

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## INTERVENTIONAL PROCEDURES PROGRAMME

### **Interventional procedure overview of deep brain stimulation for chronic, severe, treatment-resistant obsessive-compulsive disorder in adults**

Obsessive-compulsive disorder is a mental health condition in which a person has obsessive thoughts (repeated, unwanted and unpleasant thoughts, images or urges). The person feels the need to carry out compulsive (repetitive) behaviours to try to relieve the unpleasant feelings brought on by the obsessive thoughts. In this procedure, an electrode is put into the brain through 2 small holes in the skull and connected to a wire that is tunnelled under the skin behind the ear and down the neck. The wire is attached to an electrical stimulator that is put under the skin on the chest. The stimulator sends electric pulses to the brain (deep brain stimulation). The aim is to reduce the obsessive-compulsive thoughts and behaviours.

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## Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and professional opinion. It should not be regarded as a definitive assessment of the procedure.

## Date prepared

This overview was prepared in July 2020 and updated in December 2020.

## Procedure name

- Deep brain stimulation for chronic, severe, treatment-resistant obsessive-compulsive disorder in adults.

## Professional societies

- Society of British Neurological Surgeons
- Royal College of Psychiatrists
- The British Psychological Society

## Description of the procedure

## Indications and current treatment

Obsessive-compulsive disorder (OCD) is a mental health condition in which a person has obsessive thoughts (repeated, unwanted and unpleasant thoughts, images or urges). The person feels compelled to carry out compulsive (repetitive) behaviours to try to relieve the unpleasant feelings brought on by the obsessive thoughts.

[NICE's guideline on obsessive-compulsive disorder and body dysmorphic disorder](#) describes the treatment of OCD. Treatment options include

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psychological interventions and drug treatment (usually selective serotonin reuptake inhibitors).

## What the procedure involves

Deep brain stimulation (DBS) for OCD is done under general or local anaesthesia. A stereotactic frame may be used. MRI or CT imaging, or both, are used to identify the target area of the brain (commonly, the anterior limb of the internal capsule). Two small holes are drilled in the skull and electrodes are implanted into the target area. The electrodes are connected to an implantable neurostimulator by leads, which are tunnelled under the skin of the neck and scalp. The neurostimulator is surgically placed into a subcutaneous pocket below the clavicle. Postoperative imaging is usually used to confirm the location of the electrodes. A handheld remote-control programming unit is used to turn the neurostimulator on or off and adjust stimulation parameters to find the right level of stimulation.

Although the mechanisms of action of deep brain stimulation are not fully understood, the aim of the procedure is to reduce the obsessive-compulsive thoughts and behaviours. A potential advantage of the procedure is that the stimulation can be adjusted according to the clinical effect and if necessary, stopped completely. It can be used as an adjunct to medication and as an alternative to neurosurgery for treatment-resistant OCD.

## Outcome measures

The **Yale-Brown Obsessive Compulsive Scale (Y-BOCS)** is designed to rate the severity and type of symptoms in people with OCD. It consists of 10 questions, 5 about obsessive thoughts and 5 about compulsive behaviour. Each item is rated from 0 (no symptoms) to 4 (extreme symptoms) with a total range from 0 to 40.

The **Global Assessment of Functioning (GAF)** scale assesses the level of a person's psychological, social and professional functioning. It ranges from 1 (representing severe impairment) to 90 (representing a person who is virtually free of symptoms or with very minimal symptoms and who functions satisfactorily within their social environment or family). The higher scores indicate better functioning.

The **Clinical Global Impression (CGI)** rating scales are measures of symptom severity, treatment response and the efficacy of treatments in studies of treating mental health conditions. The lower scores indicate lesser severity of disease.

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The **Hamilton Depression Rating Scale (HAM-D)** is a multi-item clinician-administered depression assessment scale in which a lower score indicates normal mood and a higher score shows severity of the condition.

The **Hamilton Anxiety Rating Scale (HAM-A)** is used to measure the severity of anxiety symptoms. This clinician-administered scale consists of 14 items. Each item is scored from 0 (not present) to 4 (severe), with a total score range of 0 to 56. Less than 17 indicates mild severity, 18 to 24 mild to moderate severity and 25 to 30 moderate to severe.

The **Montgomery and Asberg Depression Rating Scale (MADRS)** explores depressive symptoms with scores ranging from 0 to 60, with higher scores indicating greater severity of depressive symptoms.

The **Brief Anxiety Scale (BAS)** is a dimensional measure of generalised anxiety with scores ranging from 0 to 70, with higher scores indicating greater severity of symptoms of anxiety.

The **Hospital Anxiety Depression Scale (HADS)**, with anxiety and depression subscales, is a measure designed to assess anxiety and depression symptoms for patients in medical practice, with emphasis on reducing the impact of physical illness on the total score. It is a 14-item scale, 7 each for depression and anxiety. The higher scores indicating greater severity of symptoms of anxiety and depression.

## Efficacy summary

### Reduction in symptoms

#### Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)

In a randomised controlled trial (RCT) of 16 patients who had active or sham stimulation of the subthalamic nucleus for refractory OCD, the Y-BOCS score was statistically significantly lower after active stimulation for 3 months (mean 19 [SD 8] vs 28 [SD 7],  $p=0.01$ ). The percentage of people with symptom response who had  $\geq 25\%$  decrease in Y-BOCS score was 75% for the active stimulation group and 38% for the sham stimulation group.<sup>1</sup>

In an RCT of 24 patients who had DBS implanted into the bilateral anterior limbs of the internal capsule (ALIC), the median Y-BOCS score improved by 37% during the stimulation ON phase compared to stimulation OFF phase ( $p<0.017$ ). The median Y-BOCS score improved by 42% during the stimulation ON phase

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compared to the preoperative score ( $p < 0.001$ ). At 4-year follow-up, the Y-BOCS score improved by 66% compared to baseline ( $p < 0.001$ ).<sup>2</sup>

In a meta-analysis of 31 studies (RCTs and non-RCTs) including 116 patients who had DBS implanted in striatal areas (72%), subthalamic nucleus (23%) and inferior thalamic (5%), the pooled percentage of reduction in Y-BOCS scores was 45% (95% confidence interval [CI] 29% to 61%;  $p < 0.001$ ;  $I^2 = 96\%$ ). The percentage of people with symptom response who had  $> 35\%$  reduction in Y-BOCS score was 60% (95% CI 49% to 69%;  $p = 0.63$ ;  $I^2 = 0\%$ ).<sup>3</sup>

In a case series of 31 patients who had DBS implanted in the bilateral anterior limb of the internal capsule (AIC) for refractory OCD, the mean Y-BOCS score improved from 34.9 (SD 2.9) at baseline to 19.8 (SD 8.3) at 6-month follow-up and 20.0 (SD 9.5) at 12-month follow-up. The percentage of people with symptom response who had more than 35% reduction in Y-BOCS score was 70% at 6-month follow-up and 60% at 12-month follow-up.<sup>4</sup>

In a case series of 20 patients who had DBS implanted in the AIC or nucleus accumbens region (NAcc), the mean Y-BOCS score improved statistically significantly from 30.9 (SD 4.0) to 20.6 (SD 7.4) at 12-month follow-up ( $p < 0.001$ ). The percentage of people with symptom response who had  $\geq 35\%$  reduction in Y-BOCS score was 40%.<sup>5</sup>

In a systematic review of 20 studies including 170 patients who had DBS or anterior capsulotomy (AC) surgery for refractory OCD, there was a 40% decrease in Y-BOCS score after mean follow-up of 19 months in patients who had DBS, compared to a 50% decrease in patients who had AC in 61 months of mean follow-up time ( $p = 0.004$ ). The percentage of people with symptom response who had  $\geq 35\%$  reduction in Y-BOCS score was 52% for DBS compared with 62% for AC, which was statistically not significant.<sup>6</sup>

In a non-randomised comparative study of 30 patients (16 who had bilateral DBS at the nucleus accumbens and 14 in the control group), the mean Y-BOCS score was 32.6 (SD 4.5) for DBS group and 31.1 (SD 4.8) for control group at 3 weeks post-op. After 8 months post-op, the DBS group experienced mean decreases of 15.7 (SD 10.8) points on Y-BOCS score but the score for the control group remained unchanged.<sup>7</sup>

In a systematic review of 8 RCTs including 80 patients who had DBS targeting different sites of the brain, there was a mean reduction in Y-BOCS of 39% from baseline to the end of the double-blind phase. When comparing DBS with sham, the mean Y-BOCS reduction was 27%.<sup>10</sup>

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In a case series of 70 patients who had DBS of the ventral anterior limb of the internal capsule, the mean Y-BOCS score decreased statistically significantly by 13.5 (SD 9.4) points 12 months after surgery (40% reduction, effect size 1.5). The percentage of people with symptom response who had at least 35% reduction in Y-BOCS score was 52% at 12-month follow-up.<sup>11</sup>

In a systematic review and meta-analysis of 225 patients from 8 RCTs and 38 observational studies, there was a statistically significant reduction of 15 points in the mean Y-BOCS score from baseline compared with the last follow-up score (95% CI -18.3 to -11.7,  $I^2=90\%$ ,  $p<0.001$ ). In the same study, the percentage of patients with complete response to treatment (defined by a decrease of more than 35% in Y-BOCS score from baseline) was also statistically significant: 58% (95% CI 50% to 70%,  $I^2=62\%$ ,  $p<0.001$ ). The percentage of patients who were in remission (defined as a Y-BOCS score of less than 6 after treatment) was not significant: 5% (95% CI 2% to 8%,  $I^2=0\%$ ,  $p=0.92$ ). The study also reported that there was no significant difference in mean Y-BOCS scores between limbic and subthalamic nucleus targets ( $\chi^2=0.21$ ,  $I^2=0\%$ ,  $p=0.65$ ).<sup>12</sup>

### **Global Assessment of Functioning (GAF) score**

In the RCT of 24 patients, during the stimulation ON phase, the median GAF score improved by 15 points compared to stimulation OFF phase ( $p<0.001$ ) and improved by 30 points compared to preoperative score ( $p<0.001$ ).<sup>2</sup>

In the case series of 20 patients, the mean GAF score improved from 35.2 (SD 2.9) to 54.4 (SD 12.5) at 12-month follow-up ( $p<0.001$ ).<sup>5</sup>

### **Quality of life (QoL)**

In a case series of 16 patients who had DBS implantation at the nucleus accumbens, the WHOQOL-BREF scores at 3 to 5-year follow-up showed 90% improvement in general score ( $p<0.05$ ), 40% improvement in physical score ( $p<0.05$ ), 40% improvement in psychological score ( $p<0.05$ ), 16% improvement in environmental score ( $p<0.05$ ) and 14% improvement in social domains score ( $p=0.073$ ). Although the decrease in Y-BOCS scores correlated with improvement in physical score ( $r_s=-0.576$ ,  $p<0.05$ ) and environmental score ( $r_s=-0.676$ ,  $p<0.05$ ) at 8-month follow-up, the study reported that it did not show any significant relation with any of the changes in WHOQOL-BREF variables at 3 to 5-year follow-up (numbers not provided).<sup>8</sup>

In the systematic review of 8 RCTs, there was a statistically significant improvement in QoL at 12 months in both of the studies reporting QoL data (the

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Huff et al. 2010 study used the Modular system of quality of life and the Goodman et al. 2010 study used the Short form-16 health survey).<sup>10</sup>

## Neuropsychological outcomes

In the RCT of 24 patients, the HAM-A and HAM-D scores improved by 67% and 58% respectively, when comparing stimulation ON phase with stimulation OFF phase ( $p < 0.001$  for both). The HAM-A and HAM-D scores improved by 71% and 54% respectively, when comparing stimulation ON phase with preoperative score ( $p < 0.001$  for both). At 4-year follow-up, the HAM-A and HAM-D scores showed improvement of 58% and 67% respectively from baseline ( $p < 0.001$  for both scores). Compared to preoperative scores, the DBS stimulation increased scores on the Complex Figure Test of Rey and subtests of the Auditory Verbal Learning Test, and lowered scores on subtests of the Stroop tests and on the Trail Making Test.<sup>2</sup>

In the case series of 20 patients, no significant changes were found at 12-month follow-up for Stroop test ( $p = 0.230$ ), Tower of London test (number of correct trials  $p = 0.42$ ; response time  $p = 0.234$ ), Stop signal task ( $p = 0.678$ ), and Go/no-go test (number of correct trials,  $p = 0.666$ ; response time,  $p = 0.108$ ). The test for depression (Beck Depression Inventory) and anxiety (State-Trait Anxiety Inventory) also did not show any significant changes at 12-month follow-up ( $p = 0.882$  and  $p > 0.5$  respectively).<sup>5</sup>

In the non-randomised comparative study of 30 patients, the DBS group had significantly reduced performance compared with the control group on measures of visual organisation. At 8-month follow-up, the Rey Complex Figure Test (Copy Score) showed a change of -2.3 (SD 3.1) for DBS group and 2.6 (SD 4.3) for the control group ( $p = 0.001$ ). The immediate recall score of the Rey Complex Figure Test at 8 months was 0.4 (SD 4.4) for the DBS group and 6.4 (SD 4.7) for control group ( $p = 0.001$ ). There was no significant difference in other cognitive tests between DBS and control groups at 8-month follow-up.<sup>7</sup>

In the case series of 70 patients who had DBS of the ventral anterior limb of the internal capsule, the mean HAM-A and HAM-D scores decreased statistically significantly by 13.4 (SD 9.7) points and 11.2 (SD 8.8) points respectively 12 months after surgery (55% and 54% reduction, effect sizes 1.4 and 1.3 respectively).<sup>11</sup>

In the systematic review and meta-analysis of 225 patients, there was a statistically significant reduction of 13.7 points in the mean weighted depression score from baseline compared with the last follow-up score (95% CI -20.1 to -7.3,  $I^2 = 76\%$ ,  $p < 0.001$ ).<sup>12</sup>

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## Safety summary

### Intracranial haemorrhage

In the RCT of 16 patients, 1 patient had intracerebral haemorrhage resulting in permanent finger palsy.<sup>1</sup>

The RCT of 24 patients reported that 2 patients had an intracerebral haemorrhage during implantation of the electrodes.<sup>2</sup>

The meta-analysis of 116 patients reported that 3% (3/116) of patients had intracerebral haemorrhage due to DBS surgery.<sup>3</sup>

In the systematic review of 170 patients (62 DBS patients), 3% (2/62) of DBS patients had asymptomatic intracranial haemorrhage.<sup>6</sup>

In the systematic review of 80 patients, 4% (3/80) of patients had an intracerebral haemorrhage after DBS.<sup>10</sup>

### Infection

In the RCT of 16 patients, 2 patients had infection leading to removal of pulse generator.<sup>1</sup>

Skin infection was reported by 1 patient in the RCT of 24 patients, requiring treatment with antibiotics.<sup>2</sup>

The meta-analysis of 116 patients reported a wound infection rate of 4% (n=5).<sup>3</sup>

In the case series of 31 patients, 1 patient had an intracranial infection.<sup>4</sup>

The case series of 20 patients reported that 10% (2/20) of patients had infection. One patient had infection at IPG pocket, and the other patient had infection at traction of IPG. Both patients required replacement surgery.<sup>5</sup>

The systematic review of 170 patients (62 DBS patients) reported a wound infection rate of 5%.<sup>6</sup>

In the systematic review of 80 patients from 8 RCTs, 3% (2/80) of patients had an infection after DBS.<sup>10</sup>

An infection at the electrode implantation site was reported in 3% (2/70) of patients in the case series of 70 patients. The DBS system was explanted in both patients and the electrodes or implantable pulse generator and extension cables

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were re-implanted 3 months later. In the same study, a superficial infection of 1 of the cranial incisions was reported in 3% (2/70) of patients. Both patients had oral antibiotics.<sup>11</sup>

## **Hypomania and anxiety**

In the RCT of 16 patients, 3 patients had serious hypomanic episodes during the active stimulation period. Two other patients had non-serious hypomanic symptoms. Three patients experienced anxiety disorder during the study.<sup>1</sup>

The RCT of 24 patients reported that 17% (4/24) of patients developed hypomania as an adverse event during the study period.<sup>2</sup>

Hypomanic symptoms were reported in 20% (23/116) of patients having DBS in the meta-analysis of 116 patients. Anxiety worsening was reported by 22% (25/116) of patients having DBS.<sup>3</sup>

The case series of 31 patients reported a hypomania rate of 6% (2/31) and anxiety disorders of 29% (9/31).<sup>4</sup>

Transient hypomanic state was reported in 1 patient in the case series of 20 patients.<sup>5</sup>

Transient hypomanic symptoms were reported in 39% of patients in the case series of 70 patients. In the same study, transient restlessness was reported in 33% of patients, transient agitation in 30%, permanent agitation in 3% and transient impulsivity in 19% of patients.<sup>11</sup>

## **Suicide and suicidal thoughts**

The RCT of 16 patients reported that 1 patient experienced depressive symptoms with suicidal ideation during sham stimulation period.<sup>1</sup>

The RCT of 24 patients reported that 3 patients attempted suicide during the 180 patient years of follow-up.<sup>2</sup>

The meta-analysis of 116 patients reported that 3% of patients had suicidal ideation.<sup>3</sup>

The case series of 31 patients reported that 1 patient reported suicidal ideation and 1 patient attempted suicide during the 12-month follow-up period.<sup>4</sup>

One patient reported suicidal ideation after acute cessation of stimulation in the case series of 20 patients. The symptoms disappeared after restarting stimulation.<sup>5</sup>

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The systematic review of 170 patients (62 DBS patients) reported that 1 patient died by suicide during the 12-month postoperative period.<sup>6</sup>

In the systematic review of 80 patients from 8 RCTs, 1% (1/80) of patients died by suicide after DBS (already reported in study 7, Pepper 2015), 3% (2/80, 3 attempts) of patients attempted suicide (already reported in study 2, Luyten 2016) and 5% (4/80) had suicidal thoughts and depression during the double-blind phase of the studies (unclear from which studies).<sup>10</sup>

Suicide attempts were reported in 4% (3/70) of patients in the case series of 70 patients within 1-year follow-up.<sup>11</sup>

## **Depression**

Depressive mood was reported as an adverse event in 4% (5/116) of patients in the meta-analysis of 116 patients.<sup>3</sup>

## **Insomnia or sleep disturbance**

Insomnia was reported by 3% (4/116) of patients in the meta-analysis of 116 patients after device implantation.<sup>3</sup>

The case series of 31 patients reported that 29% (9/31) of patients had sleep disorders and disturbances after device implantation.<sup>4</sup>

The case series of 20 patients reported that 10% (2/20) of patients experienced sleep disturbances during the study period.<sup>5</sup>

Transient sleeping disorders were reported in 46% of patients and permanent sleeping disorders were reported in 7% of patients in the case series of 70 patients within 1-year follow-up.<sup>11</sup>

## **Headache**

Headache was reported by 6% (7/116) of patients in the meta-analysis of 116 patients.<sup>3</sup>

The case series of 31 patients reported that 35% (11/31) of patients had headache due to DBS stimulation.<sup>4</sup>

Headache was reported in 36% of patients in the case series of 70 patients within 1-year follow-up.<sup>11</sup>

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## Seizure

The RCT of 24 patients reported that 5 patients developed epileptic seizures: 2 patients had tonic-clonic type and 3 had absence or partial seizures.<sup>2</sup>

The meta-analysis of 116 patients reported that 1 patient had surgery related tonic-clonic seizure.<sup>3</sup>

The case series of 31 patients reported that 13% (4/31) of patients had seizures during the study period.<sup>4</sup>

## Other

The RCT of 16 patients reported that 1 patient had clumsiness and diplopia with peri-electrode oedema. One patient had disabling dyskinesia with impulsivity and 1 patient had facial asymmetry, dysarthria, dysphagia and walking difficulties after DBS implantation.<sup>1</sup>

The RCT of 24 patients reported that 2 patients had severe sleep apnoea, 1 patient had transient ischaemic attack, 16 patients had memory complaints, 12 patients had disinhibition, 12 patients had increased assertiveness, 10 patients had logorrhoea, 10 patients had hyperactivity, 6 patients reported paraesthesia, pain or twitches in cheek or jaw, teeth grinding and 4 patients had confusion after implantation.<sup>2</sup>

The meta-analysis of 116 patients reported that 6% (7/116) of patients had scalp tingling or numbness, 6% (7/116) had disinhibition; 6% (7/116) had stomach ache, dizziness and nausea, 3% (4/116) reported olfactory perceptions; 3% (4/116) had paraesthesia and tingling, 2% (2/116) had speech disturbances, 8% (9/116) had forgetfulness, difficulty finding words or memory complaints, 10% (12/116) reported throbbing and flushing, 3% (3/116) had enuresis.<sup>3</sup>

The case series of 31 patients reported that 32% (10/31) of patients developed neurological disorders such as paraesthesia, sensory disturbance, dizziness and syncope.<sup>4</sup>

The case series of 20 patients reported that 15% (3/20) of patients had disinhibition; 10% (2/20) had lack of concentration; 5% (1/20) reported transient loss of energy and 10% (2/20) reported weight gain of >20%.<sup>5</sup>

The systematic review of 170 patients (62 DBS patients) reported that 5% of patients had persistent post-op side effects such as nausea, vomiting, headache, insomnia, and other symptoms. Weight gain was reported by 3% of patients,

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cognitive changes were reported by 13% of patients and equipment break was reported by 5% of patients.<sup>6</sup>

The non-randomised comparative study of 30 patients reported that 5 patients had forgetfulness and 3 patients reported word-finding problems after DBS implantation.<sup>7</sup>

A single case report reported an infection along the surgical path of both electrodes associated with a cytotoxic lesion in the splenium of corpus callosum 7 to 10 days after hospital discharge.<sup>9</sup>

In the case series of 70 patients, 9% (6/70) of patients had their electrodes mispositioned and had to have reimplantation or retraction of the electrodes within 8 months after the initial surgery. In the same study, patients also reported pain around the burr holes (17%), feeling of the implantable pulse generator in the chest (16%), pulling of the extension leads (30%) and paraesthesia (20%) within 1-year follow-up.<sup>11</sup>

## **Anecdotal and theoretical adverse events**

In addition to safety outcomes reported in the literature, professional experts are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, professional experts listed the following anecdotal adverse events: manic behaviour, requirement of lifelong follow-up. They considered that the following were theoretical adverse events: personality change.

## **The evidence assessed**

### **Rapid review of literature**

The medical literature was searched to identify studies and reviews relevant to DBS for OCD. The following databases were searched, covering the period from their start to 16 December 2020: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the [literature search strategy](#)). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

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**Table 1 Inclusion criteria for identification of relevant studies**

Characteristic	Criteria
Publication type	<p>Clinical studies were included. Emphasis was placed on identifying good quality studies.</p> <p>Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study.</p> <p>Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.</p>
Patient	Patients with OCD.
Intervention/test	Deep brain stimulation
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English language articles were excluded unless they were thought to add substantively to the English language evidence base.

### List of studies included in the IP overview

This IP overview is based on about 517 patients (after excluding overlapping patients) from 2 RCTs (both of which are also included in at least 1 of the meta-analyses), 2 meta-analyses, 2 systematic reviews (most of the patients who had DBS in these reviews are also included in the meta-analyses), 1 non-randomised comparative study, 4 case series and 1 case report<sup>1-12</sup>.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) are listed in the [appendix](#).

## Table 2 Summary of key efficacy and safety findings on deep brain stimulation for chronic, severe, treatment-resistant obsessive-compulsive disorder in adults

### Study 1 Mallet L (2008)

#### Details

Study type	Randomised controlled trial
Country	France
Recruitment period	2005 - 2006
Study population and number	<b>n=16</b> (8 active vs 8 sham) Patients with refractory OCD
Age and sex	Mean: 43 years; 59% (10/17) male
Patient selection criteria	<p>Inclusion criteria: 18 to 60 years old; the presence of OCD with a score on the Y-BOCS of more than 25, a disease duration of over 5 years, GAF score of less than 40, CGI scale of more than 4, and a lack of response to both drug therapy after adequate administration of at least 3 SSRIs and cognitive-behavioural therapy; normal cognitive status (a score of &gt; 130 on the Mattis Dementia Rating Scale-MDRS; normal findings on MRI and no contraindications to surgery or anaesthesia.</p> <p>Exclusion criteria: Schizophrenic disorder; bipolar disorder; substance abuse or dependence (except for dependence on nicotine); cluster A or B personality disorder according to the Diagnostic and statistical manual of mental disorders (DSM-IV) criteria; a current severe major depressive episode, determined according to DSM-IV criteria and defined by a Montgomery and Åsberg Depression Scale (MADRS) score of more than 20; and a risk of suicide (a score of &gt;2 on MADRS item 10).</p>
Technique	The subthalamic nucleus (STN) was preoperatively targeted by means of stereotactic MRI. The target in patients with OCD was 2 mm anterior to and 1 mm medial to the target that is used in patients with Parkinson's disease, at the boundary of the associative and limbic territories of the subthalamic nucleus. Intraoperative micro-recordings were performed along three to five trajectories (central, anterior, posterior, medial, and lateral) The four-contact definitive electrode (model 3389 DBS, Medtronic) was implanted along the trajectory. The position of the electrode was confirmed by atlas-based neuroimaging. Stimulation frequency and pulse duration were 130 Hz and 60 microsec, respectively, with the voltage adjusted to the individual patient.
Follow-up	<b>10 months</b>
Conflict of interest/source of funding	<p>The trial was supported by grants from the Programme Hospitalier de la Recherche Clinique Assistance Publique-Hopitaux de Paris and the Agence Nationale de al Recherche Program for Young Researchers.</p> <p>Medtronic provided funds for the meetings of the investigators of the study.</p> <p>3 authors received consulting fees from Medtronic; 3 authors received lecture fees from Medtronic; 2 authors received grant support from Medtronic.</p>

#### Analysis

**Follow-up issues:** 17 patients had DBS implantation but only 16 patients completed randomization, because one patient had device explanted due to infection.

**Study design issues:** A randomized, double-blind, crossover, multicentre study design with two 3-month phases (month 3 to month 6 and month 7 to month 10) separated by a 1-month washout period. Eligible patients were randomly assigned in a 1:1 ratio to one of two groups: one group underwent active stimulation followed by a sham-stimulation period (the on-off group) and the other underwent sham stimulation followed by an active-stimulation period (the off-on group). A blocking-scheme and a centralized procedure for randomization was used, without stratification. The primary outcome

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was the change in the Y-BOCS score at the end of each period. The secondary outcomes were two subscores of the Y-BOCS, two measures of global health and functioning (GAF and CGI), a self-reported measure of functional impairment (Sheehan Disability Scale), two measures of major psychiatric symptoms (MADRS and Brief Scale for Anxiety), and seven neuropsychological measures assessing fronto-subcortical functions (attention, executive functions, verbal learning, and decision making).

**Study population issues:** The mean duration of disease was 18 years. There was no significant difference in baseline (month 3) clinical characteristics between the patients in the two groups. Medication was held constant during the 10 months of the protocol except for a transient increase in benzodiazepine therapy in three patients (two during the on-stimulation period and one during the off-stimulation period) and augmentation of neuroleptic treatment in one patient (off-stimulation period) owing to exacerbated anxiety.

## Key efficacy and safety findings

Efficacy	Safety										
<p>Number of patients analysed: <b>16</b> (8 active vs 8 sham)</p> <p><b>Mean Y-BOCS score</b></p> <ul style="list-style-type: none"> <li>Active stimulation = 19±8</li> <li>Sham stimulation = 28±7, p=0.01</li> <li></li> </ul> <p><b>Response rate (≥25% decrease in Y-BOCS score)</b></p> <ul style="list-style-type: none"> <li>Active stimulation = 75% (6/8)</li> <li>Sham stimulation = 38% (3/8)</li> </ul> <p><b>Mean Global Assessment of Functioning (GAF) score</b></p> <ul style="list-style-type: none"> <li>Active stimulation = 56±14</li> <li>Sham stimulation = 43±8, p=0.008</li> </ul> <p>Higher scores indicate higher level of functioning.</p> <p><b>Clinical Global Impression (CGI) score</b></p> <p>The CGI score, in which lower scores indicate lesser severity of disease, was significantly lower at the end of active stimulation than at the end of sham stimulation, (p= 0.0008). (The scores were not reported.).</p> <p><b>Neuropsychological Tests</b></p> <p>There was no significant different between active and sham stimulation on scores on MADRS (p=0.58) and BAS (p=1).</p>	<p><b>Adverse events</b></p> <p><b>Intracerebral Haemorrhage</b></p> <p>1 patient had intracerebral haemorrhage resulting in permanent finger palsy.</p> <p><b>Infection</b></p> <p>2 patients had infection leading to removal of pulse generator.</p> <p><b>Hypomania</b></p> <p>3 patients experienced serious hypomanic state during active stimulation phase, 1 patient had non-serious hypomania after surgery and before randomization, 2 patients after randomization.</p> <p><b>Suicide/Suicidal ideation</b></p> <p>1 patient experienced depressive symptoms with suicidal ideation during sham stimulation period.</p> <p><b>Other serious adverse events</b></p> <table border="1"> <thead> <tr> <th>Adverse events</th><th>n</th></tr> </thead> <tbody> <tr> <td>Clumsiness and diplopia with peri-electrode oedema</td><td>1</td></tr> <tr> <td>Anxiety</td><td>3</td></tr> <tr> <td>Disabling dyskinesia with impulsivity</td><td>1</td></tr> <tr> <td>Facial asymmetry, dysarthria, dysphagia, and walking difficulties</td><td>1</td></tr> </tbody> </table>	Adverse events	n	Clumsiness and diplopia with peri-electrode oedema	1	Anxiety	3	Disabling dyskinesia with impulsivity	1	Facial asymmetry, dysarthria, dysphagia, and walking difficulties	1
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Disabling dyskinesia with impulsivity	1										
Facial asymmetry, dysarthria, dysphagia, and walking difficulties	1										
Abbreviations used: BAS, Brief Anxiety Scale; MADRS, Montgomery and Åsberg Depression Scale.											

IP overview: deep brain stimulation for chronic, severe, treatment-resistant obsessive-compulsive disorder in adults



## Study 2 Luyten L (2016)

### Details

Study type	Randomised controlled trial
Country	Belgium
Recruitment period	198 - 2010
Study population and number	<b>n=24</b> Patients with refractory OCD
Age and sex	Median age: 39 years; 50% (12/24) male
Patient selection criteria	Inclusion criteria: 18-60 years of age; the presence of OCD with a score on the Y-BOCS of at least 30/40 and a Global Assessment of Functioning (GAF) score of 45; a disease duration of over 5 years despite adequate trials (except in case of intolerance) with two selective serotonin reuptake inhibitors and clomipramine, augmentation strategies (i.e. antipsychotics), and cognitive behavioural therapy; able to understand and comply with instructions and provide their own written informed consent to be included in the study.  Exclusion criteria: current or past psychotic disorder; any clinically significant disorder or medical illness affecting brain function or structure (other than motor tics or Gilles de la Tourette syndrome), or current or unstably remitted substance abuse.
Technique	Quadripolar electrodes were stereotactically implanted into the bilateral anterior limbs of the internal capsule (ALIC), similar to the targets used for anterior capsulotomy. The most ventral contact (contact 0) was implanted in the gray matter ventral to ALIC and the other contacts (1–2–3) were placed in ALIC (lead tip position was 15 mm rostral to the posterior border of the anterior commissure in the first patient, and progressively more posterior toward the posterior border of the anterior commissure in later patients). Subsequent patients were implanted at the 'optimized' target, which was more posterior, ventral and medial, with at least one contact (usually contact 0) in the bed nucleus of the stria terminalis (BST) (0–2 mm posterior to the posterior border of the anterior commissure).  Stimulation parameters and electrode polarity were optimized for each individual patient based on clinical evaluation. Stimulation frequencies ranged from 85 to 130 Hz (median 130 Hz), pulse widths from 90 to 450 µs (median 240 µs) and amplitudes from 3 to 10.5 V (median 6.5 V).
Follow-up	<b>4 to 16 years</b>
Conflict of interest/source of funding	The authors declared no conflict of interest.

### Analysis

**Follow-up issues:** 17 patients (71%) completed the double-blind crossover trial (9 patients ON–OFF and 8 patients OFF–ON). Eighteen patients were followed up for 4 years or longer. The remaining 6 patients had a shorter follow-up period, because of cessation of stimulation within 4 years after implantation (2 patients), removal of the electrodes followed by capsulotomy (3 patients) or implantation of additional electrodes aimed at the subthalamic nucleus (1 patient).

**Study design issues:** A randomized, double-blind, crossover study design with 3 months of stimulation ON and 3 months of stimulation OFF. Medication was kept constant during the entire crossover study, and stimulation parameters remained unchanged throughout the ON phase. After completing both crossover arms (ON–OFF or OFF–ON), the patient and psychiatrist were unblinded, and the patient could choose to be continuously stimulated. Patients were evaluated using standardized psychiatric questionnaires (primary outcome: Y-BOCS; secondary outcomes: Hamilton Anxiety and Depression Rating Scales (HAM-A and HAM-D and GAF) and neuropsychological tests.

**Study population issues:** Pre-op median Y-BOCS for the patients was 35/40, indicating extreme OCD, and median GAF was 35/100, indicating major impairment in several areas of functioning. 5 patients had bilateral contacts in BST, and

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another patient was stimulated unilaterally in BST. 2 patients were stimulated in BST in one hemisphere and in the internal capsule (IC), adjacent to BST, in the other hemisphere. 2 patients received bilateral stimulation in IC or the prereticular zone, adjacent to BST. 5 patients received bilateral ALIC stimulation. 2 patients were stimulated in BST and ALIC. The median duration of the ON phase (89 days) was significantly longer than the OFF phase (44 days) ( $P < 0.01$ ).

## Key efficacy and safety findings

Efficacy					Safety	
Number of patients analysed: 24					<b>Adverse events</b>  A total of 25 serious adverse events were recorded during the 180 patient years of follow-up.	
<b>Crossover phase (n=17)</b> <ul style="list-style-type: none"><li>Median Y-BOCS score in blinded OFF phase = 32</li><li>Median Y-BOCS score in blinded ON phase = 20</li></ul>						
Scores	Improvement in ON vs OFF phase	p	Improvement in Pre-op vs ON phase	p	<b>Serious adverse events</b>	
YBOCS	37%	<0.017	42%	<0.001	<b>Adverse events</b>	
HAM-A	67%	<0.001	71%	<0.001	n	
HAM-D	58%	<0.001	54%	<0.001	Intracerebral haemorrhage	
GAF	15 points	<0.001	30 points	<0.001	2	
<b>4-year follow-up (n=18)</b>					Suicide attempt	
					3	
					Fracture (ankle, foot, arm, leg, hand, rib)	
					6	
					Polytrauma (cliff diving, car accident)	
					2	
					Tonic-clonic epileptic seizure	
					2	
					Absences or partial epileptic seizure	
					3	
<b>At last follow-up</b> For 3/24 patient, last follow-up was at 4 years For 6/24 patients, last follow-up was at <4years For 15/24 patients, last follow-up was at >4 years (range 54-171 months)					Severe obstructive sleep apnoea	
					2	
					Morbid obesity (gastric bypass)	
					1	
					Pyelonephritis and pyonephrosis	
					1	
					Transient ischemic attack	
					1	
					Prostate carcinoma (brachytherapy)	
					1	
<b>Neuropsychological tests</b> There were no significant differences between preoperative, ON or OFF measurements for the following tests: Wisconsin Card					<b>Surgery related adverse events</b>	
					Misplacement of electrode, intraoperative correction	
					1	
					Rash iodine alcohol	
					1	
					Skin infection coagulase negative S. aureus (treated with antibiotics)	
					1	
					Local transient inflammation of suture after IPG replacement	
					1	
					Uncomfortable feeling around extension cables	
12						
					Pain around implantable pulse generator (IPG)	
					7	
					Painful luxation IPG below ribs	
					3	
					<b>Stimulation related</b>	
					Memory complaints	
					16	
					Disinhibition	
					12	
					Increased assertiveness	
12						
					Logorrhea	
					10	
					Hyperactivity	
					10	
					Hypomania	
4						

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Sorting Test, Word Fluency Test and Raven's Standard Progressive Matrices.				Confusion	4
Significant test results:				Patient smells something transiently	7
				Paresthesia, pain or twitches in cheek or jaw, teeth grinding	6
				Transient perseveration in foreign language	1
				Micrographia	1
				Decreased libido	7
				Increased libido	4
				Ejaculation problems	5
				Erection problems	4
				Diarrhoea	3
				Slow gastric emptying	1
				Fatigue	18
				Cough	2
Abbreviations used: HAM-D, HAM-A, Hamilton Depression Rating Scale – anxiety and depression subscales; GAF, Global Assessment of Functioning,					

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## Study 3 Alonso P (2015)

### Details

Study type	<b>Meta-analysis</b>
Country	Not reported for the individual studies
Recruitment period	Search period: January 1999 to January 2014
Study population and number	<b>n=116 (31 studies)</b> patients with refractory OCD
Age and sex	Mean 38.6; 56% (62/111) male (gender information not available for 5 patients)
Patient selection criteria	Study inclusion criteria: human studies assessing the efficacy of DBS on OCD according to changes on the Y-BOCS scores or percentage of responders defined by standardized criteria; subjects aged 18–75 years with a diagnosis of OCD according to the Diagnostic and Statistical Manual of Mental Disorders IV or ICD criteria; English language studies  Exclusion criteria: reviews; discussions of ethical issues related to DBS; articles focused on biological correlates of DBS use in OCD–neuroimaging, electrophysiological or neuropsychological changes after DBS; articles focused on other indications of DBS different from OCD; articles focused on neurosurgical issues related to DBS implantation for OCD; studies on animal models of DBS use in OCD.
Technique	Stimulation parameters were highly heterogeneous between studies: although all of them employed high frequency stimulation (from 100 to 130 Hz), pulse width ranged from 60 to 450 $\mu$ s and voltage from 2 to 10,5 V; different models of electrodes (3387, 3887, 3487; Medtronic Inc, Minneapolis, Minnesota) as well as active contact points were used in the different samples.  24 studies including 83 patients addressed DBS of “striatal areas”, including the anterior limb of the internal capsule (ALIC), the ventral capsule and ventral striatum (VC/VS), the nucleus accumbens (NA) or the ventral caudate nucleus; 5 studies including 27 patients reported results on stimulation of the subthalamic nucleus, and 2 studies, including 6 patients, described results of DBS applied at the inferior thalamic peduncle.
Follow-up	<b>Range 3 to 36 months (not reported for 2 studies)</b>
Conflict of interest/source of funding	PA, CS, ER and JM participate in post-market clinical follow-up study sponsored by Medtronic. LG is holder of the chair of neurosurgery in psychiatric disorders t the KU Leuven, funded by Medtronic. DD and RS received unrestricted grants form Medtronic.

### Analysis

**Follow-up issues:** Mean follow-up was  $16.3 \pm 10.3$  months. However, follow-up duration varied significantly in individual studies, ranging from 3 months to 36 months.

**Study design issues:** The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Comprehensive and systematic review of the literature was performed. Authors of some studies were contacted for further information. The primary outcome measure was the score changes (pre-post DBS) on the Y-BOCS and the secondary measures were the number of responders to treatment, quality of life and acceptability as secondary measures. We did not include information on quality of life in this overview as it was only available for 3 studies and reported individually. Effect sizes were calculated with fixed and random-effect models and risk ratios were presented as a forest plot. Heterogeneity was assessed using the Q statistics and  $I^2$  index. Subgroup analyses were done to assess the effect of using different targets and patients’ demographics (age, sex and age of onset).

**Study population issues:** Mean baseline Y-BOCS scores was  $33.2 \pm 3.9$ . All patients were adults (18 to 65) except 9 patients, whose ages were not available. Out of 116 patients included in meta-analysis, 83 (71.6%) patients from 24 studies had DBS implanted in striatal areas, 27 (23.3%) patients from 5 studies had DBS at subthalamic nucleus, and 6 patients (5.2%) from 2 studies had DBS at the inferior thalamic peduncle.

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**Other issues:** Most studies included in meta-analysis have small sample sizes (9 out of 17 studies had sample size of <5), and only 1 study had sample size of >20. The meta-analysis included all available patients worldwide instead of restricting their analysis to double-blind sham-controlled studies.

## Key efficacy and safety findings

Efficacy	Safety																																										
<p>Number of patients analysed: <b>116</b></p> <p><b>Improvement in Y-BOCS scores (n=66)</b> Pooled percentage of reduction in Y-BOCS scores = 45.1% (95%CI, 29.4% - 60.8%); Q=734.6, <math>p&lt;0.001</math>; <math>I^2=96.4\%</math></p> <p><b>Responders rate (n=105)</b> Percentage of responders who had &gt;35% reduction of Y-BOCS scores = 60.0 % (95%CI, 49.0% to 69.0%); Q=13.47, <math>p=0.63</math>, <math>I^2=0\%</math></p> <p><b>Subgroup analyses</b></p> <p><b>Targets</b> % of Y-BOCS scores reduction for striatal areas(n=45): 39.0% % of Y-BOCS scores reduction for STN(n=21): 46.3%, <math>p=0.3</math></p> <p>% of responders (&gt;35% reduction) for striatal areas: 55.5% % of responders (&gt;35% reduction) for STN: 52.3%, <math>p=0.8</math> (Striatal areas include VC/VS, ALIC, NAc and NC).</p> <p><b>Age</b> Responders mean age – 38.6 Non-responders mean age – 37.2, <math>p=0.9</math></p> <p><b>Gender</b> Responders sex ratio (male/female): 26/19 Non-responders sex ratio (male/female): 20/14, <math>p=0.9</math></p> <p>% of Y-BOCS scores reduction in male: 41.7% % of Y-BOCS scores reduction in female: 43.4%, <math>p=0.2</math></p> <p><b>Age at OCD onset</b> Responders mean age of onset: 17.1 years Non-responders mean age of onset: 13.7 years, <math>p=0.04</math></p> <p><b>OCD duration prior to DBS</b> Responders mean duration of OCD: 20.5 years Non-Responders mean duration of OCD: 23.8 years, <math>p=0.1</math></p>	<p>The most severe adverse events reported were intracranial haemorrhage (2.6%), wound infection (4.3%) and suicidal ideation (3.4%).</p> <p>The most frequently reported adverse events were hypomanic state (19.8%), anxiety worsening (21.6%) and throbbing/flushing (10.4%).</p> <p>There were 5(4.7%) dropouts among 116 patients, 2 from early studies, 3 from one single study: 1 died of cocaine overdose, 1 stopped attending follow-up and 1 had tuberculous meningitis and was explanted.</p> <p><b>Surgery related</b></p> <table> <tr> <th>Adverse event</th><th>% (n)</th></tr> <tr> <td>Intracerebral haemorrhage</td><td>2.6% (3)</td></tr> <tr> <td>Wound infection</td><td>4.3% (5)</td></tr> <tr> <td>Headache</td><td>6.0% (7)</td></tr> <tr> <td>Tonico-clonic seizure</td><td>0.9% (1)</td></tr> <tr> <td>Scalp tingling or numbness</td><td>6.0% (7)</td></tr> </table> <p><b>Device related</b></p> <table> <tr> <th>Adverse event</th><th>% (n)</th></tr> <tr> <td>Feeling of extension leads, mainly in neck and ear area</td><td>8.6% (10)</td></tr> <tr> <td>Feeling of neurostimulator in chest or abdomen</td><td>1.7% (2)</td></tr> <tr> <td>Break in a stimulating lead or an extension wire</td><td>2.6% (3)</td></tr> </table> <p><b>Stimulation related</b></p> <table> <tr> <th>Adverse event</th><th>% (n)</th></tr> <tr> <td>Hypomanic symptoms</td><td>19.8% (23)</td></tr> <tr> <td>Disinhibition</td><td>6.0% (7)</td></tr> <tr> <td>Transient confusion</td><td>0.9% (1)</td></tr> <tr> <td>Stomach-ache, dizziness, nausea</td><td>6.0% (7)</td></tr> <tr> <td>Enuresis</td><td>2.6% (3)</td></tr> <tr> <td>Olfactory perceptions</td><td>3.4% (4)</td></tr> <tr> <td>Paraesthesia, tingling</td><td>3.4% (4)</td></tr> <tr> <td>Tightness at jaw area</td><td>1.7% (2)</td></tr> <tr> <td>Diplopia</td><td>0.9% (1)</td></tr> <tr> <td>Weight gain</td><td>4.3% (5)</td></tr> </table>	Adverse event	% (n)	Intracerebral haemorrhage	2.6% (3)	Wound infection	4.3% (5)	Headache	6.0% (7)	Tonico-clonic seizure	0.9% (1)	Scalp tingling or numbness	6.0% (7)	Adverse event	% (n)	Feeling of extension leads, mainly in neck and ear area	8.6% (10)	Feeling of neurostimulator in chest or abdomen	1.7% (2)	Break in a stimulating lead or an extension wire	2.6% (3)	Adverse event	% (n)	Hypomanic symptoms	19.8% (23)	Disinhibition	6.0% (7)	Transient confusion	0.9% (1)	Stomach-ache, dizziness, nausea	6.0% (7)	Enuresis	2.6% (3)	Olfactory perceptions	3.4% (4)	Paraesthesia, tingling	3.4% (4)	Tightness at jaw area	1.7% (2)	Diplopia	0.9% (1)	Weight gain	4.3% (5)
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	Weight loss	0.9% (1)
	Insomnia	3.4% (4)
	Forgetfulness, difficulty finding words, memory complaints	7.8% (9)
	Anxiety worsening	21.6% (25)
	Panic attacks	0.9% (1)
	Throbbing, flushing	10.4% (12)
	Depressive mood	4.3% (5)
	Suicidal ideation	3.4% (4)
	Impulsivity	1.7% (2)
	Speech disturbances	1.7% (2)
Abbreviations used: VC/VS, ventral capsule and ventral striatum; ALIC, anterior limb of the internal capsule; NAc, nucleus accumbens; NC, ventral caudate nucleus; STN, subthalamic nucleus.		

## Study 4 Menchon J (2019)

### Details

Study type	<b>Case series</b>
Country	Multi-centre (Europe and Israel) (country list for Europe not reported)
Recruitment period	2010 to 2014
Study population and number	<b>n= 31 (30 patients analysed)</b> Patients with severe treatment-resistant OCD
Age and sex	Mean: 41 years; male: 15/31(48%)
Patient selection criteria	Inclusion criteria: Patients with severe OCD (Y-BOCS scores at least 30/40) and seriously impaired in daily functioning; such level of impairment persisted for $\geq 5$ years despite a minimum of 3 adequate pharmacological trials and supplementary augmentation treatment; not responded to an adequate trial of CBT; $\geq 18$ years of age.  Exclusion criteria: Current Axis I disorder that is primary to the OCD as demonstrated by the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I); Substance abuse or dependence $\leq 6$ months prior to the screening test; Suicide attempts $\leq 3$ months prior to screening (or posed a serious suicide risk); Any neurological condition that could hinder the stimulation procedure; previous or current DBS for any indication; History of a neurosurgical ablation procedure in the target area.
Technique	Medtronic® model 3391 DBS leads were stereotactically implanted in the bilateral AIC and connected subcutaneously to unilateral or bilateral dual-channel neurostimulators. Each neurosurgeon chose surgical trajectory and lead end point, based on clinical expertise and individual anatomical characteristics of the patient. Postoperative imaging (CT and/or MRI) was performed to document lead location. The most common location for the centre of the active contact was the anterior internal capsule (ventral part of AIC, in 31 hemispheres, 56% of the 55 stimulated hemispheres), followed by the bed nucleus of the stria terminalis (15 hemispheres, 27%), lateral hypothalamus (3 hemispheres, 5%), globus pallidus externus (2 hemispheres) and dorsal part of AIC (1 hemisphere). Mean stimulation settings at month 12 were: amplitude 4.7 (1.8) Volts, pulse duration 221 (63) $\mu$ s, frequency 130 (3) Hz.
Follow-up	<b>12 months</b>
Conflict of interest/source of funding	3 of the study authors are employees of Medtronic and received salaries. Other authors received fees, grants and travel expenses from Medtronic. One of the authors is the first author on a patent on DBS for OCD and received grants as Chair 'Neuromodulation, an endowment from Medtronic' and 'Neurosurgery for Psychiatric Disorder', from Medtronic during the conduct of the study.

### Analysis

**Follow-up issues:** 90% (28/31) of the enrolled patients completed the study with implanted system. 1 discontinued before implantation; 1 discontinued after Month 3 due to intracranial infection, 1 had device explanted after month 3 (due to extension migration/dislodgement) but continued in the study.

**Study design issues:** A prospective, non-randomized, multicentre open-label study. The patients were recruited across 10 centres in Europe and Israel. Safety and efficacy assessment were performed during treatment phase at 3,6, and 12 months post-stimulation. Outcome assessments for the study included characterization of the adverse events related to the procedure and improvement of Y-BOCS scores from baseline. An independent Clinical Events Committee (CEC) reviewed all adverse events. The results are presented as descriptive statistics for continuous variables with mean and standard deviations. The study was not designed for performing significance testing.

**Study population issues:** Selected patients suffered from severe to extreme OCD (mean Y-BOCS 34.7, SD  $\pm$  2.9). Mean duration of OCD was 24.5 years (SD  $\pm$  9 years). 29% of patients had current CBT treatment.

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**Other issues:** The study also reported additional efficacy measures (GAF, MADRS, CGI and EQ-5D) in graphs, but they were not included in this overview.

## Key efficacy and safety findings

Efficacy			Safety		
Number of patients analysed: 30			Total number of adverse events – 195 (all patients experienced adverse events). 52% (n=102) of adverse events were mild. 37% (n=73) were moderate.		
Improvement in Y-BOCS Score			63% (123/195) of total adverse events were related to the device, procedure, or stimulation.		
Follow-up	Mean Y-BOCS (SD)	Mean % reduction from baseline (SD)	Serious adverse events		
Baseline	34.9 (2.9)		Adverse events		
Parameter selection visit	30.0 (6.1)	14% (15%)	Anxiety disorders and symptoms (including OCD worsening)		
Month 3	22.3 (8.2)	36% (23%)	N of events		
Month 6	19.8 (8.3)	43% (23%)	N of patients (%)		
Month 12	20.0 (9.5)	42% (27%)	Other adverse events		
Responders rate (% of patients with ≥35% reduction in Y-BOCS from baseline)			Other adverse events include Benzodiazepine abuse, overdose, confusional state, dissociation, marital problem, dysphoria, borderline personality disorder, hypothyroidism, axillary vein thrombosis, pleural effusion, pneumothorax, induced coma and shock. The last 5 adverse events were experienced by a single patient who also had seizure, intracranial infection and pneumonia.		
• Month 3 = 57% (17/30)			Nonserious adverse events		
• Month 6 = 70% (21/30)			The commonly reported non-serious adverse events were headache (35% of patients [11/31]), Neurological disorders (e.g. paraesthesia, sensory disturbance, dizziness, syncope) (32% [10/31]), Sleep disorders and disturbances (29% [9/31]).		
• Month 12 = 60% (18/30)					
Abbreviations used: SD, standard deviation					

## Study 5 Huys D (2019)

### Details

Study type	<b>Case series</b>
Country	Germany
Recruitment period	2010 to 2016
Study population and number	<b>n= 20</b> patients with OCD
Age and sex	Mean age: 43.2 years; 50% (10/10) male
Patient selection criteria	Inclusion criteria: Chronic severe OCD (Y-BOCS >25) with history of OCD over 5 years; GAF score <40; well documented treatment resistant to at least medical management and CBT treatment.  Exclusion criteria: current or previous diagnosis of psychosis, drug abuse or drug addiction during the last 6 months, traumatic brain injury in the past, clinically significant internal or neurological disorders, pregnancy, lactation or mental retardation.
Technique	NAcc or ALIC DBS implant  Medtronic quadripolar leads (Model 3387 or 3389) were stereotactically implanted bilaterally, guided by MRI and stereotactic cerebral CT. The two distal contacts were placed bilaterally in the NAcc, the more proximal contacts were located in the ventral part of the ALIC. The leads were connected to an implantable pulse generator (IPG) 1 to several days after the implantation. Frequency was mostly >120 Hz; pulse widths and frequency were adjusted to compensate for side effects. Stimulation settings were adjusted according to response. Amplitude was increased stepwise beneath the threshold for side effects. Mean stimulation amplitude at 12 months of follow-up was 4855 (SD 1.1).
Follow-up	<b>12 months</b>
Conflict of interest/source of funding	The authors reported no biomedical financial interests or potential conflicts of interest. 1 author received payment as a consultant for Medtronic, Boston scientific, SAPIENS, St Jude Medical, GE Medical, Bayer Healthcare, UCB Schwarz Pharma, Archimedes Pharma. Another author received payments for travelling, lodging and financial compensation for contribution to advisory boards or workshops by Medtronic, Abbott and St Jude Medical.

### Analysis

**Study design issues:** A single centre, open-label trial. Patients were recruited from the interdisciplinary outpatient clinic for OCD. The primary outcome measure was the Y-BOCS score. The secondary measures were HZI scale, GAF scale, SCL-90, BDI, STAI and neuropsychological outcomes. The outcomes were evaluated at 6 months (T1) and 12 months (T2) after surgery. Non-parametric tests were used for clinical outcomes measures; Friedman test for correlated data with list-wise exclusion of missing data for all variables. A post-hoc analysis using Wilcoxon signed-rank test was used if Friedman test indicated a significant difference.

**Study population issues:** All patients had severe refractory OCD (mean baseline Y-BOCS = 30.9). Mean age of onset of OCD was 14.24 years.

IP overview: deep brain stimulation for chronic, severe, treatment-resistant obsessive-compulsive disorder in adults

## Key efficacy and safety findings

Efficacy					Safety
Number of patients analysed: 20					<b>Adverse events</b>  <b>Infection</b> 10% (n= 2) 1 at IPG pocket and 1 attraction of IPG and cables. Both required replacement surgery.  <b>Stimulation related</b> Transient hypomanic states 5% (n=1) Disinhibition 15% (n=3) Lack of concentration 10% (n=2) Transient loss of energy 5% (n=1) Sleep disturbances 10% (n=2) Weight gain (>20%) 10% (n=2)  35% (n=7) of patients reported sudden increase in anxiety and anhedonia after acute cessation of stimulation, with 1 patient reporting suicidal tendencies. These symptoms disappeared immediately after restarting stimulation.
<b>Change in Y-BOCS score</b>					
Y-BOCS	Baseline(T0) Mean (SD)	6months(T1) Mean (SD)	12 months(T2) Mean (SD)	p (T0 v T2)	
Total	30.9(4.0)	23.8(7.0)	20.6(7.4)	<0.001	
Obsessions	15.8(3.1)	12.4(3.5)	10.3(4.0)	0.001	
Compulsions	15.1(3.2)	11.4(4.1)	10.3(4.0)	<0.001	
At 12 months, the mean Y-BOCS reduction was 33.33% (±21.50) from baseline.					
<b>Responders rate:</b>					
Full responders (≥35% reduction in Y-BOCS)		40%			
Partial responders (25% -35 reduction in Y-BOCS)		30%			
Remission of symptoms (Y-BOCS <16)		25%			
Fully recovered (Y-BOCS <8)		0%			
<b>Other outcome measures</b>					
Measures	Baseline(T0) Mean (SD)	6months(T1) Mean (SD)	12 months(T2) Mean (SD)	p*	
GAF	35.2 (2.9)	47.9(8.9)	54.4 (12.5)	<0.001	
BDI	20.3 (11.1)	18.5 (11.3)	17.8 (12.4)	0.882	
STAI-Trait	55.0(12.6)	52.6(11.7)	54.0(14.3)	0.909	
STAI-State	59.1(10.6)	55.9(12.2)	57.9(13.5)	0.646	
* Non-parametric Friedman test of differences among repeated measures, except the p-value for GAF, which is Wilcoxon signed-rank test for T0 vs T12.					
<b>Neuropsychological outcomes</b>					
At 12 months follow-up, no significant changes were found for Stroop test (p= 0.230), Tower of London test (Number of correct trials, p=0.42; Responses time, p=0.234) , Stop signal task (p=0.678) , and Go/no-go test(Number of correct trials, p=0.666; Response time, p=0.108) .					
<b>Outcome predictors</b>					
Predictors	p	r (Spearman's rho)			
Outcome difference between male and female	0.854	-			
Correlation between outcome and age of patients	0.663	0.104			
Correlation between outcome and pre-op Y-BOCS	0.697	0.093			
Data for the outcomes not reported.					
Abbreviations used: GAF, Global Assessment Functioning; BDI, Beck Depression Inventory; STAI, State-Trait Anxiety Inventory.					

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## Study 6 Pepper J (2015)

### Details

Study type	Review
Country	Not reported for the individual studies
Search period	Not reported
Study population and number	<b>170 (62 DBS vs 108 AC); 20 studies</b> Patients with OCD
Age and sex	DBS group: Mean age = 38 years; 52% male AC group: Mean age = 36 years; 54% male
Patient selection criteria	Inclusion criteria: studies with baseline characteristics (diagnosis of OCD, neurosurgical procedure conducted, patient age, and scores on the YBOCS at surgery and follow-up); minimum follow-up time of 12-moths. Exclusion criteria: not reported.
Technique	The procedure techniques are not reported.
Follow-up	<b>DBS group: mean follow-up – 19 months</b> <b>AC group: mean follow-up – 61 months</b>
Conflict of interest/source of funding	Two authors occasionally received travel expenses and honoraria for invite talks from Medtronic and St. Jude. No other conflicts of interest declared by the authors. The study is partly funded by the Department of Health National Institute for Health Research Biomedical Research Centre's funding scheme.

### Analysis

**Follow-up issues:** The mean follow-up for DBS group was 19 months (SD, 9) and for AC group was 61 months (SD, 51), ( $p < 0.0001$ ).

**Study design issues:** Review of the literature and compare the outcome of AC and DBS targeting of the area of the ventral capsule/ventral striatum (VC/VS) and nucleus accumbens (NAcc). Comprehensive search strategy was used and publications on AC or DBS on OCD were obtained from the PubMed database, from proceedings of neurosurgical meetings and references from the relevant papers. Patients in published cases were grouped according to whether they received AC or DBS and according to their preoperative scores on the Y-BOCS, and then separated according to outcome measures: remission (Y-BOCS score  $< 8$ ); response ( $\geq 35\%$  improvement in Y-BOCS score); nonresponse ( $< 35\%$  improvement in Y-BOCS score); and unfavourable (i.e., worsening of the baseline Y-BOCS score). The mean values were calculated. The Student t-test was used to compare continuous data. The Fisher exact test using a  $2 \times 2$  contingency table was used to compare the outcomes and complication rates in patients who underwent AC or DBS.

**Study population issues:** Patients who underwent DBS had significantly worse preoperative Y-BOCS scores and longer duration of OCD. Patients who underwent AC were followed up for longer time periods.

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## Key efficacy and safety findings

Efficacy				Safety			
Number of patients analysed: <b>170 (62 DBS vs 108 AC)</b>				Adverse events			
<b>Mean Y-BOCS for patients who underwent DBS vs AC</b>							
Y-BOCS	DBS	AC	p				
Pre-op score (SD)	33 (4)	30 (7)	0.002				
Post-op score (SD)	20 (7)	14 (11)	0.0002				
% improvement (SD)	51 (27)	40 (17)	0.004				
In patients treated with DBS, there was 40% decrease in YBOCS score, compared with 50% decrease for those who underwent anterior capsulotomy ( $p=0.004$ ).							
<b>Overall Responders rate</b>							
Outcome	DBS	AC	p				
Responders (Y-BOCS $\geq 35\%$ improvement)	52%	62%	NS				
Remission (Y-BOCS $< 8$ )	2%	11%	0.02				
52% of patients who underwent DBS experienced clinically significance response (improvement in Y-BOCS score $\geq 35\%$ ) compared with 62% of patients who underwent AC. However, the difference was statistically not significant.							
11% of patients who underwent AC went into remission (Y-BOCS score $< 8$ ) compared with 2% of patients after DBS ( $p=0.02$ ).							
<b>Responders rate according to severity of OCD at baseline</b>							
Severity at baseline	DBS	AC	p				
Moderate OCD (Y-BOCS 16-23)	-	63%	n/a				
Severe OCD (Y-BOCS 24-31)	~45%*	~95%*	0.002				
Extreme OCD (Y-BOCS 32-40)	52%	49%	$< 0.05$				
*figures estimated from graphs. Exact numbers not provided.							
Abbreviations used: AC, anterior capsulotomy; ICH, Intracranial haemorrhage.							

Adverse Events*	AC	DBS	p
Death (related to procedure)	0%	0%	NS
Suicide (w/in 12 months postop)	1%	2% (n=1)	NS
Symptomatic ICH	2%	0%	NS
Asymptomatic ICH	5%	3%	NS
Intracranial infection	0%	0%	NS
Residual neurological deficit at 12 months	1%	0%	NS
Sustained endocrine change	0%	0%	NS
Epilepsy	1%	0%	NS
Persistent postop side effects (nausea, vomiting, headache, insomnia and other symptoms)	7%	5%	NS
<b>Weight gain <math>&gt; 10\%</math></b>	<b>29%</b>	<b>3%</b>	<b>0.0002</b>
Cognitive changes	7%	13%	NS
Personality change	6%	0%	NS
Equipment break	NA	5%	NA
<b>Wound infection</b>	<b>0%</b>	<b>5%</b>	<b>0.02</b>

There was no difference in the rate of serious adverse events between AC and DBS.

## Study 7 Mantione M (2015)

### Details

Study type	Non-randomised comparative study
Country	The Netherlands
Recruitment period	Not reported
Study population and number	<b>n=30 (16 DBS vs 14 control)</b> Patients with refractory OCD
Age and sex	<ul style="list-style-type: none"> <li>DBS: mean 43 years; 56% (9/16) male</li> <li>Control: mean 38 years; 36% (5/9) male</li> </ul>
Patient selection criteria	<p>Inclusion criteria: 18-65 years; primary diagnosis of OCD with at least 28 points in Y-BOCS score; at least 5 years duration of disease; OCD refractory to at least two treatments with a selective serotonin reuptake inhibitor, plus a treatment with clomipramine hydrochloride, plus one augmentation trial with atypical antipsychotics, plus one CBT trial for a minimum of 16 sessions.</p> <p>Exclusion criteria: comorbid DSM-IV diagnosis (except major depressive disorder and mild anxiety disorders), severe personality disorders and substance abuse within the past 6 months.</p>
Technique	Bilateral implantation of DBS electrodes targeted at the NAc was performed according to standard stereotactic procedures. After implantation, monopolar stimulation was started using ventral contact points 0 and 1. Since no improvement was observed in any of the patients when stimulating the ventral contacts, the active contacts were switched to dorsal contacts 2 and 3, delivering active stimulation in the ventral part of the anterior limb of the internal capsule. After this switch in contacts clinical improvement on OCD symptoms was apparent in all patients. Stimulation parameters were then standardized to dorsal contacts 2 and 3, a frequency of 130 Hz and pulse width of 90 µs. Voltage ranged from 3.5 to 5.0 V.
Follow-up	<b>8 months</b>
Conflict of interest/source of funding	<p>1 author was a consultant to Medtronic on educational matters and received research grant. No other competing interest declared.</p> <p>This study was part of the study on the clinical effects of DBS of the nucleus accumbens for treatment-refractory obsessive-compulsive disorder, supported by an unrestricted investigator initiated research grant by Medtronic Inc., who provided the devices, and by the Netherlands organization for Scientific Research (NWO): ZON-MW VENI program</p>

### Analysis

**Follow-up issues:** 2 patients from DBS group were lost to follow-up at 8-months of stimulation, because they refused further participation in the study. Their results were included in the baseline to 3 weeks analyses.

**Study design issues:** A prospective, controlled study investigating the cognitive effects of bilateral DBS targeted at the NAcc. DBS patients were recruited from an outpatient clinic for anxiety disorder in Amsterdam. A control group was a group of patients with treatment-refractory OCD who received conventional therapy and who were on a waiting list for the DBS study. The groups were matched for age, premorbid intelligence and Y-BOCS score. A neuropsychological test battery was administered 1 to 3 months preoperatively, 3 weeks postoperatively and after an open 8-month treatment phase. Neuropsychological tests included assessment on Memory, Visuoconstructional function and memory, Executive function and inhibition, Attention and Motor system. At baseline, differences between the DBS and control groups in age and clinical symptoms were examined using independent 2-tailed t tests. Sex differences were analysed using a  $\chi^2$  test. A linear mixed model analysis was used to assess changes in cognitive test parameters over 3 different time points. Effect sizes were calculated according to Cohen *d*. An effect size of 0.2 reflects a small effect, 0.5 a medium effect and 0.8 or higher a large effect.

**Study population issues:** 6 of 16 patients in the DBS group and 5 of 14 patients in the control group fulfilled the criteria for comorbid major depressive disorder ( $\chi^2_1 = 0.01$ ;  $p = 0.92$ ). There were no significant differences between the groups  
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with respect to mean age; education; IQ; age at onset of illness; duration of illness or baseline Y-BOCS, HAM-A and HAM-D scores. For the DBS group, SSRIs were tapered off preoperatively but resumed Immediately after surgery at a low dosage and was gradually increased to presurgery levels. Medication was kept constant for both the DBS and control groups.

## Key efficacy and safety findings

Efficacy	Safety															
Number of patients analysed: <b>30 (16 DBS versus 14 control)</b>	<b>Adverse events</b> 5 patients reported forgetfulness 3 patients reported word-finding problems  No other safety events were reported.															
<b>Clinical outcomes at 3 weeks post-op</b>																
<table><tr><th>Outcome</th><th>DBS group, Mean (SD)</th><th>Control group, Mean (SD)</th></tr><tr><td>Y-BOCS</td><td>32.6 (4.5)</td><td>31.1 (4.8)</td></tr><tr><td>HAM-A</td><td>15.5 (5.4)</td><td>18.9 (8.2)</td></tr><tr><td>HAM-D</td><td>16.3 (5.8)</td><td>16.4 (6.5)</td></tr></table>		Outcome	DBS group, Mean (SD)	Control group, Mean (SD)	Y-BOCS	32.6 (4.5)	31.1 (4.8)	HAM-A	15.5 (5.4)	18.9 (8.2)	HAM-D	16.3 (5.8)	16.4 (6.5)			
Outcome		DBS group, Mean (SD)	Control group, Mean (SD)													
Y-BOCS		32.6 (4.5)	31.1 (4.8)													
HAM-A		15.5 (5.4)	18.9 (8.2)													
HAM-D		16.3 (5.8)	16.4 (6.5)													
After 8 months post-op, the DBS group experienced mean decreases of 15.7±10.8 points on Y-BOCS, 10.7±8.1 points on the HAM-A and 9.0±6.2 points on the HAM-D score. In control group, Y-BOCS, HAM-A and HAM-D scores remained unchanged.																
<b>Neuropsychological tests</b>																
<b>Rey Complex Figure Test (RCFT) – Copy Score</b>																
<table><tr><th>Follow-up</th><th>DBS, Mean (SD)</th><th>Control, Mean (SD)</th><th><i>p</i></th></tr><tr><td>Baseline score</td><td>31.6(2.7)</td><td>30.9(4.1)</td><td></td></tr><tr><td>Change score at 3 weeks</td><td>-1.7(1.9)</td><td>1.7(3.7)</td><td>0.001</td></tr><tr><td>Change score at 8 months</td><td>-2.3(3.1)</td><td>2.6(4.3)</td><td>0.001</td></tr></table>	Follow-up	DBS, Mean (SD)	Control, Mean (SD)	<i>p</i>	Baseline score	31.6(2.7)	30.9(4.1)		Change score at 3 weeks	-1.7(1.9)	1.7(3.7)	0.001	Change score at 8 months	-2.3(3.1)	2.6(4.3)	0.001
Follow-up	DBS, Mean (SD)	Control, Mean (SD)	<i>p</i>													
Baseline score	31.6(2.7)	30.9(4.1)														
Change score at 3 weeks	-1.7(1.9)	1.7(3.7)	0.001													
Change score at 8 months	-2.3(3.1)	2.6(4.3)	0.001													
<b>Rey Complex Figure Test (RCFT) – Immediate Recall Score</b>																
<table><tr><th>Follow-up</th><th>DBS, Mean (SD)</th><th>Control, Mean (SD)</th><th><i>p</i></th></tr><tr><td>Baseline score</td><td>21.6(7.6)</td><td>19.9(6.3)</td><td></td></tr><tr><td>Change score at 3 weeks</td><td>-1.8(5.9)</td><td>3.1(5.0)</td><td>0.03</td></tr><tr><td>Change score at 8 months</td><td>0.4(4.4)</td><td>6.4(4.7)</td><td>0.001</td></tr></table>	Follow-up	DBS, Mean (SD)	Control, Mean (SD)	<i>p</i>	Baseline score	21.6(7.6)	19.9(6.3)		Change score at 3 weeks	-1.8(5.9)	3.1(5.0)	0.03	Change score at 8 months	0.4(4.4)	6.4(4.7)	0.001
Follow-up	DBS, Mean (SD)	Control, Mean (SD)	<i>p</i>													
Baseline score	21.6(7.6)	19.9(6.3)														
Change score at 3 weeks	-1.8(5.9)	3.1(5.0)	0.03													
Change score at 8 months	0.4(4.4)	6.4(4.7)	0.001													
<b>Verbal Fluency Test (Semantic - occupations)</b>																
<table><tr><th>Follow-up</th><th>DBS, Mean (SD)</th><th>Control, Mean (SD)</th><th><i>p</i></th></tr><tr><td>Baseline score</td><td>15.6(2.9)</td><td>14.8(3.5)</td><td></td></tr></table>	Follow-up	DBS, Mean (SD)	Control, Mean (SD)	<i>p</i>	Baseline score	15.6(2.9)	14.8(3.5)									
Follow-up	DBS, Mean (SD)	Control, Mean (SD)	<i>p</i>													
Baseline score	15.6(2.9)	14.8(3.5)														

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Change score at 3 weeks	-0.9(3.9)	2.9(2.5)	0.002
Change score at 8 months	3.1(3.5)	-0.5(4.0)	0.98

#### Raven Advanced Progressive Matrices (RAPM)

Follow-up	DBS, Mean (SD)	Control, Mean (SD)	<i>p</i>
Baseline score	9.2(1.7)	8.4(3.0)	
Change score at 3 weeks	-0.8(1.9)	0.6(1.7)	0.05
Change score at 8 months	-0.4(2.5)	0.5(2.4)	0.46

#### Correlation between change in clinical symptoms and cognitive function

No significant correlations were found between change in symptoms and change in cognitive functioning.

Reduced performance on the RCFT copy test did not significantly correlate with decrease of OCD ( $r = -0.42$ ,  $p = 0.14$ ), anxiety ( $r = -0.30$ ,  $p = 0.29$ ) or depression symptoms ( $r = -0.15$ ,  $p = 0.61$ ).

Reduced performance on the RCFT recall test did not significantly correlate with decrease of OCD ( $r = -0.28$ ,  $p = 0.34$ ), anxiety ( $r = 0.42$ ,  $p = 0.14$ ) or depression symptoms ( $r = 0.40$ ,  $p = 0.15$ ).

Reduced performance on the semantic verbal fluency task did not significantly correlate with decrease of OCD ( $r = 0.10$ ,  $p = 0.75$ ), anxiety ( $r = 0.25$ ,  $p = 0.40$ ) or depression symptoms ( $r = 0.27$ ,  $p = 0.35$ ).

Reduced performance on the RAPM did not correlate significantly with decrease of OCD ( $r = -0.20$ ,  $p = 0.52$ ), anxiety ( $r = 0.070$ ,  $p = 0.82$ ) or depression symptoms ( $r = 0.37$ ,  $p = 0.20$ ).

Abbreviations used: HAM-D, HAM-A, Hamilton Depression Rating Scale – anxiety and depression subscales.

## Study 8 Ooms P (2014)

### Details

Study type	Case series
Country	The Netherlands
Recruitment period	2005 to 2011
Study population and number	<b>n=16</b> Patients with refractory OCD
Age and sex	Mean 42 years; 56% (9/16) female.
Patient selection criteria	Inclusion criteria: Diagnosis of primary OCD with at least 28 points in Y-BOCS score; at least 5 years duration of disease; OCD refractory to at least two treatments with a selective serotonin reuptake inhibitor, plus a treatment with clomipramine hydrochloride, plus one augmentation trial with atypical antipsychotics, plus one CBT trial for a minimum of 16 sessions;
Technique	Bilateral implantation of DBS electrodes targeted at the NAc was performed according to standard stereotactic procedures.
Follow-up	<b>Mean – 4 years and 3 months</b>
Conflict of interest/source of funding	The authors declared no competing interests.  The study was funded by an unrestricted investigator-initiated research grant by Medtronic Inc, which provided the devices used herein, and by grant from the Netherlands Organisation for Scientific Research ZON-MW VENI programme.

### Analysis

**Follow-up issues:** 3 patients were excluded from QOL analysis: 1 patient was excluded because of incomplete data at T0; 1 patient at T1 because of incomplete data and 1 patient failed to cooperate at both T1 and T2 stages.

**Study design issues:** This is a long-term QOL analysis for another study, which was included in the meta-analysis by Alonso et al (Study 1). QOL was measured with the Dutch version of WHO Quality of Life Scale-Brief Version (WHOQOL-BREF). Outcomes were measure at 3 time points: 1 month before electrode implantation (T0), after the end of CBT programme ca. 8 months after DBS surgery (T1) and after 3 to 5 years of active stimulation (T2). Paired samples t tests were used to compare scores at different time points. Data are presented as mean (SD) at a two-tailed 5% level of significance. All p values are nominal (not adjusted for multiple comparisons) to preserve statistical power. Psychologists were trained regularly to ensure inter-rater reliability.

**Study population issues:** The mean duration of illness was 29 years. The mean age of onset of OCD was 14 years. 1 patient who was excluded at T1 and T2, had disappointment in the effect of treatment and did not want to cooperate.

**Other issues:** Only QOL outcomes from this study are reported in this overview. The clinical outcomes for these patients were included in the meta-analysis by Alonso et al. (see study 1).

## Key efficacy and safety findings

Efficacy					Safety
Number of patients analysed: 16					No safety data were reported.
Mean improvement of WHOQOL-BREF Scores from baseline (T0)					
Domains	T1 (after 8 months of active stimulation)	p	T2 (after 3-5 years of active stimulation)	p	
General Score	74%	<0.05	90%	<0.05	
Physical score	23%		39.5%		
Psychological Score	27%		39.5%		
Environmental Score	8%		16%		
Social	5.6%	0.482	14.2%	0.073	
At 3-5 years follow-up, the general score improved by a total of 90%, the physical and psychological domains both improved by 39.5% and the environmental domains improved by 16% (p<0.05 for all). The social domains failed to show statistically significant effect at follow-up assessments(p>0.05).					
Relationship between in Y-BOCS score and Quality of Life					
At 8 months follow-up, the decrease in Y-BOCS scores correlated with improvement in physical score (rs=-0.576, p<0.05) and environmental (rs=-0.676, p<0.05) domains.					
At 3 to 5 years follow-up, changes in Y-BOCS score did not show a significant relation with any of the changes in WHOQOL-BREF variables (figures not provided).					
Abbreviations used: WHOQOL-BREF, World Health Organization Quality of Life scale- brief version.					

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## Study 9 Bagatti D (2020)

### Details

Study type	<b>Single case report</b>
Country	Italy
Recruitment period	2006
Study population and number	n=1 patient with chronic refractory OCD
Age and sex	33 years; male
Patient selection criteria	None
Technique	Bilateral DBS of the nucleus accumbens. The patient received 1 g of intravenous cefazolin sodium before the skin incision and 240 mg of intravenous gentamicin after the surgery.
Follow-up	<b>5 years</b>
Conflict of interest/source of funding	None

### Key efficacy and safety findings

Efficacy	Safety
At the 5-year follow-up examination, the patient's Yale-Brown scale score for obsessive-compulsive disorder had decreased from 40 to 10.	At about 7 to 10 days after hospital discharge, the patient developed an <b>infection</b> along the surgical path of both electrodes <b>associated with a cytotoxic lesion in the splenium of corpus callosum</b> . He was treated with antibiotics. The 1-month follow-up MRI scan showed nearly complete regression of the signal alterations.

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## Study 10 Vicheva P (2020)

### Details

Study type	<b>Systematic review of RCTs</b>
Country	UK
Recruitment period	Studies published between 2005 and 2019 (search date: March 2019)
Study population and number	n=80 patients with severe treatment-resistant OCD
Age and sex	Not available
Patient selection criteria	<p><u>Study inclusion criteria:</u> RCTs using DBS for OCD as compared with sham or those comparing different target areas.</p> <p><u>Study exclusion criteria:</u> studies with a primary focus on other diseases, the ethical aspects of DBS, interventions other than DBS, letters, case-reports, clinical experiences, reviews, posters, animal studies, editorials, comments, conference abstracts, and book chapters.</p>
Technique	DBS
Follow-up	Not available
Conflict of interest/source of funding	None

### Analysis

#### Study design issues:

- Methods of the analysis and inclusion criteria were specified in advance, documented in a protocol and registered on PROSPERO (International prospective register of systematic reviews). The systematic review adhered to the items of preferential reports for systematic reviews and meta-analyses (PRISMA), the PRISMA harms checklist and the Cochrane Handbook of Systematic Reviews of Interventions.
- Results were analysed separately by DBS target site and collectively. Primary outcomes were change in the severity of symptoms in OCD (as assessed according to percentage Y-BOCS change at the end of each double-blind phase from baseline), quality of life and adverse events.
- Across all included studies, the criterion for a full response was more than 35 % improvement of Y-BOCS score from baseline.
- A meta-analysis was not done due to the small number of studies and their heterogeneity.
- All studies selected for the final analysis were double blind crossover sham-controlled trials with 2 exceptions: 1 study had a double-blind staggered onset design (Goodman et al., 2010) and in the other a different target area served as a control instead of a sham stimulation (Tyagi et al., 2019).
- The goal of the authors was to focus on the controlled period of the included studies to reduce the risk of bias, but because the outcomes of interest were not assessed during or at the end of the double-blind phase in some studies, they could not entirely meet this goal.
- The length of exploratory testing and the length of double-blind and follow-up assessments varied mostly between studies.

**Study population issues:** The DBS targets varied between studies (see table below).

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## Key efficacy and safety findings

Efficacy						Safety
Number of patients analysed: <b>80</b>						Most adverse events were mild and transient.
Study	DBS target	Number of patients reaching a full response	% Y-BOCS reduction from baseline at the end of the double-blind phase	% Y-BOCS reduction active vs sham stimulation	QoL improvement from baseline	Severe adverse events (% of patients)
Abelson et al. 2005	ALIC (bilateral)	1/4	19.08	9.40	Non-applicable	<ul style="list-style-type: none"> <li><u>Surgery-related</u> <ul style="list-style-type: none"> <li><b>intracerebral haemorrhage:</b> 4% (3/80)</li> <li><b>infection:</b> 3% (2/80)</li> </ul> </li> <li><u>Mood-related:</u> <ul style="list-style-type: none"> <li><b>completed suicide:</b> 1% (1/80)</li> <li><b>suicide attempts:</b> 3% (2/80, 3 attempts)</li> <li><b>suicidal thoughts and depression:</b> 5% (4/80)</li> </ul> </li> </ul>
Mallet et al. 2008	STN (2 unilateral, 14 bilateral)	7/16	40.73	32.14	Non-applicable	
Huff et al. 2010	right NAcc (unilateral)	1/10	13.35	10.29	Significant improvement at 12-month follow-up as assessed by MSQoL	
Goodman et al. 2010	VC/VS (bilateral)	3/6	36.74	16.92	Significant improvement at 12-month follow-up for the vitality scale of the SF-16	
Denys et al. 2010	NAcc (bilateral)	8/14	37.55	29.88	Non-applicable	
Luyten et al. 2016	ALIC/BST (bilateral)	12/17	48.56	37.91	Non-applicable	
Barcia et al. 2019	NAcc/CN (bilateral)	6/7	52.44	26.04	Non-applicable	
Tyagi et al. 2019	amSTN, VC/VS (bilateral)	3/6 for anteromedial subthalamic nucleus 3/6 for ventral capsule/ventral striatum	45.17 52.99	-	Non-applicable	
<b>TOTAL</b>			<b>38.68%</b>	<b>27.05%</b>	<b>-</b>	
Abbreviations used: amST, anteromedial subthalamic nucleus; ALIC, anterior limb of the internal capsule; BST, bed nucleus of the stria terminalis; CN, caudate nucleus; MSQoL, modular system of quality of life; NAcc, nucleus accumbens; SF-16, short form health survey; STN, subthalamic nucleus; VC/V, ventral capsule/ventral striatum.						

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## Study 11 Denys D (2020)

### Details

Study type	<b>Case series</b>
Country	the Netherlands (single centre)
Recruitment period	2005-17
Study population and number	n=70 consecutive patients with refractory OCD
Age and sex	Mean 42 years; 69% (48/70) female
Patient selection criteria	<p><u>Inclusion criteria</u>: refractory OCD, score of 28 or more on the Y-BOCS, at least a 5-year history of OCD and substantial functional impairment.</p> <p><u>Exclusion criteria</u></p> <ul style="list-style-type: none"> <li>- absolute contraindications: presence of psychotic disorders, substance abuse within the past 3 months, and unstable neurological or coagulation disorders.</li> <li>- relative contraindications: severe comorbid DSM diagnoses, such as bipolar disorder, autism, or personality disorder.</li> </ul>
Technique	<p>Bilateral implantation of 4-contact DBS electrodes (model 3389, Medtronic) under general anaesthesia with frame-based MRI for target determination. The target area for the electrodes was the ventral anterior limb of the internal capsule.</p> <ul style="list-style-type: none"> <li>- In patients 1 to 28, the lower 2 contact points targeted the NAcc and the upper 2 contact points the vALIC.</li> <li>- In patients 29 to 70, the lower contact point targeted the NAcc and the upper three the vALIC.</li> </ul> <p>Electrodes were connected to an implantable pulse generator (Soletra or ActivaPrimaryCell, Medtronic). Initially, 2 Soletra implantable pulse generators were implanted and starting from 2010, 1 Activa Primary Cell implantable pulse generator was placed unilaterally inside the right infraclavicular pocket while the patient. All patients received a non-rechargeable implantable pulse generator during the initial surgery that needed to be replaced approximately every 14 months.</p> <p>DBS was activated 2 weeks after surgery. Effectiveness and tolerability were evaluated every 2 weeks to optimize DBS parameter settings.</p>
Follow-up	<b>1 year</b>
Conflict of interest/source of funding	One of the authors serves as an independent adviser for Boston Scientific, Elekta, and Medtronic. The other authors report no financial relationships with commercial interests.

### Analysis

**Follow-up issues:** Scales were completed by nurses or physicians before DBS implantation, 2 weeks after implantation, and then monthly up to 6 months after surgery. The last measurement was 12 months after DBS implantation. Data on adverse events were acquired during each visit from spontaneous reports by the patient, by questioning the patient, or by observation of the patient.

**Study design issues:** The primary outcome measure was the Y-BOCS. Secondary effectiveness measures were the HAM-A and the HAM-D.

**Study population issues:**

- The first 16 patients participated in a previously published efficacy study and were also included in this study. The subsequent 54 patients received DBS in a regular clinical setting.
- The average duration of illness was 25 years.
- The average baseline scores on the Y-BOCS and HAM-D were 34 (SD=3) and 21 (SD=6), respectively.
- The most prevalent comorbid disorders included major depressive disorder (43%) and obsessive-compulsive personality disorder (10%). At baseline, 86% of patients were receiving pharmacotherapy.

IP overview: deep brain stimulation for chronic, severe, treatment-resistant obsessive-compulsive disorder in adults



- Patients with comorbidities, such as bipolar disorder, autism, and severe personality disorders, were included in our study.

## Key efficacy and safety findings

Efficacy				Safety															
Number of patients analysed: 70																			
Clinical outcomes at 12 months																			
	Y-BOCS	HAM-A	HAM-D																
% reduction from baseline	40% (Cohen's d=1.5, very large effect size)	55% (Cohen's d=1.4, very large effect size)	54% (Cohen's d=1.3, very large effect size)																
Change in score (mean±SD)	-13.5±9.4	-13.4 points ±9.7	-11.2 points ±8.8																
<p>The authors found a statistically significant effect of DBS stimulation on Y-BOCS scores (<math>\beta</math>= -9.54, 95% CI [-11.98 to -7.11], <math>p</math>&lt;0.001) and time on Y-BOCS scores (<math>\beta</math>= -0.34, 95% CI [-0.57 to -0.11], <math>p</math>=0.004), showing that OCD symptoms decreased after active stimulation and further decreased over time.</p> <p>The authors found a statistically significant effect of DBS stimulation on HAM-A scores (<math>\beta</math>= -12.94, 95% CI [-15.27 to -10.61], <math>p</math>&lt;0.001) and on HAM-D scores (<math>\beta</math>= -9.23, 95% CI [-11.13 to -7.33], <math>p</math>&lt;0.001). They found no statistically significant effect of time on HAM-A and HAM-D scores, showing that stimulation had an immediate effect on affective symptoms.</p>																			
Categorical analysis of responders after 12 months of DBS																			
	Responders (score decrease of at least 35%)	Partial responders (score decrease between 25% and 34%)	Non-responders (score decrease less than 25%)																
% of patients	52% (36/70) mean Y-BOCS decrease of 20.9±6.4 points (62%)	17% (12/70) mean Y-BOCS decrease of 9.9±1.5 points (29%)	31% (22/70) mean Y-BOCS decrease of 3.3±3.0 points (10%)																
				<table><tr><th>Surgery-related adverse event</th><th>% of patients</th></tr><tr><td>Infection of the electrode implantation site*</td><td>3% (2/70)</td></tr><tr><td>Superficial infection of a cranial incision**</td><td>3% (2/70)</td></tr><tr><td>Mispositioned electrodes***</td><td>9% (6/70)</td></tr></table> <p>* The DBS system was explanted in both patients and the electrodes or implantable pulse generator and extension cables were re-implanted 3 months later.</p> <p>** Both patients were treated with oral antibiotics.</p> <p>*** The electrodes were re-implanted or retracted within 8 months after the initial surgery.</p>		Surgery-related adverse event	% of patients	Infection of the electrode implantation site*	3% (2/70)	Superficial infection of a cranial incision**	3% (2/70)	Mispositioned electrodes***	9% (6/70)						
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				<table><tr><th>Stimulation-related adverse events</th><th>% of patients</th></tr><tr><td>Transient hypomanic symptoms</td><td>39%</td></tr><tr><td>Transient restlessness</td><td>33%</td></tr><tr><td>Agitation</td><td>30% transient; 3% permanent</td></tr><tr><td>Transient impulsivity</td><td>19%</td></tr><tr><td>Sleeping disorders</td><td>46% transient; 7% permanent</td></tr></table> <p>Most of these adverse events were related to changes in stimulation and lasted between several days and several weeks.</p>		Stimulation-related adverse events	% of patients	Transient hypomanic symptoms	39%	Transient restlessness	33%	Agitation	30% transient; 3% permanent	Transient impulsivity	19%	Sleeping disorders	46% transient; 7% permanent		
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				<table><tr><th>Other adverse events</th><th>% of patients</th></tr><tr><td>Headache</td><td>36%</td></tr><tr><td>Pain around the burr holes</td><td>17%</td></tr><tr><td>Feeling of the implantable pulse generator in the chest</td><td>16%</td></tr><tr><td>Pulling of the extension leads</td><td>30%</td></tr><tr><td>Paraesthesia</td><td>20%</td></tr><tr><td>Suicide attempts****</td><td>4% (3/70)</td></tr></table> <p>The authors observed that temporary disruptions of the stimulation led to severe anxiety and depression.</p> <p>****One attempt was classified as a serious stimulation-related adverse event because it occurred 1 day after a DBS voltage increase of 0.5 V. The patient's suicidal ideation resolved without changes to the stimulation settings. The other 2 suicide attempts were related to comorbid bipolar disorder and borderline personality disorder. These attempts occurred at least 3 months after the last change in stimulation settings.</p>		Other adverse events	% of patients	Headache	36%	Pain around the burr holes	17%	Feeling of the implantable pulse generator in the chest	16%	Pulling of the extension leads	30%	Paraesthesia	20%	Suicide attempts****	4% (3/70)
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Suicide attempts****	4% (3/70)																		

Abbreviations used: DBS, deep brain stimulation; DSM, diagnostic and statistical manual of mental disorders; HAM, Hamilton anxiety rating scale; NAcc, nucleus accumbens; OCD, obsessive-compulsive disorder; vALIC, ventral anterior limb of the internal capsule; Y-BOCS, Yale-Brown obsessive-compulsive scale.

## Study 12 Martinho F P (2020)

### Details

Study type	<b>Systematic review and meta-analysis</b>
Country	Portugal
Recruitment period	Literature search up to November 2019
Study population and number	n= <b>225</b> patients with OCD from 8 RCTs and 38 observational studies (13 case reports and 25 case series)
Age and sex	Mean 40 years; 46% female
Patient selection criteria	<p><b>Inclusion criteria:</b> RCTs and observational studies of people with OCD (main diagnosis of OCD of disabling severity) treated with DBS. Studies published in English. Studies needed to report data on at least 1 of the following outcomes:</p> <ul style="list-style-type: none"> <li>-primary efficacy outcome: variation of obsessive and/or compulsive symptoms measured by the Y-BOCS.</li> <li>-primary safety outcome: proportion of participants with serious adverse events.</li> <li>-secondary outcomes: proportion of patients with complete response or in remission; variation of mood symptoms; proportion of participants with any adverse event; proportion of dropouts and predictors of response.</li> </ul> <p><b>Exclusion criteria:</b> narrative or systematic reviews; articles on neurophysiological, neuropsychological, or functional imaging effects of DBS; or articles focused solely on acute effects.</p>
Technique	<p>DBS of various targets, mostly bilateral (42/46).</p> <p>The average stimulation frequency used was 132 Hz, the average pulse width was 143 ms and the average voltage was 4.9 V.</p>
Follow-up	<b>Mean 33 months</b>
Conflict of interest/source of funding	None

### Analysis

#### Study design issues:

- 2 of the RCTs reported on the same cohort so the data from these studies were analysed together on a single cohort. Data from duplicate patients were merged and, of the 46 included studies, 39 cohorts were analysed.
- The systematic review and meta-analysis was conducted according to the PRISMA guidelines.
- The risk of bias was assessed with the Cochrane risk of bias tool for the RCTs and with the Newcastle-Ottawa scale for the observational studies. In the RCTs, the risk of bias in the performance and detection parameters was considered high in all but 2 studies in which it was uncertain. None of the observational studies had a comparison arm.
- Depression scores were standardised by calculating the percentage of each patient's score from the maximum score of the instrument used and subsequent statistical analysis was done with this value that was named weighted depression score (WDS).
- All studies collected Y-BOCS scores and 31 collected data on depression.
- Analyses were done on 2 aggregates of studies: RCTs only for ON and OFF stimulation results and all selected studies for baseline and last follow-up results.

#### Study population issues:

- The average duration of illness was 24 years (from 5 to 52 years). The most frequent stimulation sites were limbic.

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## Key efficacy and safety findings

Efficacy	Safety
<p>Number of patients analysed: <b>225</b></p> <p><b>Y-BOCS</b></p> <p><u>Mean baseline scores <math>\pm</math> SD:</u></p> <ul style="list-style-type: none"> <li>RCTs: 33.8 <math>\pm</math> 4.2</li> <li>Overall: 33.7 <math>\pm</math> 3.8</li> </ul> <p><u>Decrease in Y-BOCS score</u> (mean difference between sham and DBS [RCTs] or from baseline [overall]):</p> <ul style="list-style-type: none"> <li>RCTs: -7.8 (95 % CI -11.2 to -4.3, <math>I^2</math> = 40%, <b>p&lt;0.0001</b>)</li> <li>Overall: -15.0 (95 % CI -18.3 to -11.7, <math>I^2</math> = 90%, <b>p&lt;0.001</b>)</li> </ul> <p><u>Complete response to treatment</u> (defined by a decrease of more than 35% in Y-BOCS score)</p> <ul style="list-style-type: none"> <li>RCTs: 51% [DBS] versus 18% [sham] (RR=2.4 [95% CI 1.3 to 4.3, <math>I^2</math>=0%, p=0.003], risk difference=0.33 [95% CI 0.16 to 0.49], <math>I^2</math>=37%, <b>p=0.0001</b>, NNT=3.03)</li> <li>Overall: 57.9% (95% CI 49.7% to 69.9%, <math>I^2</math> =62%, <b>p&lt;0.001</b>)</li> </ul> <p><u>Remission</u> (Y-BOCS score of less than 6)</p> <ul style="list-style-type: none"> <li>RCTs: 8% versus 5% (RR=1.3 [95% CI 0.2 to 10.44], <math>I^2</math>=26%, p=0.80, NNT=33.3)</li> <li>Overall: 5.4% (95% CI 2.4% to 8.4%, <math>I^2</math>=0%, p=0.92)</li> </ul> <p><u>Subgroup analysis</u></p> <ul style="list-style-type: none"> <li>Limbic targets: MD=-7.4, 95% CI -11.7 to -3.2, <math>I^2</math>=47%, <b>p=0.0006</b></li> <li>STN: MD=-9.0, 95% CI -14.2 to -3.8, <b>p=0.0007</b> (only 1 study included)</li> <li>Test for subgroup differences: <math>\chi^2</math>=0.21, <math>I^2</math>=0%, p=0.65</li> </ul> <p><u>Predictors of response</u></p> <p>No consistent predictor of response was found.</p> <p><b>Effect on mood</b> (31 studies, WDS)</p> <p><u>Mean baseline WDS <math>\pm</math> SD:</u></p> <ul style="list-style-type: none"> <li>RCTs: 33.7 <math>\pm</math> 39.8</li> <li>Overall: 36.6 <math>\pm</math> 17.0</li> </ul> <p><u>Decrease in HDRS (RCTs) or WDS (overall)</u> (mean difference between sham and DBS [RCTs] or from baseline [overall]):</p> <ul style="list-style-type: none"> <li>RCTs (2 studies): -7.3 (95 % CI -11.5 to -3.0, <math>I^2</math> = 0%, <b>p=0.0009</b>)</li> <li>Overall: -13.7 (95 % CI -20.1 to -7.3, <math>I^2</math> = 76%, <b>p&lt;0.001</b>)</li> </ul> <p>There was a correlation between response in Y-BOCS and response in WDS, both in RCTs and at last follow-up (Spearman <math>\rho</math>=0.989, p=0.006 and Spearman <math>\rho</math>=0.454, p=0.000).</p>	<p><b>Adverse events</b></p> <p>Total: 814</p> <ul style="list-style-type: none"> <li>Psychiatric: 36% (289/814) (<b>hypomania, sleep complaints, irritability, apathy, depression</b>)</li> <li>Medical: 26% (215/814) (<b>weight change, sexual complaints, infections, gastrointestinal symptoms, orthopaedic/ musculoskeletal symptoms</b>)</li> <li>Neurologic symptoms: 25% (202/814) (<b>paraesthesia, cognitive complaints, headache, sensorial complaints</b>)</li> <li>Device-related symptoms: 5% (41/814) (<b>sensation with extension leads or stimulation</b>)</li> <li>Other: 8% (67/814)</li> </ul> <p>Serious adverse events: 8% (66/814, 24 medical, 19 neurologic, 13 psychiatric, 10 device-related)</p> <p><b>Deaths:</b> 4 (breast cancer, 1 overdose, 1 tuberculosis, 1 suicide)</p> <p>There were 0.68 adverse events (95% CI = 0.59 to 0.78, <math>I^2</math> = 88%, 30 cohorts, 195 patients), 0.32 serious adverse events (95% CI = 0.12 to 0.52, <math>I^2</math> = 96%, 27 cohorts, 158 patients), and 0.13 dropouts (95% CI = 0.07 to 0.16, <math>I^2</math> = 16%, 30 cohorts, 175 patients) per treated patient.</p>
<p>Abbreviations used: CI, confidence interval; DBS, deep brain stimulation; HDRS, Hamilton depression rating scale; Hz, hertz; MD, mean difference; ms, millisecond; NNT, number needed to treat; OCD, obsessive-compulsive disorder; RCT, randomised controlled trial; RR, risk ratio; SD, standard deviation; STN, subthalamic nucleus; V, volt; WDS, weighted depression score; Y-BOCS, Yale-Brown obsessive-compulsive scale.</p>	

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## Validity and generalisability of the studies

- The studies were heterogeneous in terms of anatomical targeting, electrode design and stimulation parameters. Different areas were targeted for stimulation within and between studies.
- All patients in the included studies were adults and almost all the patients had a severe form of OCD that was resistant to conventional treatments.
- Most of the primary studies included in this overview have very small sample sizes and low quality of evidence. The two RCTs included in table 2 were cross-over trials.
- Most studies reported numerous conflicts of interest held by the investigators, mostly receiving support from the main manufacturer of the device.
- Some studies excluded patients with comorbid depression. In those studies that included patients with comorbid anxiety and depression, some improvement in OCD symptoms could be secondary to improvements in anxiety and depression.

## Existing assessments of this procedure

The international college of obsessive-compulsive spectrum disorders published a position statement on clinical advances in obsessive-compulsive disorder in 2020.<sup>13</sup> It said:

*'In summary, studies of both DBS and ablative neurosurgery have shown these techniques are clinically effective for this highly refractory and extremely chronically disabled patient group. However, there is as yet insufficient evidence to determine which technique to choose at an individual patient level. Further clarification of the differential effects of ablation and stimulation across the different candidate neural targets, as well as better understanding of the interaction between somatic, pharmacological and psychological interventions, have the potential to advance the field towards a personalized approach. Agreement over standardized patient selection and treatment protocols that would allow clinical outcomes data to be collected and compared across treatment centres, represents an achievable milestone towards this goal*

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*(Menchón et al., 2019). Meanwhile, technological innovations, for example, MRI-guided focused ultrasound, laser interstitial thermal therapy (Miguel et al., 2019), offer potential for safer and more cost-effective surgical approaches.'*

## Related NICE guidance

Below is a list of NICE guidance related to this procedure.

### Interventional procedures

- Deep brain stimulation for refractory chronic pain syndromes (excluding headache). NICE interventional procedures guidance 382 (2011). Available from <https://www.nice.org.uk/Guidance/IPG382>
- Deep brain stimulation for intractable trigeminal autonomic cephalalgias. NICE interventional procedures guidance 381 (2011). Available from <https://www.nice.org.uk/Guidance/IPG381>
- Deep brain stimulation for tremor and dystonia (excluding Parkinson's disease). NICE interventional procedures guidance 188 (2006). Available from <https://www.nice.org.uk/Guidance/IPG188>
- Deep brain stimulation for Parkinson's disease. NICE interventional procedures guidance 19 (2003). Available from <http://www.nice.org.uk/guidance/IPG19>

### NICE guidelines

- Obsessive-compulsive disorder and body dysmorphic disorder: treatment. NICE clinical guideline 31 (2005). Available from <http://www.nice.org.uk/guidance/CG31>

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## **Additional information considered by IPAC**

### **Professional experts' opinions**

Expert advice was sought from consultants who have been nominated or ratified by their professional Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by professional experts, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Two Professional expert questionnaires for DBS for OCD were submitted and can be found on the [NICE website](#).

### **Patient commentators' opinions**

NICE's Public Involvement Programme sent questionnaires to 1 NHS trust for distribution to patients who had the procedure (or their carers). NICE received 4 completed questionnaires.

### **Company engagement**

A structured information request was sent to 1 company who manufacture a potentially relevant device for use in this procedure. NICE received 1 submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

### **Issues for consideration by IPAC**

- In 2009, the U.S Food and Drug administration (FDA) approved DBS for treatment-resistant OCD under a Humanitarian Device Exemption (HDE). The approval statement stated that the device is indicated for bilateral stimulation of the anterior limb of the internal capsule, as an adjunct to medications.
- One of the professional experts stated in their PEQs that an international registry is being set up under the auspices of the WSSFN (World Society for Stereotactic and Functional Neurosurgery) and is expected to start collecting data in 2020.

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- Ongoing trials:
  - Deep Brain Stimulation (DBS) for the Treatment of Refractory Obsessive-compulsive Disorder (OCD), [NCT04217408](#), start date September 2019, estimated enrolment: 10, estimated completion date: May 2021.
  - Combined Cortical/Subcortical Recording and Stimulation as a Circuit-Oriented Treatment for Obsessive-Compulsive Disorder, [NCT03184454](#), start date October 2016, estimated enrolment: 5, estimated completion date: October 2021.
  - Reclaim™ Deep Brain Stimulation (DBS) Therapy for Obsessive-Compulsive Disorder (OCD) (DBS), [NCT02773082](#), start date: November 2018, estimated enrolment: 50, estimated completion date: April 2020.
  - Development of Adaptive Deep Brain Stimulation for OCD (Phase Ib), [NCT04281134](#), start date: October 2019, estimated enrolment: 2, estimated study completion date: June 2023.
  - Development of Adaptive Deep Brain Stimulation for OCD (Phase 1a/1b), [NCT03457675](#), start date: July 2018, estimated enrolment: 2, estimated study completion date: June 2023.
  - The Efficacy and Mechanism of DBS in VIC and NAcc for Refractory OCD, [NCT04228744](#), start date: January 2020, estimated enrolment: 20, estimated study completion date: December 2022.
  - European Study of Quality of Life in Resistant OCD Patients Treated by STN DBS (EQOLOC), [NCT02844049](#), start date: September 2016, estimated enrolment: 60, estimated study completion date: December 2023.

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- Patient-specific, Effective, and Rational Functional Connectivity Targeting for DBS in OCD (PERFECT DBS), [NCT03244852](#), start date: September 2017, estimated enrolment: 11, estimated completion date: June 2022.
- ON/OFF Stimulation and Impulsivity in Patients With Deep Brain Stimulators, [NCT01506206](#), start date: February 2012, estimated enrolment: 60, estimated completion date: December 2020.
- ON/OFF Stimulation and Reward Motivation in Patients With Deep Brain Stimulators, [NCT01590862](#), start date: June 2012, estimated enrolment: 60, estimated completion date: December 2020.

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12. Martinho FP, Duarte GS, Simoes do Couto F (2020). Efficacy, effect on mood symptoms, and safety of deep brain stimulation in refractory obsessive-compulsive disorder: a systematic review and meta-analysis. *Journal of Clinical Psychiatry* 81(3):19r12821
13. Fineberg NA, Hollander E, Pallanti S et al (2020). Clinical advances in obsessive-compulsive disorder: a position statement by the International College of Obsessive-Compulsive Spectrum Disorders. *International Clinical Psychopharmacology* 35(4):173–193.

## Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	16/12/2020	Issue 12 of 12, December 2020
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	16/12/2020	Issue 12 of 12, December 2020
International HTA database (INAHTA)	16/12/2020	n/a
MEDLINE (Ovid)	16/12/2020	1946 to 15 December 2020
MEDLINE In-Process (Ovid)	16/12/2020	1946 to 15 December 2020
MEDLINE Epubs ahead of print (Ovid)	16/12/2020	15 December 2020

### Trial sources searched

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

### Websites searched

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1	Deep Brain Stimulation/
2	((deep or electric*) adj4 brain* adj4 stimul*).tw.
3	(dbs or dbs-stn).tw.
4	(neurostimulat* or neuro-stimulat* or neuromodulat* or neuro-modulat*).tw.
5	or/1-4
6	Electric Stimulation Therapy/

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7	(electric* adj4 stimul* adj4 (therap* or treat*)).tw.
8	(stimulat* adj4 (lead* or wire*)).tw.
9	or/6-8
10	exp Brain/
11	brain*.tw.
12	or/10-11
13	9 and 12
14	5 or 13
15	Obsessive-Compulsive Disorder/
16	((obsess*-compuls* or (obsess* adj4 compuls*)) adj4 (disord* or neuros*)).tw.
17	(OCD or OCPD).tw.
18	(anankast* adj4 personalit*).tw.
19	((obsess* or compuls* or repeat* or repetit* or unwanted* or unpleas*) adj4 (thought* or feeling* or imag* or urge* or react* or sensitiv* or activit* or reflex* or respons* or function* or behav*)).tw.
20	or/15-19
21	14 and 20
22	dbs therapy.tw.
23	activa.tw.
24	or/22-23
25	20 and 24
26	21 or 25
27	Animals/ not Humans/
28	26 not 27
29	limit 28 to english language
30	limit 29 to ed=20200701-20201231

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## Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Case series with fewer than 10 patients have been excluded. Case reports have been excluded unless they describe a safety event.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Ashkan K, Mirza AB, Tambirajoo K et al. (2020) Deep brain stimulation in the management of paediatric neuropsychiatric conditions: current evidence and future directions. European journal of paediatric neurology.	Systematic review  n=73 studies  OCD n=20 studies	The application of DBS for psychiatric indications has progressed at a steady pace in the adult population and at a much slower pace in the paediatric population. Future studies in children should be done in a trial setting with strict and robust criteria. A move towards personalising DBS therapy with new stimulation paradigms will provide new frontiers and possibilities in this growing field.	Majority of the studies were included in table 2 (Martinho 2020)).
Baldermann JC, Hahn L, Dembek TA, et al. (2019) Weight change after striatal/capsule deep brain stimulation relates to connectivity to the bed nucleus of the stria terminalis and hypothalamus. Brain Sci. 9(10):264.	Retrospective case series n=20 OCD patients FU=12 months	DBS of the ventral striatum/ventral capsule influences weight depending on localisation and connectivity of stimulation sites.	Same patients as in Huys (2019) that is already included.
Borders C, Hsu F, Sweidan AJ et al. (2018) Deep brain stimulation for obsessive compulsive disorder: A review of results by anatomical target. Ment Illn. 10(2):7900. doi: 10.4081/mi.2018.7900.	Review	The average YBOCS reduction and percent of participants responding to therapy did not follow the same trend. This may be due to a significant difference in response in the sample despite similar intervention.	Review. No pooled data.
Chabardes S, Krack P, Piallat B et al. (2020) Deep brain stimulation of the subthalamic nucleus in obsessive-compulsives disorders: long-term follow-up of an open, prospective, observational cohort. J Neurol Neurosurg Psychiatry 91:1349-56	Case series  n=19	At a 24-month follow-up, the mean Yale and Brown Obsessive-Compulsive Scale score improved by 53.4% from 33.3±3.5 to 15.8±9.1 (95% CI 11.2 to 20.4; p<0.0001). Fourteen out of 19 patients were considered as responders, 5 out of 19 being improved over 75% and 10 out	Studies with a larger sample or better design were included in Table 2

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		of 19 over 50%. Global Assessment Functioning scale improved by 92% from 34.1±3.9 to 66.4±18.8 (95% CI 56.7 to 76.1; p=0.0003). The most frequent adverse events consisted of transient DBS-induced hypomania and anxiety.	
de Koning P, Figuee M, van den Munckhof P et al, (2011) Current Status of Deep Brain Stimulation for Obsessive-Compulsive Disorder: A Clinical Review of Different Targets. Curr Psychiatry Rep.;13(4):274-282.	Review n=115	Small studies with various designs indicate an overall average Yale-Brown Obsessive Compulsive Scale score decrease ranging from 6.8 to 31 points. The average overall responder rate is ±50%. The frequency of adverse events seems to be limited. We conclude that DBS may be a promising and safe therapy for treatment-resistant OCD.	Review. No pooled results. Most studies are included in the meta-analysis in table 2.
de Koning PP, Figuee M, Endert E et al. (2016). Rapid effects of deep brain stimulation reactivation on symptoms and neuroendocrine parameters in obsessive-compulsive disorder. Translational psychiatry, 6(1), e722.	Case series n=16	After 1 week of DBS discontinuation, DBS reactivation results in a rapid and simultaneous ±50% improvement of anxiety, depression and obsessive-compulsive symptoms in 8 out of 10 initial DBS responders. Furthermore, active DBS is associated with a rapid increase in neuroendocrine hormones compared with DBS OFF, although no significant correlation was found between clinical symptoms and neuroendocrine outcomes.	Investigated rapid effects of DBS reactivation and neuroendocrine parameters. Not relevant.
Denys D, Mantione M, Figuee M et al. (2010) Deep Brain Stimulation of the Nucleus Accumbens for Treatment-Refractory Obsessive-Compulsive Disorder. Arch Gen Psychiatry.67(10):1061–1068.	RCT n=16  FU=8 months	Bilateral deep brain stimulation of the nucleus accumbens. In the double-blind, sham-controlled phase (n = 14), the mean (SD) Y-BOCS score difference between active and sham stimulation was 8.3 (2.3), or 25% (P = .004).	Patients included in the meta-analysis in table 2 and in the Denys 2020 study.
Graat I, Mocking R, Figuee M et al. (2020) Long-term outcome of deep brain stimulation of the ventral part of the anterior limb of the internal capsule in a cohort of 50 patients with treatment-refractory obsessive-compulsive disorder. Biological Psychiatry.	Case series n=50	At long-term follow-up, OCD symptoms decreased by 39% (p<0.001), and half of the patients were responders (≥35% decrease of Yale-Brown Obsessive Compulsive Scale score). Anxiety and depressive symptoms decreased significantly, with reductions of 48% and 50%, respectively. The World Health Organization	Studies with a larger sample or better design were included in Table 2

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		Quality of Life Scale-Brief Version general score improved significantly, as did 3 of 4 subdomains. Both clinician and patient-rated functioning improved substantially ( $p<0.001$ ). The unemployment rate decreased from 78% at baseline to 58% at last follow-up ( $z=21.90$ , $p=0.058$ ), and 21 patients stopped or decreased psychotropic medication ( $z=22.887$ , $p=0.004$ ). Long-term adverse effects included cognitive complaints and fatigue. Serious adverse events included 1 suicide attempt, related to comorbid depression.	
Greenberg B, Malone D, Friehs G. et al. (2006) Three-Year Outcomes in Deep Brain Stimulation for Highly Resistant Obsessive–Compulsive Disorder. <i>Neuropsychopharmacol</i> 31, 2384–2393	Case series n=10 FU=36 months	Four of eight patients had a $\geq 35\%$ decrease in YBOCS severity at 36 months. GAF scores improved from $36.6\pm 1.5$ at baseline to $53.8\pm 2.5$ at 36 months ( $p<0.001$ ). Depression and anxiety also improved, as did self-care, independent living, and work, school, and social functioning. This open study found promising long-term effects of DBS in highly treatment-resistant OCD.	Included in the meta-analysis in table 2.
Greenberg B, Gabriels L., Malone D. et al. (2010) Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: worldwide experience. <i>Mol Psychiatry</i> 15, 64–79	Case series n=26	After deep brain stimulation of the ventral anterior limb of the internal capsule and adjacent ventral striatum (VC/VS), clinically significant symptom reductions and functional improvements were seen in about two-thirds of highly treatment-resistant patients. Results were generally better for patients implanted more recently.	Included in the meta-analysis in table 2.
Hamani C, Pilitsis J, Rughani AI et al. (2014) Deep Brain Stimulation for Obsessive-Compulsive Disorder: Systematic Review and Evidence-Based Guideline Sponsored by the American Society for Stereotactic and Functional Neurosurgery and the Congress of Neurological Surgeons (CNS) and Endorsed by the CNS and	Systematic review n=80	There is Level I evidence, based on a single class I study, for the use of bilateral subthalamic nucleus DBS for the treatment of medically refractory OCD. There is Level II evidence, based on a single class II study, for the use of bilateral nucleus accumbens DBS for the treatment of medically refractory OCD. There is insufficient evidence	All the studies from this systematic review are included in the meta-analysis in table 2.

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American Association of Neurological Surgeons, Neurosurgery, Volume 75, Issue 4, Pages 327–333		to make a recommendation for the use of unilateral DBS for the treatment of medically refractory OCD.	
Huff, W., Lenartz, D., Schormann, M et al. (2010) Unilateral deep brain stimulation of the nucleus accumbens in patients with treatment-resistant obsessive-compulsive disorder: Outcomes after one year, Clinical Neurology and Neurosurgery, Volume 112, Issue, Pages 137-143	RCT N=10	DBS of the unilateral right nucleus accumbens showed encouraging results in patients with treatment-resistant OCD. Five out of ten patients reached at least a partial response after the first year.	Included in the meta-analysis in table 2.
Kisely S, Hall K, Siskind, D et al. (2014). Deep brain stimulation for obsessive-compulsive disorder: A systematic review and meta-analysis. Psychological Medicine, 44(16), 3533-3542.	Systematic review n=44	DBS may show promise for treatment-resistant OCD but there are insufficient randomized controlled data for other psychiatric conditions. DBS remains an experimental treatment in adults for severe, medically refractory conditions until further data are available.	All the studies from this review are included in the meta-analysis in table 2.
Kohl S, Schönherr D.M, Luigjes J et al. (2014) Deep brain stimulation for treatment-refractory obsessive-compulsive disorder: a systematic review. BMC Psychiatry 14, 214	Systematic review n=109	Deep brain stimulation in treatment-refractory obsessive-compulsive disorder seems to be a relatively safe and promising treatment option. However, based on these studies no superior target structure could be identified.	All the studies from this review are included in the meta-analysis in table 2.
Kubu, C.S., Malone, D.A., Chelune, G et al. (2013) Neuropsychological Outcome after Deep Brain Stimulation in the Ventral Capsule/Ventral Striatum for Highly Refractory Obsessive-Compulsive Disorder or Major Depression. Stereotact Funct Neurosurg 91:374-378.	Case series n=10	No significant cognitive declines were seen after ventral capsule/ventral striatum DBS for OCD.	Larger studies are included.
Kumar KK, Appelboom G, Lamsam L, et al (2019) Comparative effectiveness of neuroablation and deep brain stimulation for treatment-resistant obsessive-compulsive disorder: a meta-analytic study Journal of Neurology, Neurosurgery & Psychiatry 90:469-473	Meta-analysis n=314 (DBS only)	Pooled ability to reduce Y-BOCS scores was 50.4% ( $\pm 22.7\%$ ) for ABL and was 40.9% ( $\pm 13.7\%$ ) for DBS. Meta-regression revealed no significant change in per cent improvement in Y-BOCS scores over the length of follow-up for either ABL or DBS. Adverse events occurred in 43.6% ( $\pm 4.2\%$ ) of ABL cases and 64.6% ( $\pm 4.1\%$ ) of DBS	Comparative effectiveness study using utility as a parametric measure. No direct meta-analysis was done for outcome measures (Y-BOCS score). Most studies from this meta-

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		cases ( $p<0.001$ ). Complications reduced ABL utility by 72.6% ( $\pm 4.0\%$ ) and DBS utility by 71.7% ( $\pm 4.3\%$ ). ABL utility ( $0.189\pm 0.03$ ) was superior to DBS ( $0.167\pm 0.04$ ) ( $p<0.001$ ). Overall, ABL utility was greater than DBS, with ABL showing a greater per cent improvement in Y-BOCS than DBS.	analysis are also included in the meta-analysis in table 2.
Lakhan SE. & Callaway E. (2010). Deep brain stimulation for obsessive-compulsive disorder and treatment-resistant depression: systematic review. BMC research notes, 3, 60.	Systematic review N=58 (DBS for OCD only)	While not everyone responded, about half the patients did show dramatic improvement. Associated adverse events were generally trivial in younger psychiatric patients but often severe in older movement disorder patients. DBS is considered a promising technique for OCD.	Most studies from this systematic review are included in the meta-analysis in table 2.
Maatoug R, Valero-Cabre A, Duriez P et al. (2020) Sustained recovery in a treatment-refractory obsessive-compulsive disorder patient after deep brain stimulation battery failure. Frontiers in psychiatry 11: 572059	Case report n=1	The patient had bilateral implantation of ventral striatum/ventral capsule DBS leads attached to a battery-operated implanted pulse generator. After a 3-month post-implantation period, the DBS protocol started. Three months after the onset of DBS treatment, the patient's Y-BOCS score had dropped to 3, and he became steadily asymptomatic. However, inadvertently, at this time, it was found out that the implanted pulse generator battery had discharged completely, interrupting brain stimulation. The medical team carried on with the original therapeutic and evaluation plan in the absence of active DBS current. After 12 additional months under off-DBS, the patient remained at a Y-BOCS score of 7 and asymptomatic.	Single case report
Mallet L, Du Montcel ST, Clair AH et al. (2019) Long-term effects of subthalamic stimulation in obsessive-compulsive disorder: Follow-up of a randomized controlled trial. Brain Stimulation, Elsevier. 12 (4), pp.1080-1082	Case series (follow-up of RCT)  n=14  FU=46 months	Mean Y-BOCS change (baseline vs 46 months):-16.8, 51%.  Full responders: 75% (9/12)	Same patients as in Mallet 2008 study and also included in Martinho (2020) systematic review and meta-analysis.

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Mangas, M & Moreira, R (2013) Deep brain stimulation for obsessive compulsive disorder: A literature review, Journal of Obsessive-Compulsive and Related Disorders, Volume 2, Issue 4, Pages 391-398,	Literature review	Although about two-thirds of patients in the available studies showed clinically significant improvement in OCD symptoms with DBS, design issues, methodology weaknesses, and conflicts of interest prevent definitive conclusions. The evidence to date is unconvincing that DBS is specifically efficacious in OCD.	Review. No pooled results.
Ranjan M, Ranjan N, Deogaonkar M et al. (2020) Deep brain stimulation for refractory depression, obsessive-compulsive disorder and addiction. Neurol India, 68(8): 282-7	Review	DBS is effective and safe in severe treatment-refractory OCD in carefully selected cases. Several brain targets have been tried and actively investigated. Currently there is no clear consensus about the best or optimum DBS target for OCD but the ventral capsule and ventral striatum DBS has the most explored with encouraging results.	Review article
Raviv N, Staudt MD, Rock AK et al. (2020) A systematic review of deep brain stimulation targets for obsessive compulsive disorder. Neurosurgery 87(6): 1098-110	Systematic review  n=28 studies	Selected publications included 9 randomized controlled trials, 1 cohort study, 1 case-control study, 1 cross-sectional study, and 16 case series. Striatal region targets such as the anterior limb of the internal capsule, ventral capsule/ventral striatum, and nucleus accumbens were identified, but stereotactic coordinates were similar despite differing structural names. Only 15 of 28 articles included coordinates.	Majority of the studies were included in table 2 (Martinho 2020).
Raymaekers, S., Vansteelandt, K., Luyten, L. et al. (2017) Long-term electrical stimulation of bed nucleus of stria terminalis for obsessive-compulsive disorder. Mol Psychiatry 22, 931–934	Case series  n=24	Investigated the evolution of symptomatic and functional status of the patients and examined if baseline variables could predict this evolution. analysis showed a long-term, sustained effect of electrical stimulation in the the anterior limb of the internal capsule/bed nucleus of the stria terminalis (IC/BST). After a fast initial decline of OCD	The same patients were included in Luyten (2015). Also, direct efficacy results(Y-BOCS) were not reported.

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		symptoms, these symptoms remain relatively stable.	
Sullivan CRP, Olsen S and Widge AS (2021) Deep brain stimulation for psychiatric disorders: from focal brain targets to cognitive networks. <i>Neuroimage</i> , 225: 117515	Review	Psychiatric deep brain stimulation is a promising clinical and research technique, but still needs to establish a strong clinical evidence base.	Review article
Tyagi H, Apergis-Schoute AM, Akram H, et al. (2019) A Randomized Trial Directly Comparing Ventral Capsule and Anteromedial Subthalamic Nucleus Stimulation in Obsessive-Compulsive Disorder: Clinical and Imaging Evidence for Dissociable Effects. <i>Biol Psychiatry</i> . 85(9):726–734	RCT n=6	DBS at ventral capsule/ventral striatal (VC/VS) and anteromedial subthalamic nucleus (amSTN) significantly and equivalently reduced OCD symptoms with little additional gain following combined stimulation. amSTN but not VC/VS DBS significantly improved cognitive flexibility, whereas VC/VS DBS had a greater effect on mood. The VC/VS effective site was within the VC.	Larger studies are included.
Vázquez-Bourgon J, Martino J, Sierra Peña, M et al. (2019) Deep brain stimulation and treatment-resistant obsessive-compulsive disorder: A systematic review. <i>Revista de Psiquiatría y Salud Mental (English Edition)</i> 12(1):37–51	Systematic review n= 162	The evidence shows that the use of DBS in treatment-resistant OCD is providing satisfactory results regarding efficacy, with assumable side-effects. However, there is insufficient evidence to support the use of any single brain target over another.	Review. No pooled results. Most studies are included in the meta-analysis in table 2.
Winter L, Saryyeva A, Schwabe K et al. (2020) Long-term deep brain stimulation in treatment-resistant obsessive-compulsive disorder: outcome and quality of life at four to eight years follow-up. <i>Neuromodulation</i> . DOI: 10.1111/ner.13232	Case series n=6	With chronic DBS for four to eight years, 4 of the 6 patients had sustained improvement. Two patients remitted and 2 patients responded (defined as >35% symptom reduction), while the other 2 patients were considered non-responders on long-term. Quality of life markedly improved in remitters and responders. Peri-interventional side effects or adverse effects of chronic stimulation were not observed.	Studies with a larger sample or better design were included in Table 2
Wu H, Hariz M, Visser-Vandewalle V et al. (2021) Deep brain stimulation for refractory obsessive-compulsive disorder (OCD): emerging or established therapy? <i>Molecular Psychiatry</i> , 26: 60-5	Review	There are convincing beneficial effects of DBS on OCD symptoms in carefully selected patients who are refractory to expert psychological therapy (typically cognitive behavioural therapy) and rigorous pharmacological treatment.	Review article

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Yamasue H and Sugiyama K (2020) Application of deep brain stimulation for treatment-resistant obsessive-compulsive disorder: current status and future perspectives in Japan. <i>Neurol Med Chir</i> (Tokyo) 60: 521-4	Review	Evidence showed that DBS therapy for patients with treatment-resistant OCD had efficacy and was safe.	Review article
Zarzycki MZ and Domitrz I (2019) Stimulation-induced side effects after deep brain stimulation – a systematic review. <i>Acta Neuropsychiatrica</i> 32: 57-64	Systematic review  OCD n=3 studies	Deep brain stimulation of subthalamic nucleus should be seen as the most hazardous place of implantation. As a result, there is a strong need of 'gold standards' based on the connectivity research and closer cooperation of scientists and clinicians.	Two of the 3 studies were included in Table 2.

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