received DBS and were followed for one year.[32] The remission rate at this time was 50% and improved psychosocial functioning was described for a majority of patients, including taking up of leisure activities, initiation of social relationships and decreased need for assistance with personal care.

An attempt to commercialise the DBS SAC treatment approach has been made by medical device company St Jude Medical, who have licensed intellectual property from Lozano and Mayberg. The company commenced a multi-site clinical trial that was expanded to 20 sites in 2011. However, this clinical trial was halted in 2013 after a failed futility analysis (interim analysis of the data suggested that it was unlikely a trial would show clinical benefit) (www.neurotechreports.com/pages/St_Jude_Medical_profile.html).

Anterior limb of the internal capsule

A second significant DBS target is the white matter of the ALIC and the associated ventral striatal structures including the nucleus accumbens (NA). The ALIC was initially the target for psychosurgical treatment of OCD. It was upon this basis that DBS to this region was subsequently investigated for OCD. These studies noted a prominent antidepressant effect, often in excess of the benefits obtained in the core symptoms of OCD (Dr Greenberg and Dr Malone, pers. comm., May 2004). This led to interest in the conduct of studies of DBS at the ALIC specifically for the treatment of treatment resistant depression.

There has been one published study that specifically targeted the ALIC: Malone et al. described the effects of DBS to the ALIC in 17 depressed patients. In the first publication, they described outcomes for 15 patients at 12 months and at last follow-up (up to three years).[33] In a second publication, the sample was extended to 17 patients, and the follow-up was up to 67 months (mean of 37.4 months).[34] In this later report, the 12-month remission rate was 41% (and 35% at last follow-up). However, a recent multi-site blinded trial failed to show significant differences between active ALIC stimulation and sham (Medtronic Ltd executives, pers. comm., August 2012) and was terminated at the time of futility analysis.

Nucleus accumbens

An approach related to ALIC stimulation has been to directly target the grey matter of the NA, which sits at the ventral end of the ALIC.[35] It is a promising target for DBS as stimulation in this region could potentially disrupt or augment the amygdala–basal ganglia–prefrontal circuitry that is abnormally active in mood and anxiety disorders. The shell region has been thought to potentially be a 'bottle-neck' for information flow from the amygdala to the basal ganglia, and hence to the prefrontal cortex.[35] Blocking this in the grey matter of the NA would require considerably less electrical charge than blocking activity in the white matter tracts such as the internal capsule. This would have considerable advantage in that it might be possible to use smaller electrodes and less charge producing a considerably longer lifetime for the battery in the stimulation unit.

Only one group has directly targeted the NA to date. Following 12 months of persistent stimulation, five out 10 patients had achieved antidepressant response, three were in remission and anxiety was significantly reduced in all. All five patients who responded were still classified as responders (i.e. had no worsening of symptoms) at two- and four-year post-implantation follow-up.[36] This group initially reported on the outcomes in three patients [37]who were subsequently included in a larger group of 10 followed up for 12 months.[38] The sample was then extended to 11 patients who were followed for two to four years.[36] The 12-month remission rate was 30% but the two-year remission rate had fallen to 9% (45% met response criteria persistently).

Other implantation targets

A recent study described outcomes of seven patients treated with DBS targeting the supero-lateral branch of the medial forebrain bundle.[39] After experiencing a rapid onset of antidepressant symptoms, four patients were remitters at last follow-up (between 12 and 33 weeks). Two case reports have described DBS at other targets in the treatment of depression: one of these described DBS of the inferior thalamic peduncle (ITP)[40] and one of the lateral habenula.[41] These described remission of depression at 24 and 12 months respectively.

Deep brain stimulation in obsessive compulsive disorder

Since 1999, some 100 patients with chronic severe refractory OCD have undergone DBS. The neuroanatomical targets for implantation have included the anterior limb of the ALIC, NA, ventral capsule/ventral striatum (VC/VS), STN and the ITP.

While neuroimaging investigations have contributed much to our understanding of the network of brain regions involved in the pathophysiology of OCD, functional neuroanatomical models are not yet sufficient to identify precise surgical targets. Instead, these targets have been suggested based on experience from lesional psychosurgery procedures, following observations of response to surgery for other conditions (such as Parkinson's disease, as is the case with the STN), or reflect gradual target refinement following ongoing evaluation of clinical outcomes in relation to lead location.

Anterior limb of the internal capsule and the ventral striatum/ventral capsule

One open-label case study and two small studies have described the efficacy of DBS applied to the ALIC in a total of 11 patients. The case study reported a marked reduction in OCD symptoms and improved psychosocial functioning 10 months post-stimulation onset.[42] The two subsequent studies included some periods of blinded 'on-off' stimulation. Insufficient detail is provided in the manuscript to understand the outcomes of the six patients described in Nuttin et al.[43] Two of the four patients described in Abelson et al.[44] were reported to be responders to treatment.

A larger number of reports have presented the results of stimulation at sites described as within the VC or VS. There is a significant overlap between the stimulation site in these studies and those ascribing implantation in the ALIC, with the localisation of stimulation typically several millimetres anterior to the anterior commissure and with a similar lateral and ventral localisation. There have been four open-label case series describing a total of 19 patients with response rates ranging from 40–100%. In the largest study, Greenberg et al.[45] reported a 40% response rate in 10 patients followed for three years. Goodman et al.[46] reported four out of six responders in a partially blinded study where the onset of stimulation was staggered in a blinded fashion.

Data from a number of these studies was combined in a report in 2010 which describe the outcomes of a total of 26 patients implanted at the ALIC or VC/VS and followed for between three and 36 months.[47] The overall response rate was 62%. In addition to a reduction in OCD severity, there was a substantial global reduction in severity of depression and generalised anxiety.

Importantly, as well as an improvement in core symptoms of psychopathology, there was a significant improvement in overall functioning in these patients. At last follow-up, 80% had demonstrated marked improvements in social and occupational functioning and ability to perform activities of daily living, with performance in each of these areas assessed as 'fair to good'. No patients were reported to have deteriorated as a result of participation in DBS treatment and only four out of 26 were unchanged. Despite these impressive outcomes, it is notable that a significant proportion of patients continued to experience moderately severe symptoms of OCD in spite of DBS treatment, with only 38% achieving symptom scores considered consistent with remission. When it was performed, interruption of DBS stimulation was typically associated with a worsening of symptoms.

A number of important further observations were made in this study. Specifically, it was notable that overall outcomes improved to a greater degree in patients implanted at later dates. This reflected a change in the site of DBS implantation to an area more posteriorly in the internal capsule. Patients implanted at this more posterior site were also noted to require substantially lower stimulation voltages to achieve therapeutic effect.

Nucleus accumbens

A small number of reports have specifically targeted the NA rather than the more dorsal striatal or white matter regions. Strum et al.[48], described three out of four responders and Franzini et al.[49] one out of two responders with open-label DBS. In addition, there have been two studies were slightly larger numbers and blind periods of stimulation.

In one of these studies, 10 patients received three months of active stimulation and three months of sham stimulation in a double-blind crossover fashion with subsequent open-label treatment and follow-up for 12 months.[50] Despite this provision of double-blind stimulation, a direct quantitative analysis of outcomes across the double-blind phase was not provided. Five patients met partial response criteria by 12 months, and significant improvements in quality of life and global functioning were reported.

The second study[51] involved 16 patients who received eight months of open-label treatment followed by two-week blocks of blinded active or sham stimulation. Nine patients responded in the open-label phase. Fourteen patients participated in the double-blind phase during which there was a significantly greater reduction in OCD symptoms with active stimulation. Small but significant functional improvements in work, social and family life were observed following the initial open-label phase and benefit in each of these areas had increased further at last follow-up.

Subthalamic nucleus

Interest in the STN as a potential target for DBS in OCD was sparked by observations of diminished compulsiveness in patients with Parkinson's disease after undergoing implantation at this site. Mallet (2002)[52] and Fontaine (2004)[53] initially described promising results with open-label stimulation in a total of three patients with OCD and Parkinson's disease, all of whom were responders.

Subsequently, in 2008 Mallet et al. reported outcomes of a multi-site sham-controlled, double-blind, cross-over trial of STN DBS in 16 patients with refractory OCD.[54] Three months after surgery and following individualised determination of optimal stimulation parameters, patients were randomised to three months of active or sham (i.e. off) stimulation. Following a one-month wash-out period (i.e. stimulation off) they crossed over to receive three months of the other condition. Under active stimulation the severity of OCD symptoms were reduced and global functioning improved relative to sham. At the conclusion of three months of active stimulation 75% of patients met response criteria in contrast to 38% following three months of sham stimulation. Neuropsychological measures, depression and anxiety were not modified by stimulation. This study reported a relatively high incidence of severe adverse effects, with one intracerebral haemorrhage (resulting in persistent contralateral hand palsy) and two hardware infections that necessitated explanation of the stimulators.

Most recently, Chabardes et al.[55] described positive outcomes for two additional patients who experienced a 78% and 34% reduction in OCD severity following six months of persistent stimulation.

Deep brain stimulation in other psychiatric indications

Research investigating DBS for other psychiatric disorders is comparative scarce. A small number of studies have been conducted in anorexia nervosa and addiction. These are briefly summarised below.

Anorexia nervosa

A number of small recent studies have described the possible use of DBS in the treatment of anorexia nervosa. The first of these involve a case report of the treatment of a 56-year-old woman with comorbid depression and anorexia, where DBS stimulation occurred in the SAC.[56] Improvement in symptoms of anorexia appeared at least partially independent of improvement in depression. A subsequent report has described outcomes for six patients stimulated at the same site.[57] Six patients had substantially improved functional symptoms at nine months, including in mood, with three appearing to have had a substantial improvement in core symptoms of anorexia with associated improvement in weight. Patients whose symptoms of anorexia improved also reported a greatly increased quality of life.

Another report described the outcomes of four patients treated with DBS applied to the NA.[58] All four patients appeared to achieve a substantial improvement in symptoms of anorexia with an average follow-up period of more than three years.

Addiction

A small literature has also explored the potential use of DBS for the treatment of addictive disorders, primarily with a focus on stimulation of the NA reward system. There have been a number of individual case reports suggesting remission of symptoms in the treatment of alcohol and heroin addiction[59, 60] and a small case series.[61]

In this latter report, Muller et al. described the successful treatment of three patients with alcohol dependence.[61] Stimulation of the NA resulted in a dramatic reduction in alcohol craving that resulted in abstinence in two patients, and a significant reduction of use in a third.

A further study has reported on rates of nicotine dependence in patients receiving NA stimulation for other disorders including Tourette's syndrome, OCD or anxiety disorders.[62] This study reported slightly higher rates of successful smoking sensation compared to what would typically be expected across the same time points.

Caveat regarding comparison of clinical outcomes

Caution is warranted when considering the relationship between clinical outcomes for a particular illness and implantation at different anatomical targets, as currently there is insufficient evidence to ascertain whether DBS at one site is clinically superior to another. The variance in reported efficacy between individual studies and disparate brain regions likely reflects the influence of the small number of patients in each sample, heterogeneity of patient characteristics, differing levels of treatment-resistance, widely divergent follow-up durations, and differences in research design and outcome measures.

Until specifically designed head-to-head clinical comparator trials of DBS at different implantation targets are conducted the superiority of one site over another cannot not be confidently determined for any indication. In addition, as with DBS for movement disorders, it may be that certain implantation sites are more efficacious for patients with specific types of symptoms. However confirmation of this possibility awaits future dedicated research trials.

4 Safety and adverse effects

There are two major types of safety concerns associated with administration of DBS: those related directly to the neurosurgical procedure and implanted device hardware, and the adverse effects arising from the stimulation itself.

Procedure and device related adverse events

Concerns directly related to the neurosurgical procedure are similar when DBS is being applied for a psychiatric indication as to when it is being used for neurological disorder. Procedure related adverse effects include haemorrhage (1–2% of procedures), seizure induction (<1%, usually in the first 24-hours following implantation), infection (2–3%, usually superficial) and other general surgical or anaesthetic complications.[7, 63, 64]

It is worth noting that different target sites in the brain do require different DBS implantation trajectories and it is possible that higher rates of haemorrhage could result from implantation sites in less accessible brain regions, for example where there are a greater number of blood vessels in the immediate region. However there is no evidence to date that this impinges on the overall safety of DBS at the major targets used to treat psychiatric disorders.

In general, the procedure-related complication rate is dependent on the competency and experience of the surgical team. Currently, the rate of DBS complications is typically low and usually mild and reversible.[7] In one case series of 60 patients who underwent DBS for Parkinson's disease only one patient left with any deficit associated with a surgical complication, which was a mild aphasia resulting from a small haemorrhage.[65]

Device-related complications can occur. This includes lead fracture and malfunction of the neurostimulator. Both have been reported in relation to DBS for psychiatric indications[38, 66, 67], but with advances in device technology they are increasingly uncommon and there is no evidence to suggest that occurrence rates differ from DBS for neurological indications.

Stimulation related adverse events

Adverse effects arising directly from stimulation itself are common and strongly linked to the neuroanatomical site of stimulation. They most often occur at contacts and stimulation parameters that are not optimal for therapeutic benefit and are elicited during the trial-and-error style search for optimal stimulation settings. Stimulation-induced side effects are frequently transient and rapidly reversible with adjustment or cessation of stimulation.

Transient induction of hypomania and agitation/anxiety are two of the most commonly reported stimulation related side effects and both have been induced via stimulation at a number of brain regions.[45, 46, 50, 51, 66] Insomnia is common following voltage increases and can necessitate temporary increases in sedative medications.[46] Temporary worsening of other psychiatric symptoms such as further reduced mood, increased irritability and obsessionality can also occur and patients should be monitored closely for these.[28, 66, 68]

Sensory disturbances such as tingling/pins-and-needles, hot and cold flushes, metallic tastes and other gustatory and olfactory experiences can occur. Autonomic symptoms such as nausea, dizziness, sweating and changes in blood pressure, have also been described following stimulation at numerous implantation sites.[36, 67-69] Motor effects include oculomotor disturbance, orofacial muscle contractions and temporary motor slowing.[68, 70]

With respect to cognition: transient confusion, memory disturbance and verbal perseveration have been described in response to certain DBS parameters. In all cases these have been temporary and there is no evidence of persistent cognitive impairment or related functional decline.[66, 68, 71, 72] There are, however, relatively few dedicated studies that have examined neuropsychological outcomes in detail.

Stimulation 'off' effects have also been described; this refers to the sudden return of psychiatric symptoms if the device is turned off or malfunctions.[46, 63] In patients who obtained therapeutic benefit from DBS, this is a common occurrence when their stimulator battery becomes depleted. Early DBS devices had a battery life of approximately 18–24 months (dependant on individual stimulation parameters) before replacement was required, which was performed via surgical day procedure. Recently, a rechargeable battery has been developed. This allows patients to charge the battery using an external plug-in re-charger, with device manufactures estimating these models will run for approximately nine years before replacement is required.

Suicide risk following deep brain stimulation

There have been a number of suicide attempts and completed suicides following DBS for psychiatric indications.[29, 36, 68] Without exception, all patients undergoing psychiatric DBS suffer from chronic severe mental illness and are at substantially elevated risk of suicide prior to surgery. The suicidality observed in these individuals' post-DBS was not associated with acute alterations in stimulation parameters and is not thought to be related to the procedure itself, but rather a consequence of a severe psychiatric disease that has not responded to psychosurgery.[29, 38]

Composition of the treating team

Clinical management of patients undergoing DBS for a psychiatric indication can be an extremely complex and lengthy process. Expertise from numerous clinical disciplines is required to both monitor for adverse events and maximise potential for therapeutic benefit. There is a general consensus among many of the larger and more experienced research groups in this area that optimal care is provided by multidisciplinary treating teams that include expert input from psychiatry, neurosurgery, clinical psychology and neuropsychology.[73, 74]

It also appears important that follow-up is provided for a protracted period of time following surgical implantation. Adjustment of DBS stimulation voltages and the stimulation parameters can take very long periods of time (months to years) to optimise. Patients need to be monitored to ensure that optimal clinical outcomes are achieved and to monitor for the emergence of stimulation-related adverse events.

It also appears likely that optimal outcomes are obtained when post-operative management includes recovery oriented psychological therapy in order to translate reductions in symptom severity into functional improvement in day-to-day life.[7]

Table 1: DBS for OCD: Studies with a blinded component

Target and study	n	FU mths	FU Y-BOCS change	% responders	Blinding ON/OFF Protocol	Y-BOCS on vs off
Anterior Limb of the Internal Capsule						
Nuttin et al 2003 [43]	6	3–31	NS	NA	3 months on, 5–10 weeks off (4 patients only)	19.8 vs 32.3
Abelson et al 2005 [44]	4	4–23	↓ 9.8 pts	50%	4 blinded on/off periods (duration NR)	26.5 vs 29.3
Subthalamic Nucleus						
Mallet et al 2008 [54]	16	3	↓ 8.9 pts	NA	3 months on, 3 months off	19.8 vs 28.7
Ventral Capsule/Ventral Striatum						
Goodman et al 2010 [46]	6	12	↓ 15.7 pts	67%	Staggered stimulation onset: 30 or 60 days post-surgery	NR
Nucleus Accumbens						
Huff et al 2010 [50]	10	12	↓ 6.8 pts	10%	3 months on, 3 months off	27.9 vs 31.1
Denys et al 2010 [51]	16	21	↓ 17.5 pts	56%	2 weeks on, 2 weeks off	8.3 pts difference

( ) = extended sample/follow-up outcomes of previously described cohort, FU mnths = duration of follow-up in months, NR = not reported, NA = not applicable, NS = not significant, % responders = percentage of patients whose Y-BOCS score was decreased by $\geq$ 35% from baseline at last follow-up

Table 2: DBS for OCD: Open-label case reports and case series

Target and study	n	FU mths	FU Y-BOCS change	% responders
Subthalamic nucleus				
Mallet et al 2002[a][52]	2	6	↓ 20 pts	100%
Fontaine et al 2004[a][53]	1	12	↓ 31 pts	100%
(Chabardes et al 2013)[^][55]	4	6	↓ 18 pts	75%
Nucleus accumbens				
Strum et al 2003 [48]	4	24–30	NA	75%
Franzini et al 2010 [49]	2	24–27	↓ 13 pts	50%
Anterior limb of the internal capsule				
Anderson & Ahmed 2003 [42]	1	10	↓ 27 pts	100%
Ventral capsule/ventral striatum				
Greenberg et al 2006 [45]	10	36	↓ 12.3 pts	40%
Tsai et al 2014 [76]	4	15	↓ 12 pts	50%
Roh et al 2012 [77]	4	24	↓ 22 pts	100%
Aouizerate et al 2005 [78]	1	18	↓ 13 pts	100%
ALIC & VC/VS combined				
(Greenberg et al 2010) [+][47]	26	3–36	↓ 13.1 pts	62%
Inferior thalamic peduncle				
Jimenez-Ponce et al 2009 [69]	5	12	↓ 17.2 pts	100%

( ) = extended sample/follow-up outcomes of previously described cohort, n = number of patients in study, FU mths = duration of follow-up in months, % responders = percentage of patients whose Y-BOCS score was decreased by ≥ 35% from baseline at last follow-up, ALIC & VC/VS = combined outcomes from DBS to anterior limb of the internal capsule and ventral capsule/ventral striatum

[a] patient/s with Parkinson's disease and comorbid OCD

[^] includes 2 patients described in Mallet et al 2002

[†] includes 5 patients described in Greenberg et al 2006, 5 patients described in Goodman et al 2010, 4 patients described in Nuttin et al 2003

Table 3: DBS for TRD: Studies with a blinded component

Target and Study	n	Mean AD's trialled	Psycho therapy (Y/N)	ECT (Y/N)	Primary Outcome Measure	FU mths	FU change	% responders	% remitters	Blinding ON/OFF Protocol	HAMD on *vs* off
Subgenual anterior cingulate											
Mayberg et al 2005 [27]	6	NR[a]	6/0	5/1	HAMD$_{17}$	6	↓ 14.3 pts	66.6%	33.3%	4 weeks blinded off (1 patient only)	5 vs 10[b]
Holtzheimer et al 2012[b] [79]	17	6.2[c]	17/0	16/1	HAMD	24	↓ 16.6 pts	92.0%	58.0%	4 weeks blinded off (all patients), further 2 weeks blinded off (3 patients only [d])	17.9 vs 20.5
Merkl et al 2013 [80]	6	NR	6/0	5/1	HAMD$_{24}$	6	↓ 11.5 pts	33.3%	33.3%	24 hours blinded off	NS
Ramasubbu et al 2013 [81]	4	8.5	4/0	4/0	HAMD$_{17}$	6	↓ 11 pts	50%	0%	10 one week periods, 2 off and 8 on[e]	NA
Inferior thalamic peduncle											
Jimenez et al 2005 [40]	1[h]	NR	1/0	1/0	HAMD	24	↓ 39 pts	100%	100%	12 months blinded off	NR[i]
Nucleus accumbens											
Schlaepfer et al 2008 [37]	3	10.7[f]	3/0	3/0[*]	HAMD$_{24}$ & MADRS	6 – 23 wks	NR	66.6%	0%	5 periods of 1 volt difference, 0–4V's (duration NR)	NRD[9]

n = number of patients in study, AD's = antidepressant medications, FU mths = follow-up in months, FU change = change from baseline in primary outcome measure, % responders = percentage of patients who achieved a reduction of ≥ 50% in depression severity from baseline, % remitters = percentage of patients who achieved remission

according to the primary outcome measure, HAMD = Hamilton Depression Rating Scale, MADRS = Montgomery Asberg Depression Rating Scale, NR = not reported, NA = not applicable, NS = not significant, NRD = not reported in detail

[a] treatment resistance inclusion criteria = failure to respond to a minimum of four different antidepressant treatments, including medications, evidence-based psychotherapy, or electroconvulsive therapy administered at adequate doses and duration during the current episode

[b] includes 7 patients with bipolar depression; during stimulation 'off' phase maintenance of positive mood but substantial deterioration in Positive and Negative Affect Scale Positive score and onset of anergia described

[c] medications in current episode only, not specified if AD's only or includes other psychotropics

[d] abandoned after rapid relapse observed in initial 3 patients and poorer than anticipated restoration of antidepressant response following re-initiation of stimulation

[e] weekly manipulation of pulse width, frequency and voltage

[f] medications in current episode only

[g] on reported as superior to off for both outcome measures; insufficient detail to make direct comparison of scores

[h] comorbid bulimia and borderline personality disorder

[i] no relapse with OFF stimulation, but oscillations in mood accompanied by functional deterioration observed

* bilateral and unilateral ECT trialled

Table 4: DBS for TRD: Open-label reports and case series

Target and Study	n	Mean AD's trialled	Psychotherapy (Y/N)	ECT (Y/N)	Primary Outcome Measure	FU mths	FU change	% responders	% remitters
Subgenual anterior cingulate									
Neimat et al 2008 [82]	1	NR	NR	1/0	HAMD$_{17}$	30	↓ 12 pts	100%	100%
(Kennedy et al 2011)^ [29]	20	NR[a]	20/0	17/3	HAMD$_{17}$	36 - 72	NR	64.3%	42.9%
Puigdemont et al 2011 [83]	8	9.75	6/2	8/0	HAMD$_{17}$	12	NR	62.5%	50.0%
Lozano et al 2012 [31]	21	16[b]	21/0	18/3	HAMD$_{17}$	12	↓ 8 pts	29.0%	NR
Torres et al 2013 [84]	1[c]	NR	NR	1/0	HAMD$_{NR}$	9	↓ 18 pts	100%	100%
Nucleus accumbens									
(Bewernick et al 2010)[†][38]	10	14.1	10/0	10/0*	HAMD$_{28}$	12	↓ 11.7 pts	50.0%	NR
(Bewernick et al 2012)[†][36]	11	13.8	11/0	11/0*	HAMD$_{28}$	12 - 48	↓ 12.7 pts	45.5%	9.0%
Ventral capsule/ventral striatum									
Malone et al 2009 [85]	15[c]	NR[d]	15/0	15/0*	HAMD$_{24}$	6 - 51	↓ 18.8 pts	53.3%	40.05
(Malone et al 2010)[#][34]	17	NR[e]	17/0	17/0*	MADRS	14 - 67	↓ 18.7 pts	71.0%	35.0%
Lateral habenula									
Sartorius et al 2010 [86]	1	NR	NR	1/0	HAMD$_{21}$	12	NR	100%	100%
Medial forebrain bundle									
Schlaepfer et al 2013 [70]	7	21.9[f]	7/0	7/0	MADRS	12 – 23 wks	↓ 15.3 pts	86%	57%

( ) = extended sample/follow-up outcomes of previously described cohort, AD's = antidepressant medications, n = number of patients in study, FU mths = duration of follow-up in months, FU change = change from baseline in primary outcome measure, % responders = percentage of patients who achieved a reduction of $\geq$ 50% in depression severity from baseline, % remitters = percentage of patients who achieved remission according to the primary outcome measure, HAMD = Hamilton Depression Rating Scale, MADRS = Montgomery Asberg Depression Rating Scale, NR = not reported

[a] treatment resistance inclusion criteria = failure to response to a minimum of four different antidepressant treatments, including medications, evidence-based psychotherapy, or electroconvulsive therapy, administered at adequate doses and duration during the current episode

[b] not specified if AD's only or includes other psychotropics

[c] includes 1 patient with bipolar depression

[d] treatment resistance inclusion criteria = adequate trials (>6 weeks at maximum recommended or tolerated dose) of primary antidepressant drugs from at least three different classes; adequate trials (>4 weeks) of augmentation/combination strategies using a primary antidepressant with at least two other different agents; at least one adequate trial of ECT (six or more bilateral treatments); and an adequate trial of psychotherapy (at least 20 sessions with an experienced therapist).

[e] treatment resistance inclusion criteria is identical to [f] and all patients had trialled at least five courses of medication

[f] includes psychotropic medications other than antidepressants

* bilateral and unilateral ECT trialled

^ includes 6 patients described in Mayberg et al. 2005

includes 15 patients described in Malone et al. 2009

[†] includes 3 patients described in Schlaepfer et al. 2008

5 Evidence gaps

The primary evidence gaps in evaluation of the use of DBS as a treatment for psychiatric disorders is the absence of substantive medium- to long-term double-blind, randomised controlled trials. Given the complexity of conducting this type of research, it is unlikely that a significant number of these trials will be conducted in the near future and conclusions will need to be drawn from mostly small studies and possibly one or two large multicentre research efforts. There are a number of specific areas in which further research is required beyond the basic establishment of efficacy.

Patient characteristics

Little information is currently available as to patient characteristics that may predict successful response to DBS treatment. Studies have included insufficient samples to allow an exploration as to the differential effectiveness of DBS in illness subtypes. In the context of depression, research should investigate the relationship between melancholia and treatment response. In OCD, future studies are required to explore whether subtypes of disorder (i.e. hoarding), are differentially more or less responsive to treatment. Research is also required to establish whether the presence of illness comorbidities is a positive or negative predictor of treatment response.

Level of treatment resistance

All patients included in OCD and depression trials to date have been considered to have some degree of treatment resistance: that is, they have failed to respond to other treatment modalities. However, the degree of treatment resistance does vary across studies. For example, some studies require patients to have exhausted an extensive range of antidepressant strategies. Others have not required patients to have previously tried treatments with established efficacy, such as electroconvulsive therapy.

Optimal neuroanatomical target/s

Most studies exploring DBS in OCD have applied treatment to the ALIC or the adjacent striatum or NA. In this general area of the brain, there is an emerging suggestion that posterior stimulation sites are more effective. However, no comparative research has explored the differential efficacy of DBS at this site compared to other regions, such as the STN.

DBS targets for the treatment of depression have been more heterogeneous with data predominantly from one group focusing on the SAC, and studies from other groups providing treatment in the VS/VC, NA and other related regions. No comparative studies have been conducted of stimulation across different brain regions.

Stimulator programing and stimulation parameters

There is marked heterogeneity in the procedures used to determine optimal DBS stimulation settings. In some studies these are set by a nonflexible fixed protocol. In other settings stimulation levels are determined based upon an initial interrogation of multiple stimulation settings that are adjusted frequently across time. It is possible that different protocols will suit different clinical applications and may be associated with different trajectories of clinical response. It is clear that programing of the DBS device should be undertaken by a clinician with a comprehensive understanding of the technical aspects of stimulation parameters and clinical expertise in the disorder in question.

6 Recommendations

The use of DBS treatment cannot be recommended at this stage in the clinical management of any psychiatric disorder. The provision of DBS for psychiatric indications should only occur for patients who are enrolled in a clinical trial. In a clinical trial DBS use should be approved by an institutional human subjects research and ethics committee (HREC) constituted consistently with National Health and Medical Research Council guidelines.

The conduct of this type of research should be done only by adequately experienced and trained multidisciplinary clinical research teams. At a minimum this should include individuals with expertise in neurosurgery, psychiatry and neuropsychology. DBS implantation should be done by a neurosurgeon with substantive expertise in stereotactic DBS procedures, and who is currently performing these operations for other indications on a regular basis. The programming of a DBS device should be conducted under the close supervision of a psychiatrist with substantial experience in the clinical management of patients with the disorder being treated.

The context of the modern application of DBS is also worthy of consideration. There is a long history of invasive psychosurgical procedures being used in psychiatry, often with very negative consequences for individual patients, and certainly for the reputation of psychiatry in general. Although many of the stimulation effects produced with DBS are considered reversible, it is clearly an invasive neurosurgical procedure and, as such, there are both operative- and stimulation-related risks.

Given that DBS is not a proven treatment at this stage its provision should be provided to only individuals who are able to fully consent to undertaking the procedure and are cognisant of the relative risk/benefit ratio. It is our opinion that the consent of these patients and their individual suitability for DBS treatment should be reviewed by an independent body prior to commencement of any DBS procedure. This review process should consider the psychiatric appropriateness of the proposed research based treatment, the neurosurgical expertise of the individual performing the DBS procedure, the quality of the team providing long-term care for the patient and the patient's capacity to provide informed consent to and engage in the treatment process. This review should be undertaken for each individual patient undergoing the procedure and be in addition to formal ethics review of the research protocol in which DBS is being performed.

7 Conclusions

DBS is a promising and emerging form of treatment for a range of neurological and psychiatric disorders. However, at this point in time there is insufficient evidence to justify its use in clinical practice for any psychiatric indication. There is no evidence that the use of DBS in psychiatric disorders is associated with greater risks than when this treatment is used for the treatment of neurological conditions. However, insufficient studies have been conducted to date to establish its effectiveness or to comprehensively characterise its safety.

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9 Appendices

Appendix A: List of abbreviations, critical terms and clinical measures

DBS	Deep brain stimulation.
ECT	Electroconvulsive therapy.
Global Assessment of Functioning	A subjective clinician-rated score ranging from 0 to 100 that rates a patient's current psychological, social and occupational functioning in day-to-day life.
HAMD	Hamilton Depression Rating Scale, a clinician-rated clinical scale that assesses the severity of common symptoms of major depression. The original version comprised 17 items ($HAMD_{17}$), but subsequent revisions contain up to 28 items ($HAMD_{28}$). Each item is scores from 0 (no symptoms) to 4 (extreme symptoms) such that higher scores denote greater depression severity. The maximum score is dependent on the version utilised. Remission is typically defined as HAMD score ≤ 7.
Indication	The illness or disease for which the treatment is being administered.
ITP	Inferior thalamic peduncle.
MADRS	Montgomery Asberg Depression Rating Scale, a clinician-rated clinical scale that assesses the severity of common symptoms of major depression. Comprises 10 items each of which are rated from 0 (no symptoms) to 6 (extreme symptoms), where higher scores denote greater depression severity. The maximum score is 60. Remission is typically defined as MADRS score ≤ 10.
NA	Nucleus accumbens.
OCD	Obsessive compulsive disorder.
Remission	Term used to describe the absence of a formerly present illness; the patient is deemed to have fully recovered in response to treatment.
Response	Term used to describe a partial therapeutic response to treatment. Clinically significant symptoms remain, but are improved from pre-treatment levels. The percentage change threshold differs between illnesses and research studies, but most often a reduction of $\geq 50\%$ is utilised in major depression and ≥ 25–35% in OCD (as this condition is frequently more difficult to treat).
SAC	Subgenual anterior cingulate.
STN	Subthalamic nucleus.

TRD   Treatment resistant depression.

VC/VS   Ventral capsule/ventral striatum.

Y-BOCS   Yale-Brown Obsessive Compulsive Scale, a clinician-rated clinical scale that assesses the severity of obsessions and compulsions. Considered the gold-standard rating scale for OCD and used by most clinical trials. Comprises 10 items each of which are rated from 0 (no symptoms) to 4 (extreme symptoms), where higher scores denote greater psychopathology. The maximum score is 40. Remission score cut offs range from $\leq$ 7 to < 14.

Appendix B: Methods of literature search

A search of relevant academic literature published was conducted using the search engines PubMed, Scopus, OVID Medline and Google Scholar using combinations of the following key words:

- Deep brain stimulation
- Psychosurgery
- Psychiatry
- Depression
- Major depressive disorder
- Obsessive compulsive disorder
- Anorexia
- Addiction
- Substance dependence
- Substance abuse.

Where review articles were identified their reference lists were also searched for additional relevant publications.

Where multiple publications describing outcomes from the same patient cohorts were identified only the most recent publication was included. When publications were identified that included a subset of patients described in a prior publication as well as a number of new patients, both publications were included. The latter of these studies was marked with a symbolic identifier (^, #, †) and the overlap between the patient samples outlined beneath the table in question. Studies concerned with surgical outcomes and not reporting clinical data were excluded.