

Deep brain stimulation for obsessive-compulsive disorder: A systematic review of worldwide experience after 20 years

Lorea Mar-Barrutia, Eva Real, Cinto Segalás, Sara Bertolín, José Manuel Menchón, Pino Alonso

ORCID number: Lorea Mar-Barrutia 0000-0002-7531-0316; Eva Real 0000-0003-4523-1649; Cinto Segalás 0000-0002-0959-0356; Sara Bertolín 0000-0003-1468-7862; José Manuel Menchón 0000-0002-6231-6524; Pino Alonso 0000-0002-5779-9111.

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Lorea Mar-Barrutia, Eva Real, Cinto Segalás, Sara Bertolín, José Manuel Menchón, Pino Alonso, OCD Clinical and Research Unit, Department of Psychiatry, Hospital de Bellvitge, Barcelona 08907, Spain

Eva Real, Cinto Segalás, José Manuel Menchón, Pino Alonso, Bellvitge Biomedical Research Institute-IDIBELL, Barcelona 08907, Spain

Eva Real, Cinto Segalás, José Manuel Menchón, Pino Alonso, CIBERSAM (Centro de Investigación en Red de Salud Mental), Carlos III Health Institute, Madrid 28029, Spain

José Manuel Menchón, Pino Alonso, Department of Clinical Sciences, Faculty of Medicine, University of Barcelona, Barcelona 08907, Spain

Corresponding author: Pino Alonso, PhD, Senior Researcher, OCD Clinical and Research Unit, Department of Psychiatry, Hospital de Bellvitge, C/Feixa Llarga s/n, Barcelona 08907, Spain. mpalonso@bellvitgehospital.cat

Abstract

BACKGROUND

Twenty years after its first use in a patient with obsessive-compulsive disorder (OCD), the results confirm that deep brain stimulation (DBS) is a promising therapy for patients with severe and resistant forms of the disorder. Nevertheless, many unknowns remain, including the optimal anatomical targets, the best stimulation parameters, the long-term (LT) effects of the therapy, and the clinical or biological factors associated with response. This systematic review of the articles published to date on DBS for OCD assesses the short and LT efficacy of the therapy and seeks to identify predictors of response.

AIM

To summarize the existing knowledge on the efficacy and tolerability of DBS in treatment-resistant OCD.

METHODS

A comprehensive search was conducted in the PubMed, Cochrane, Scopus, and ClinicalTrials.gov databases from inception to December 31, 2020, using the following strategy: "(Obsessive-compulsive disorder OR OCD) AND (deep brain stimulation OR DBS)." Clinical trials and observational studies published in English and evaluating the effectiveness of DBS for OCD in humans were included and screened for relevant information using a standardized collection

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tool. The inclusion criteria were as follows: a main diagnosis of OCD, DBS conducted for therapeutic purposes and variation in symptoms of OCD measured by the Yale-Brown Obsessive-Compulsive scale (Y-BOCS) as primary outcome. Data were analyzed with descriptive statistics.

RESULTS

Forty articles identified by the search strategy met the eligibility criteria. Applying a follow-up threshold of 36 mo, 29 studies (with 230 patients) provided information on short-term (ST) response to DBS in, while 11 (with 155 patients) reported results on LT response. Mean follow-up period was 18.5 ± 8.0 mo for the ST studies and 63.7 ± 20.7 mo for the LT studies. Overall, the percentage of reduction in Y-BOCS scores was similar in ST (47.4%) and LT responses (47.2%) to DBS, but more patients in the LT reports met the criteria for response (defined as a reduction in Y-BOCS scores $> 35\%$: ST, 60.6% *vs* LT, 70.7%). According to the results, the response in the first year predicts the extent to which an OCD patient will benefit from DBS, since the maximum symptom reduction was achieved in most responders in the first 12-14 mo after implantation. Reports indicate a consistent tendency for this early improvement to be maintained to the mid-term for most patients; but it is still controversial whether this improvement persists, increases or decreases in the long term. Three different patterns of LT response emerged from the analysis: 49.5% of patients had good and sustained response to DBS, 26.6% were non responders, and 22.5% were partial responders, who might improve at some point but experience relapses during follow-up. A significant improvement in depressive symptoms and global functionality was observed in most studies, usually (although not always) in parallel with an improvement in obsessive symptoms. Most adverse effects of DBS were mild and transient and improved after adjusting stimulation parameters; however, some severe adverse events including intracranial hemorrhages and infections were also described. Hypomania was the most frequently reported psychiatric side effect. The relationship between DBS and suicide risk is still controversial and requires further study. Finally, to date, no clear clinical or biological predictors of response can be established, probably because of the differences between studies in terms of the neuroanatomical targets and stimulation protocols assessed.

CONCLUSION

The present review confirms that DBS is a promising therapy for patients with severe resistant OCD, providing both ST and LT evidence of efficacy.

Key Words: Deep brain stimulation; Obsessive-compulsive disorder; Predictors of response; Side effects; Short-term; Long-term

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Core Tip: This systematic review describes worldwide experience in the use of deep brain stimulation (DBS) in severe resistant patients with obsessive-compulsive disorder over the last twenty years, comparing short-term (ST) and long-term (LT) response to the treatment (in 230 and 155 patients respectively). Both ST and LT studies report similar, stable reductions in severity of around 47%, although the number of patients who met the criteria for response was significantly higher in the LT studies (60.6% *vs* 70.7%). DBS is a safe and well-tolerated technique, since most side effects are mild and reversible on adjusting stimulation parameters. However, no clear predictors of response can be established at present.

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INTRODUCTION

Obsessive-compulsive disorder (OCD) is a neuropsychiatric condition characterized by the presence of persistent intrusive thoughts, images or urges (obsessions) that lead to compulsions, repetitive mental or motor acts, or avoidance behaviors, in order to reduce anxiety[1]. OCD has a lifetime prevalence of 2%-3%. It begins in childhood, puberty or early adult life, and thus affects a critical period in relational and academic development[2,3]. The standard treatment for OCD combines psychotropic medication - typically serotonin reuptake inhibitors and antipsychotic potentiation - and cognitive behavioral therapy (CBT), mainly exposure with response prevention. However, around 10% of patients continue to present chronic and severe obsessive-compulsive symptoms despite exhausting all available pharmacological strategies and undergoing intensive behavior therapy[4,5]. In this group of severely disabled OCD patients, for some decades now neurosurgical interventions have been considered as a potential treatment, in spite of the possible risks.

Beyond ablative surgery, advances in many areas of neurosurgery and neuroimaging over the last 20 years have made it possible to test the capacity of different brain stimulation techniques. These techniques include deep brain stimulation (DBS) for modulating the activity of dysfunctional brain areas located in, or intimately connected with, the cortico-striato-thalamo-cortical circuitry in treatment-refractory OCD[6]. DBS was first used in 1999 as a surgical option for patients with severe OCD who had not responded to other treatments[7], but it was not until 2009 that the US Food and Drug Administration and Conformité Européenne approved it under the Humanitarian Device Exemption Program[8]. This new status means that DBS may be used as an alternative to more invasive procedures, such as anterior capsulotomy, for the treatment of chronic, severe, treatment-resistant OCD. Indeed, DBS is a reversible, focal, and adjustable neuromodulation technique that is usually well tolerated. Serious adverse effects are infrequent; they are typically psychiatric (*e.g.*, hypomania, sleep complaints, disinhibition, and depression)[9,10], and can be minimized by adjusting the stimulation parameters[11]. Although adverse effects have been described in somatic domains (*e.g.*, weight change, sexual complaints, infection, and gastrointestinal symptoms) and neurological domains (*e.g.*, headache, paresthesia, sensorial complaints, or cognitive difficulties), they are relative-ly rare[12,13].

Literature reports indicate that, to date, more than 300 patients with OCD have undergone surgery for DBS implantation. Among these reports, three meta-analyses[9-11] have reported that approximately 60% achieved reductions of > 35% on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS, the gold standard of OCD symptom assessment), a rate accepted as indicating response to treatment[14,15]. This mean reduction in the Y-BOCS score is reported to range from 38.6% to 45.1%, and the major differences between studies has been attributed to the heterogeneity of the targets stimulated and the parameters programmed[16,17]. Recently, studies have begun to publish data on the long-term (LT) outcome of these patients[18-22]. Despite all these advances, however, and 20 years after the first DBS implantation in a patient with OCD, our knowledge of the benefits and risks of DBS use in OCD is still limited, due to the small sample sizes, the lack of adequate control conditions, and the heterogeneity of the anatomical targets and stimulation parameters applied. Therefore, a systematic and critical review of all the data published to date can help us resolve some of the doubts regarding the extension and likelihood of treatment response to DBS, the need for concomitant pharmacological or behavioral treatments after implantation, the recommended duration of stimulation in both responsive and non-responsive patients, and the risk of severe adverse effects.

Therefore, the aim of this systematic review is to summarize the existing knowledge on the efficacy and tolerability of DBS in treatment-resistant OCD and to compare the short-term (ST) and LT results. This analysis should indicate whether differential response patterns exist and whether response predictors can be established so as to optimize the use of DBS in patients with OCD.

MATERIALS AND METHODS

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidance[23,24]. Studies with ST and LT follow-up periods are referred to as "ST studies" and "LT studies" respectively.

Search strategy

A comprehensive search was conducted in the PubMed, Cochrane, Scopus, and ClinicalTrials.gov databases from inception to December 31, 2020, using the following strategy: “(Obsessive-compulsive disorder OR OCD) AND (deep brain stimulation OR DBS).” The search identified a limited number of studies and was therefore completed by manual selection of relevant studies included in the reference lists of previously published articles. Any available meta-analyses and systematic reviews were also assessed in order to include all references.

Eligibility criteria

We conducted a systematic review of studies evaluating the effectiveness of DBS for OCD in humans, searching for both clinical trials and observational studies. The inclusion criteria were as follows: (1) A main diagnosis of severe and disabling OCD according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth or fifth edition[1,25], regardless of comorbidities; (2) DBS conducted for therapeutic purposes; (3) A primary outcome of variation in OCD symptoms measured by the Y-BOCS[14,15]. The Y-BOCS is the gold standard for OCD symptom assessment and was used in all studies assessing response to DBS in OCD; (4) Publication in English; and (5) Randomized clinical trials (parallel or crossover) or observational studies designs. Articles were excluded if their focus was sham stimulation, neuroanatomy, functional imaging, or neurophysiology.

Study selection and outcome measures

Articles were initially extracted and screened (title, abstract, and full article) by one reviewer (Mar-Barrutia L) with regard to the eligibility criteria and were subsequently reviewed by a second reviewer (Alonso P) to confirm their eligibility. Disagreements were resolved by consensus. The following data were then extracted: authors, year of publication, sample size, and study design; patient age, sex, and illness duration; DBS target site and follow-up since implantation; Y-BOCS, depression assessment, and global function (*e.g.*, Global Assessment of Functioning, GAF score) at baseline and last follow-up; adverse effects; and suicide attempts and/or death by suicide. Data were double-checked to exclude duplication. If a patient was included in more than one study, only their most recent/most detailed data were considered.

Risk of bias assessment

We used the Cochrane Handbook for Systematic Reviews of Interventions to assess the risk of bias in randomized controlled trials (RCT)[26], classifying the risk as low, high, or unclear risk in the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. To assess the risk of bias in observational studies we used the Newcastle-Ottawa Scale[27] (Table 1 and Table 2).

Ethics

The review did not require ethics committee approval because it analyses anonymous, previously published information.

RESULTS

Study characteristics: ST vs LT follow-up

Using the search strategy, we identified 896 articles for abstract review. Of these, 40 met the eligibility criteria (Figure 1), and a further three meta-analyses were also assessed[9-11]. Based on a follow-up threshold of 36 mo, we classified 29 articles as ST (230 cases) and eleven as LT (155 cases). Some LT studies described the LT follow-up of patients who had previously been included in ST studies (a total of 41 cases).

To assess the differences between ST and LT studies, the mean values for clinical and methodological variables were compared between the two study types (Table 3). Most ST studies (23) and most LT studies (9) were observational. The mean follow-up period in the ST studies was 1.5 years and in the LT studies 5.3 years, and the mean sample sizes were 7.9 and 14 respectively. No significant differences were detected in gender distribution, mean age at inclusion, mean Y-BOCS scores at baseline and last observation, or the percentage of reduction in Y-BOCS scores. However, the mean percentage of responders (patients with a > 35% reduction in Y-BOCS scores) rose from 60.6% in the ST studies to 70.7% in the LT studies. There was considerable

Table 1 Risk of bias for randomized controlled trials

Ref.	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Abelson <i>et al</i> [67], 2005			-	-	+		
Barcia <i>et al</i> [32], 2019		+	-	-	-		
Goodman <i>et al</i> [16], 2010			-	-	+		
Huff <i>et al</i> [31], 2010					+		
Luyten <i>et al</i> [20], 2016	+		-	-			
Tyagi <i>et al</i> [17], 2019		+			+	+	
Welter <i>et al</i> [39], 2020		+	-	-	-		

+: High risk of bias; -: Low risk of bias. If there is no sign, the risk of bias is uncertain.

variability in the programming parameters reported in the studies: both monopolar and bipolar stimulation were used, and the average frequency of stimulation ranged from 100-130 Hz, average pulse width from 60-450 μ s, and average voltage from 2-7.4 V.

The level of depression, as assessed by different scales, was reported more frequently in LT than in ST studies. However, depressive symptoms improved regardless of the follow-up duration. The characteristics and results for the ST and LT studies, grouped into RCT and non-RCT designs, are presented in Tables 4-7.

Primary outcomes: Obsessive symptoms

The minimum Y-BOCS score required for DBS implantation was 30-32 in most studies, a score range consistent with severe illness; some studies applied less restrictive inclusion criteria (scores > 24)[28-32]. The mean changes in Y-BOCS scores from pre- to post-treatment were similar in the ST studies (change from 33.0 to 17.2) and the LT studies (change from 34.4 to 18.0). Thus, the percentage reduction in Y-BOCS scores remained stable when comparing ST and LT responses to DBS (47.4% *vs* 47.2%), but significantly more patients in the LT reports met the criteria for response (ST: 60.6%, *vs* LT: 70.7%). These results are consistent with those of previous meta-analyses[9-11].

Given that DBS has only been authorized for the treatment of OCD for 20 years, the evidence available on the LT clinical course remains limited. Our systematic review includes information on 155 patients from different parts of the world treated for a mean follow-up period of 5.3 years. Those responding to DBS, either completely or partially, tended to achieve the maximum symptom reduction in the first 12-14 mo after implantation[19,21]. Graat *et al*[19] followed the largest sample to date (50 patients) from 3 years to 13 years and found that most responders at LT follow-up had responded in the first year. This initial period of improvement coincided with a time when more stimulator adjustments were performed and the patient engaged in simultaneous behavioral therapy. Holland *et al*[21] reported that their nine patients needed > 1 year to achieve maximum improvement, but their mean results of 32.5 mo were seriously affected by an outlier with a significantly prolonged response time. After excluding this subject, the mean response time fell to 14.6 mo, again suggesting that response in the first year significantly predicts the extent to which an OCD patient will benefit from DBS.

Reports indicate a consistent tendency for the improvement to be maintained to the mid-term for most patients[19,22,33-38], but it is controversial whether this improvement persists, increases or decreases in the LT. Winter *et al*[28], Holland *et al* [21] and Mallet *et al*[22] found progressive decreases in obsessive symptoms over time. For example, while Mallet *et al*[22] reported that the mean Y-BOCS score decreased by one point per year up to 46 mo, Graat *et al*[19] reported a slight increase of 1.8 points at the end of their follow-up period. Luyten *et al*[20] also reported a 66% reduction in Y-

Table 2 Risk of bias for non-randomized controlled trials

Ref.	Selection	Comparability	Outcome
Anderson and Ahmed[74], 2003	++	+	++
Aouizerate <i>et al</i> [75], 2009	++	+	+++
Azriel <i>et al</i> [76], 2020	++	+	+++
Chabardes <i>et al</i> [29], 2020	++	+	++
Chang <i>et al</i> [77], 2017	++	+	+++
Choudhury <i>et al</i> [78], 2017	++	+	+++
Coenen <i>et al</i> [79], 2017	++	+	+++
Denys <i>et al</i> [44], 2020	++	+	++
Doshi <i>et al</i> [80], 2019	++	+	+++
Farrand <i>et al</i> [42], 2018	++	+	+++
Fayad <i>et al</i> [33], 2016	++	+	+++
Franzini <i>et al</i> [81], 2010	+++	+	+++
Gabriëls <i>et al</i> [53], 2003	++	+	+++
Graat <i>et al</i> [19], 2020	++	+	+++
Grant <i>et al</i> [34], 2016	++	+	+++
Greenberg <i>et al</i> [36], 2010	++	+	+++
Gupta <i>et al</i> [35], 2019	++	+	+++
Holland <i>et al</i> [21], 2020	++	+	+
Huys <i>et al</i> [30], 2019	++	+	+++
Islam <i>et al</i> [40], 2015	++	+	+++
Jiménez <i>et al</i> [55], 2013	++	+	+++
Lee <i>et al</i> [37], 2019	++	+	+++
Maarouf <i>et al</i> [45], 2016	+++	+	++
Mallet <i>et al</i> [22], 2019	++	+	+++
Menchón <i>et al</i> [13], 2021	++	+	++
Mulders <i>et al</i> [82], 2017	++	+	+++
Plewnia <i>et al</i> [83], 2008	++	+	+++
Polosan <i>et al</i> [38], 2019	++	+	+++
Roh <i>et al</i> [61], 2012	++	+	+++
Sachdev <i>et al</i> [84], 2012	++	+	++
Senova <i>et al</i> [85], 2020	++	+	+++
Tsai <i>et al</i> [49], 2012	++	+	++
Winter <i>et al</i> [28], 2021	++	+	+++

Each “+” symbol indicates lower risk of bias.

BOCS scores 4 years after DBS implantation, which had become a 45% reduction by 14 years. The percentage of responders (67%) remained significant at the end of follow-up.

The lack of individual data from the studies analyzed rules out a statistical classification of the LT evolution of OCD after treatment with DBS. Nevertheless, the data available suggest at least three patterns of LT response. First, 26.6% of subjects in all the studies were non responders, in whom the clinical effect was negligible despite all attempts to adjust the stimulation parameters for months or years[21,28,29,33,39,40]. Second, 49.5% of patients were responders who showed a maximum improvement in

Table 3 Differences in mean characteristics between the short-term and long-term studies

Characteristic	Short-term		Long-term	
	mean \pm SD	Range	mean \pm SD	Range
Sample size, <i>n</i>	7.9 \pm 13.6	1-70	14 \pm 14.4	1-50
Female, %	54 \pm 36.9	0-100	61.5 \pm 22	33-100
Average age, yr	41.7 \pm 9.9	28-72	40.5 \pm 4.3	32-45
Average duration of illness, yr	24 \pm 16.4	5-52	20.4 \pm 3.2	16-25
Follow-up since DBS, mo	18.5 \pm 8	7-36	63.7 \pm 20.7	38-96
Follow-up since DBS, yr	1.5 \pm 0.6	1-2.7	5.3 \pm 1.7	3-7.7
Baseline Y-BOCS, mean score	33 \pm 3.7	19-39	34.4 \pm 1.7	32-38
Last Y-BOCS, mean score	17.2 \pm 7.4	1-31	18 \pm 3.2	11-21
Y-BOCS improvement, %	47.4 \pm 21	10-97	47.2 \pm 9.9	36-71
Responders, %	60.6 \pm 36.2	0-100	70.7 \pm 24.8	22-100
	Yes/no		Yes/no	
RCT	6/23		1/10	
Depression assessment	21/6		9/11	
Depression improvement	15/4		8/1	
Functionality assessment	16/13		7/4	
Functionality improvement	14/1		7/0	

DBS: Deep brain stimulation; NR: Not reported; RCT: Randomized controlled trial; Y-BOCS: Yale-Brown Obsessive Compulsive scale.

the first 12-24 mo and remained in stable remission for years. A third group of partial responders (22.5% of patients) improved at some point during treatment, but then experienced relapses during follow-up. Although some of the relapses among partial responders were linked to external stressors, such as the loss of a family member[19], device-related events (*e.g.*, battery depletion[41]), or comorbid conditions (*e.g.*, depression or generalized anxiety[42]), no clear external stressors have been associated with relapses in other patients with fluctuating courses[33]. Thus, some patients will be expected to show an oscillating response to DBS that we still cannot explain. Virtually all studies agree that battery depletion is accompanied by severe symptom deterioration, which may be very abrupt[22]. While this finding reinforces the therapeutic benefit of DBS for OCD, it also highlights the need to monitor patients closely for this risk.

Secondary outcomes: Depression and global function

Depressive symptoms: Depressive disorders are the most frequent comorbidity among patients with OCD treated by DBS[10,41,43], with 63.3% being diagnosed with any mood disorder and 40.7% meeting the diagnostic criteria for a major depressive disorder[2]. Twenty-nine of the 40 studies assessed changes in depressive symptoms after DBS implantation, but the use of seven different scales (HDRS, MADRS, BDI, DASS, QIDS, IDS-30, POMS) makes direct comparisons difficult. In most studies, maximum improvement of depressive symptoms was observed in the first year after DBS therapy, regardless of the follow-up period. These improvements tended to parallel those for obsessive symptoms and tended to endure over time[20,21,36] (Table 2), but there was not always a clear correlation. Winter *et al*[28], for example, found a greater decrease in the MADRS score in patients who responded to DBS, whereas both Denys *et al*[44] and Graat *et al*[19] described a significant improvement in depressive symptoms in patients who experienced no change in their OCD symptomatology. In fact, these patients requested continued stimulation despite an improvement in obsessive symptoms. The same research group has previously described the improvement process as a sequence that begins with the amelioration of affective symptoms (in seconds), followed by anxious symptoms (in minutes), obsessive symptoms (in days), and compulsions (in weeks or months)[43]. Unfortunately, a significant worsening of mood symptoms in some patients who respond to

Table 4 Participant characteristics in the short-term studies

	Ref.	n	Female %	Average age (yr)	Average duration of illness (yr)	Average follow-up since DBS implantation (mo)	Target site
RCT	Abelson <i>et al</i> [67], 2005	4	50	40.2	22.5	12.8	ALIC
	Barcia <i>et al</i> [32], 2019	7	57.1	35.2	25.3	21	NAcc/CN
	Goodman <i>et al</i> [16], 2010	6	66	36.2	24	12	VC/VS
	Huff <i>et al</i> [31], 2010	10	40	36.3	22.2	12	NAcc
	Tyagi <i>et al</i> [17], 2019	6	16.6	45.5	24.1	12	VC/VS, STN, VC/VS/STN
	Welter <i>et al</i> [39], 2020	8	12.5	42.5	NR	22	STN, CN, NAcc
Non-RCT	Anderson and Ahmed[74], 2003	1	100	35	10	10	ALIC
	Aouizerate <i>et al</i> [75], 2009	2	0	51	33.5	15	NAcc/CN
	Azriel <i>et al</i> [76], 2020	1	100	67	44	16	amGPI
	Chabardes <i>et al</i> [29], 2020	19	63.1	39	20.7	24	STN
	Chang <i>et al</i> [77], 2017	1	100	28	8	12	VC/VS
	Coenen <i>et al</i> [79], 2017	2	0	41.5	29	12	MFB
	Denys <i>et al</i> [44], 2020	70	69	41.7	25	12	ALIC
	Doshi <i>et al</i> [80], 2019	1	100	42	NR	12	NAcc
	Farrand <i>et al</i> [42], 2018	7	57.1	46	25	31	NAcc or BNST
	Franzini <i>et al</i> [81], 2010	2	0	37	21.5	25.5	NAcc
	Gabriëls <i>et al</i> [53], 2003	3	67	41.7	24.3	27	NAcc/ALIC
	Grant <i>et al</i> [34], 2016	1	0	30	5	36	NAcc
	Huys <i>et al</i> [30], 2019	20	50	40.1	26.1	12	ALIC-NAcc
	Islam <i>et al</i> [40], 2015	8	17	45.8	30.2	25	BNST, NAcc
	Jiménez <i>et al</i> [55], 2013	6	50	34.7	16.2	24	ITP
	Maarouf <i>et al</i> [45], 2016	4	75	39.3	23.5	11.5	MD/VA
	Menchón <i>et al</i> [13], 2021	29	52	41	24.5	12	ALIC
	Mulders <i>et al</i> [82], 2017	1	100	49	34	24	VC/VS
	Plewnia <i>et al</i> [83], 2008	1	100	51	NR	24	ALIC/NAcc
	Roh <i>et al</i> [61], 2012	4	25	45.5	24.2	24	VC/VS
Sachdev <i>et al</i> [84], 2012	1	100	32	28	7	NAcc	
Senova <i>et al</i> [85], 2020	1	100	72	52	36	STN	
Tsai <i>et al</i> [49], 2012	4	0	25.5	8.3	15	VC/VS	

ALIC: Anterior limb on internal capsule; amGPI: Anteromedial globus pallidus internus; BNST: Bed nucleus of stria terminalis; CN: Caudate nucleus; ITP: Inferior thalamic peduncle; MD/VA: Medial dorsal and the ventral anterior nucleus of the thalamus; MFB: Medial forebrain bundle; NAcc: Nucleus

accumbens; NR: Not reported; RCT: Randomized controlled trial; VC/VS: Ventral caudate/ventral striatum.

Table 5 Participant characteristics in the long-term studies

	Ref.	n	Female %	Average age (yr)	Average duration of illness (yr)	Average follow-up since DBS implantation (mo)	Target site
RCT	Luyten <i>et al</i> [20], 2016	24	50	39	NR	77	ALIC/BST
Non-RCT	Choudhury <i>et al</i> [78], 2017	1	100	45	21	51	ALIC
	Fayad <i>et al</i> [33], 2016	6	66	44.5	NR	92.5	VC/VS
	Graat <i>et al</i> [19], 2020	50	68	41.6	25.2	81.6	ALIC
	Gupta <i>et al</i> [35], 2019	2	100	46.5	23	42	VC/VS/ ALIC
	Greenberg <i>et al</i> [36], 2010	26	46	35.3	22	96	VC/VS
	Holland <i>et al</i> [21], 2020	9	44.4	40.2	NR	54.8	VC/VS
	Lee <i>et al</i> [37], 2019	5	60	32.4	16.2	49.8	IIP
	Mallet <i>et al</i> [22], 2019	14	42.8	43.8	NA	46	STN
	Polosan <i>et al</i> [38], 2019	12	67	38.3	18	38	STN
Winter <i>et al</i> [28], 2021	6	33.3	39.6	18	72	ALIC/BNST	

The study sample conducted by Fayad *et al*[33] corresponds to the follow-up of Goodman *et al*[16]'s study sample. Greenberg *et al*[36] conducted a multicenter study in which some patients from Fayad *et al*[33]'s study were included. The patients in the studies by Mallet *et al*[22] and Chabardes *et al*[29] are included in the STOC study. ALIC: Anterior limb on internal capsule; BNST: Bed nucleus of stria terminalis; IIP: Inferior thalamic peduncle; NR: Not reported; RCT: Randomized controlled trial; VC/VS: Ventral caudate/ventral striatum.

DBS has also been observed, which supports the relative independence of the antidepressant and antiobsessive effects[33,42].

Global functioning: Consideration of DBS for OCD presupposes the presence of extremely severe obsessive symptoms that severely impair patient function in all areas of life. The GAF was the most frequently used scale of functionality in the studies included, with median baseline scores of 40 indicating impairment in work or school, family relations, judgment, thinking, or mood[41]. Of the 40 studies analyzed, 23 included an assessment of global functioning as a secondary outcome, using the GAF scale, the Instrumental Activities of Daily Living scale, the Clinical Global Impressions Severity Scale, or the Social and Occupational Functioning Assessment Scale. All but one study reported a progressive and significant improvement in the functionality of patients with OCD after DBS treatment, which was maintained in parallel to their obsessive symptoms in the LT follow-up studies. However, the improvement was not always universal; some studies described the persistence of social difficulties despite an abrupt increase in the GAF scale in the first 24 mo[29]. In the only article to report no functional improvement, stimulation of the medial dorsal and ventral anterior nucleus of the thalamus did not produce any improvement in obsessive symptoms [45].

Adverse effects

The side effects of DBS can also be divided into surgical or hardware-related complications, stimulation-induced side effects, and others[46]. The first observable side effects are those related to the device implant; they are associated with the surgery or the presence of the electrodes in the brain, and are usually temporary. Some patients needed reoperation due to poor electrode positioning[19,44,45] or intracranial infection [36,39] enforcing removal and reimplantation[19,36], a situation that significantly increased the surgical risks. Intracranial hemorrhage was the most severe secondary

Table 6 Summary of results for the short-term studies

	Ref.	Average baseline Y-BOCS	Average Y-BOCS at LFU	Average Y-BOCS improvement (%)	Average responders (%)	Depression (HDRS, BDI, MADRS, DASS, POMS)	Depression scale improvement	Global functionality (GAF, CGIS, SOFAS)	Functionality improvement
RCT	Abelson <i>et al</i> [67], 2005	32.7	23	30	50	Yes, HDRS	Yes	NR	NR
	Barcia <i>et al</i> [32], 2019	32.2	15.4	51	85.7	Yes, HDRS and BDI	No	NR	NR
	Goodman <i>et al</i> [16], 2010	33.7	18	46	67	Yes, HDRS	Yes	Yes, CGISS	Yes
	Abelson <i>et al</i> [67], 2005	32.3	25.4	21	8.3	Yes, HDRS and BDI	Yes	Yes, GAF	Yes
	Barcia <i>et al</i> [32], 2019	36.1	14.1	61	NR	Yes, MADRS	Yes	NR	NR
	Goodman <i>et al</i> [16], 2010	33.5	23.2	30	37.5	Yes, MADRS	No	NR	NR
Non-RCT	Anderson and Ahmed [74], 2003	34	1	97	100	NR	NR	Yes, GAF	Yes
	Aouizerate <i>et al</i> [75], 2009	25	11	56	100	Yes, HDRS	Yes	NR	NR
	Azriel <i>et al</i> [76], 2020	33	16	48	100	NR	NR	NR	NR
	Chabardes <i>et al</i> [29], 2020	33.3	15.8	53	73	NR	NR	Yes, GAF	Yes
	Chang <i>et al</i> [77], 2017	36	25	30	0	Yes, HDRS	NR	Yes, GAF	Yes
	Coenen <i>et al</i> [79], 2017	30	20.5	31	50	Yes, BDI	Yes	Yes, GAF	NR
	Denys <i>et al</i> [44], 2020	33.7	20.2	40	52	Yes, HDRS	Yes	NR	NR
	Doshi <i>et al</i> [80], 2019	19	5	73.7	100	Yes, HDRS	Yes	NR	NR
	Farrand <i>et al</i> [42], 2018	32.8	24	26	42.8	Yes, DASS-D	Yes	Yes, SOFAS	Yes
	Franzini <i>et al</i> [81], 2010	34	20	41	50	Yes, HDRS	Yes	Yes, GAF	Yes
	Gabriëls <i>et al</i> [53], 2003	33.6	21	37.5	66.6	Yes, POMS	No	NR	NR
	Grant <i>et al</i> [34], 2016	32	9	71	100	NR	NR	NR	NR
	Huys <i>et al</i> [30], 2019	30.9	20.7	33	40	Yes, BDI	No	Yes, GAF	Yes
	Islam <i>et al</i> [40], 2015	35.3	20.8	41	50	Yes, HDRS	NR	Yes, GAF	NR
	Jiménez <i>et al</i> [55], 2013	35.8	15.5	56	100	NR	NR	Yes, GAF	Yes
	Maarouf <i>et al</i> [45], 2016	34.7	31	10	0	Yes, BDI	NR	Yes, GAF	No
Menchón <i>et al</i> [13], 2021	34.7	20	42	60	Yes, MADRS	Yes	Yes, GAF	Yes	
Mulders <i>et al</i> [82], 2017	34	17	48	100	NR	NR	NR	NR	

Plewnia <i>et al</i> [83], 2008	31	24	25	0	NR	NR	Yes, GAF	Yes
Roh <i>et al</i> [61], 2012	38	14.8	59.7	100	Yes, HDRS	NR	Yes, GAF	Yes
Sachdev <i>et al</i> [84], 2012	39	5	87.1	100	NR	NR	NR	NR
Senova <i>et al</i> [85], 2020	31	1	96	100	Yes, MADRS	Yes	NR	NR
Tsai <i>et al</i> [49], 2012	36.3	24	33.8	25	Yes, HDRS	Yes	Yes, GAF	Yes

BDI: Beck depression inventory; CGISS: Clinical global impression severity scale; DASS-D: Depression anxiety stress scale-depression; GAF: Global Assessment of Functioning; HDRS: Hamilton depressive rating scale; LFU: Last follow-up; MADRS: Montgomery Asberg Depression rating scale; NR: Not reported; POMS: Profile of mood states; RCT: Randomized controlled trial; SOFAS: Social and Occupational Functioning Assessment scale; Y-BOCS: Yale-Brown Obsessive Compulsive scale.

Table 7 Summary of results for the long-term studies

	Ref.	Average baseline Y-BOCS	Average Y-BOCS at LFU	Average Y-BOCS improvement (%)	Average responders (%)	Depression (HDRS, BDI, MADRS, QIDS, IDS-30)	Depression scale improvement	Global functionality (GAF, IADL, SF-36)	Functionality improvement
RCT	Luyten <i>et al</i> [20], 2016	35	19.3	45	67	Yes, HDRS	Yes	Yes, GAF	Yes
Non-RCT	Choudhury <i>et al</i> [78], 2017	37	21	43	100	Yes, BDI	Yes	Yes, IADL	Yes
	Fayad <i>et al</i> [33], 2016	33.6	15.1	55	66	Yes, HDRS	No	Yes, SF-36	Yes
	Graat <i>et al</i> [19], 2020	33.3	20.5	39	50	Yes, HDRS	Yes	Yes, GAF	Yes
	Gupta <i>et al</i> [35], 2019	38	11	71	100	Yes, BDI	Yes	NR	NR
	Greenberg <i>et al</i> [36], 2010	34	21.5	36	61	Yes, HDRS	Yes	Yes, GAF	Yes
	Holland <i>et al</i> [21], 2020	34.5	20.7	40.3	22	Yes, HDRS, MADRS, QIDS, IDS-30 and BDI	Yes	Yes, GAF	NR
	Lee <i>et al</i> [37], 2019	35	16	54	100	Yes, HDRS	Yes	NR	NR
	Mallet <i>et al</i> [22], 2019	32.4	15.4	50	75	Yes, BDI	Yes	Yes, GAF	Yes
	Polosan <i>et al</i> [38], 2019	34.3	20	41	NR	NR	NR	NR	NR
	Winter <i>et al</i> [28], 2021	32.1	17.7	45	66	Yes, BDI	Yes	NR	NR

BDI: Beck depression inventory; GAF: Global Assessment of Functioning; HDRS: Hamilton depressive rating scale; IADL: Lawton instrumental activities of daily living scale; IDS-30: Inventory of depressive symptomatology; LFU: Last follow-up; MADRS: Montgomery Asberg Depression rating scale; NR: Not reported; QIDS: Quick inventory of depressive symptomatology; RCT: Randomized controlled trial; SF-36: Short form survey; Y-BOCS: Yale-Brown Obsessive Compulsive scale.

effect related to surgery. Although its frequency was very low in most studies[13,22], in others[20,36] rates were as high as 4.8% or 7.7%. Seizures have been described during both ST follow-up[13,36,40] and LT follow-up after 2-5 years[20], with poor electrode positioning[13], intracranial infection[40], somatic complications (*e.g.*, hypoglycemia), and abrupt changes in the stimulation parameters cited as risk factors [40].

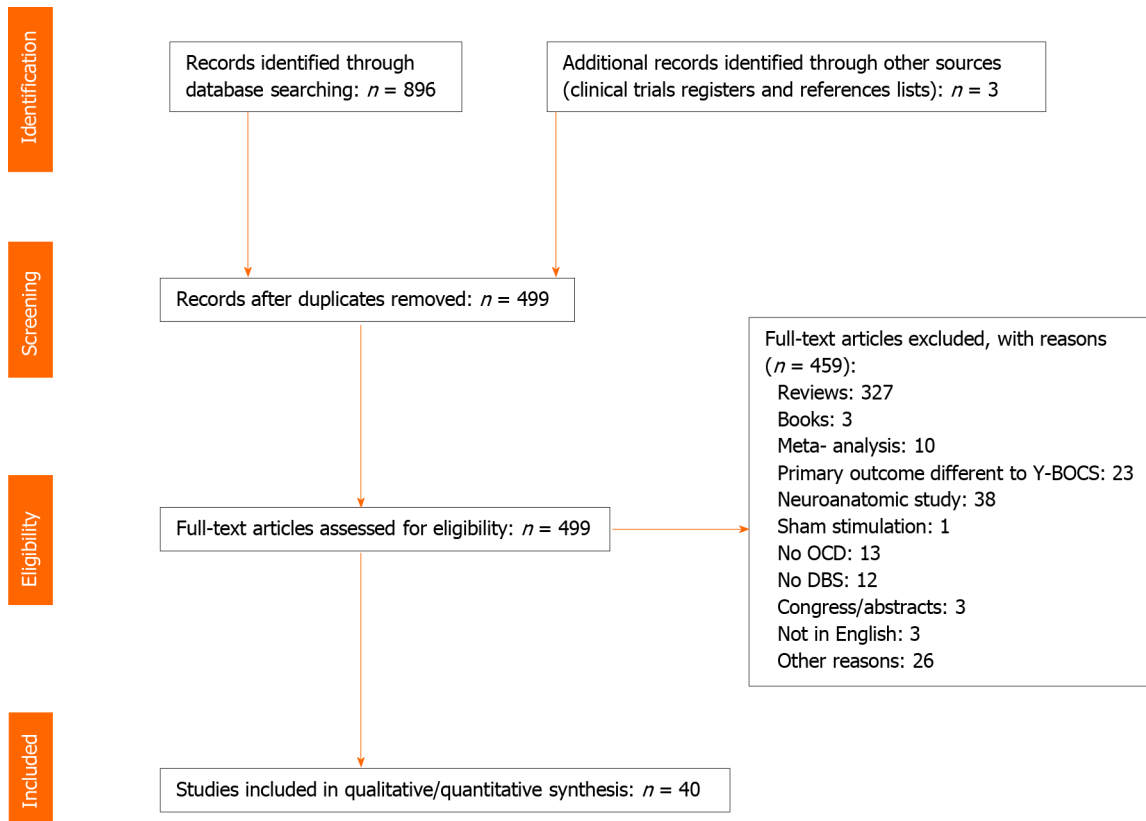


Figure 1 PRISMA flow diagram for add-on deep brain stimulation and obsessive-compulsive disorder in PubMed, Cochrane, Scopus databases and ClinicalTrials.gov databases. DBS: Deep brain stimulation; OCD: Obsessive-compulsive disorder; Y-BOCS: Yale-Brown Obsessive-Compulsive scale.

The most frequent side effect of stimulation is hypomania[21,22,43], although this usually resolves after adjusting the stimulation parameters[16,47,48]. Hypomania has been reported to be a predictor of good response to DBS in other studies, and this has confused the perceptions of its relevance as a side effect[48,49]. Denys *et al*[44] attributes the occurrence of hypomanic symptoms to the stimulation of the anterior limb of the internal capsule (ALIC) and argues that they should be considered not as an adverse effect but as a sign of effective treatment. However, the predictive utility of hypomania is controversial, because other authors have reported that it occurs equally in DBS responders and non-responders[44]. Indeed, the risk of manic and hypomanic symptoms may be modulated by clinical factors, with right monopolar stimulation and female sex predicting manic symptoms during DBS[50,51]. Other adverse effects related to stimulation include insomnia or sleep disturbances[16,33], weight gain[19], fatigue, subjective cognitive problems[19,52], and increased anxiety. Despite subjective reports of cognitive complaints, studies specifically addressing neuropsychological performance have detected no significant impact of DBS[16,20,53].

The relationship between DBS and the risk of suicide attempts or suicide is also controversial. Suicide may be related to the disease itself, to the DBS, or to the ineffectiveness of the treatment. Fernández de la Cruz *et al*[54] reported that patients with severe OCD symptoms were more likely to present suicide attempts (odds ratio = 5.45) and die from suicide (odds ratio = 9.83), and that a history of prior suicide attempt was the strongest predictor. Most studies associate suicide attempts or suicide after DBS in patients with OCD to a comorbid diagnosis of major depressive disorder[19,28,29] or to a lack of response to DBS and the persistence of disabling symptoms[19,20,29]. Comorbidities, including drug use and personality disorders, also appear to increase the risk of death by suicide during DBS among patients with OCD[22,55]. Finally, Graat *et al*[19] reported death by euthanasia in two nonresponding patients with no history of suicide attempts and an average of 4.5 years from DBS implantation to death.

We found no significant differences in these adverse effects between the ST and LT studies.

Predictors of response

DBS is not only expensive but also poses the risk of severe side effects. Given the risks involved, the significant consumption of human and clinical resources, and the need for lifelong follow-up, establishing reliable predictors of response would help to improve patient selection, guide DBS implantation, and optimize stimulation parameters. To date, however, no clinical variables or biomarkers have been clearly defined, probably because of the heterogeneity of the neuroanatomical targeting, the electrodes used, and the stimulation protocols.

Clinical variables: Few published studies have addressed the existence of clinical predictors of response to DBS. Among those that have, most have failed to uncover any clear predictive factors. In the study by Huys *et al*[30], gender, age, preoperative severity (Y-BOCS score), and personality traits did not predict patient improvement after DBS. Similarly, Chabardes *et al*[29] detected no significant differences by age at OCD onset, age at surgery, disease duration, or obsession and compulsion types between responders and nonresponders after 24 mo of subthalamic nucleus (STN)-DBS; however, they detected a significantly higher female-to-male ratio in the responder group, with all females meeting the response criteria. Nevertheless, contradictory results have been reported for age at OCD onset. In a meta-analysis of 16 studies Alonso *et al*[9] reported that patients with later onset OCD exhibited higher response rates and greater Y-BOCS reductions, whereas Mallet *et al*[22] found that patients with early onset OCD showed better LT outcomes after 46 mo of STN-DBS. In another meta-analysis, Martinho *et al*[10] observed that illness duration positively predicted ST response in RCTs, but not LT response in the open phases of those studies. Illness severity at baseline did not predict ST response, but it negatively predicted response at the last follow-up.

Differences in response to DBS between specific symptom profiles have also been hypothesized, as occurs with selective serotonin reuptake inhibitors and CBT. Intuitively, this is highly probable in a focal neuromodulating tool like DBS in which the different symptom dimensions of OCD are reported to have partially distinct neural substrates[56]. Nevertheless, the data on this topic are scarce and often contradictory. Many published trials lack detailed descriptions of symptom profiles and no single study has used a specific psychometric tool to assess OCD symptom dimensions. Two of the ten patients in the study by Greenberg *et al*[57] who had the poorest response to ventral caudate (VC)/ventral striatum (VS) DBS suffered OCD symptoms motivated principally by a feeling of incompleteness and a need to repeat actions until they felt that everything was “just right”. Nevertheless, four other patients who also reported “just right” experiences significantly improved with DBS. Patients with contamination and washing symptoms showed lower response to DBS (45.5%) than those who suffered doubts and checking compulsions (100%).

According to Denys *et al*[43], patients needing perfection, symmetry, or reassurance, as well as those with hoarding, showed poor response to nucleus accumbens (NAcc) stimulation. In other series[49,58-61], patients with symmetry or ordering obsessions and compulsions have been reported to respond to DBS. Results for hoarding symptoms are also controversial. Welter *et al*[39] described that hoarding was the main symptom in one of two patients resistant to DBS of the STN, NAcc, and caudate nucleus; by contrast, Fontaine *et al*[62] reported that prominent hoarding symptoms almost disappeared after STN stimulation in a patient with Parkinson's disease, while Guehl *et al*[60] described a woman with hoarding, contamination/cleaning, and symmetry/ordering symptoms who improved significantly with caudate nucleus stimulation. Similarly, some authors have reported that somatic obsessions improve with DBS[59], but others have not[53]. In the meta-analysis by Alonso *et al*[9], it was notable that the presence of sexual or religious obsessions and compulsions was associated with a better response.

Interestingly, two recent studies by Barcia *et al*[32,63] raise the possibility of personalizing the targets in DBS in patients with OCD depending on the obsessional focus. They stimulated seven patients with OCD by placing a tetrapolar electrode along the striatum and observed that those with mainly washing obsessions and compulsions responded better to the more ventral contacts, while those presenting checking, ordering, and incompleteness symptoms responded better to activation of the more dorsal contacts. The authors concluded that the most effective neuroanatomical target structure for each patient could be calculated by combining a preoperative index derived from functional MRI symptom provocation and probabilistic tractography.

Electrode location, intraoperative changes and electrophysiological data: Haq *et al* [48] first reported that patients who showed higher percentages of laughing conditions

(smiling or laughter with euphoria) during intraoperative DBS testing for electrodes placed at the ALIC and NAcc showed the greatest reduction in Y-BOCS scores in the LT. Similarly, Tsai *et al*[49] reported that the appearance of smiling/Laughter on postoperative test stimulations performed two weeks after implantation at the VC/VS also significantly predicted good response in the LT (at 15 mo). Goodman *et al*[16] reported that experiencing hypomania as an early stimulation-induced side effect made clinical response more likely. Hypomania is the most frequent side effect of DBS programming in OCD and is reported to affect 40%-45% of subjects[44,50], but it remains unclear whether it necessarily predicts a good response to DBS in OCD.

Optimal electrode location is an anatomical factor that markedly affects response to DBS. Current targets in OCD include the ALIC, the VS, the anteromedial limbic STN, and midbrain. These four targets affect orbitofrontal cortex (OFC) or anterior cingulate cortex (ACC) connections passing through, entering, or leaving the internal capsule. This explains why stimulation at different brain locations can target different components of the same circuit. To optimize outcomes, the initial electrode position within the ALIC has changed over the years; several studies have concluded that more posteriorly targeted stimulation at the bilateral bed nucleus of the stria terminalis and the VC/VS near the ACC appears to improve outcomes, producing greater symptom reduction than more dorsal or anterior stimulation of the ALIC[13,20,36] or NAcc[40]. Although most studies indicate that differences between targets in relation to the antiobsessive effect of DBS are not significant, the different electrode locations do produce specific effects: For example, DBS of the anteromedial STN, but not the VC/VS, improves cognitive flexibility, while DBS of the VC/VS achieves greater mood improvement than STN stimulation[17].

Regarding electrophysiological measures, Welter *et al*[64] reported a correlation between presurgical STN neuronal activity and response to bilateral high-frequency STN stimulation. Good response was associated with higher mean presurgical neuronal discharges, bursts, and intraburst frequencies, but with lower mean presurgical interburst intervals. van Westen *et al*[65] replicated these findings and reported that patients with lower interburst intervals and higher intraburst frequencies had the best Y-BOCS outcome.

Neuroimaging data: With respect to neuroimaging data, in a small sample (six patients) Van Laere *et al*[66] found that higher preoperative activity in the subgenual ACC assessed by positron emission tomography with fluorodeoxyglucose integrated with computed tomography (¹⁸F-FDG PET/CT) correlated with greater response to DBS. Abelson *et al*[67] reported that such scans detected decreased OFC activity in only two of four patients who responded to bilateral ALIC stimulation, suggesting that DBS improves OCD symptoms only when it restores the inhibitory function of the ventral cortico-striato-thalamo-cortical pathway. Le Jeune *et al*[68] similarly reported a reduction in Y-BOCS after DBS that correlated with decreased metabolic activity in the ventro-medial prefrontal region of the OFC. Regarding connectivity, Figuee *et al*[69] detected that clinical improvement after DBS correlated with a normalization of functional connectivity in the NAcc prefrontal cortex, and Baldermann *et al*[70] recently showed that response to DBS could be predicted by analyzing the effects of stimulation on structural connectivity to prefrontal and frontal regions. Modulation of structural connectivity to the right middle frontal gyrus with DBS was associated with a better clinical response in a sample of six patients, whereas changes in connectivity to the OFC were associated with nonresponse. The same group has recently reported that response to ALIC and STN in four OCD cohorts predicted whether electrodes could or could not stimulate a fiber bundle connecting medial prefrontal regions to the STN[71].

DISCUSSION

In this study we aimed to summarize the efficacy and tolerability of DBS for treatment-resistant severe OCD, comparing ST and LT response to stimulation, and assessing whether different patterns and predictors of response emerged from the data available from 40 studies including a total of 344 patients. Of these, 29 studies (with 230 patients) covered ST response over an average of 18.5 mo, and 11 studies (with 155 patients) covered LT response over an average of 63.7 mo. The mean decreases in Y-BOCS scores from baseline to final follow-up were 47.4% in the ST studies (Y-BOCS fell from 33 to 17.2) and 47.7% in the LT studies (Y-BOCS fell from 34.4 to 18). The percentage of responders increased from 60.6% in the ST studies to 70.7% in the LT

studies, indicating that DBS provided effective therapy for severe resistant OCD in at least two-thirds of subjects in the long term, comparable with data published in previous meta-analyses[9-11]. Our results suggest that the first year of stimulation is critical to obtaining benefit from DBS. Three patient groups could be described according to their pattern of LT response to DBS: sustained good responders (49.5%), persistent non responders (resistant patients with no or almost no improvement) despite treatment adjustments (28.1%), and fluctuating responders who presented relapses of their symptoms irrespective of environmental factors (22.5%). At this point no clear predictors of response can be established, in terms of either clinical features or biomarkers.

Although DBS in OCD is far less effective than in neurological disorders such as essential tremor, its therapeutic potential should not be overlooked if we consider that candidates for DBS have typically proven treatment-resistant. Indeed, they usually show no improvement with multiple pharmacological approaches, including all selective serotonin reuptake inhibitors, clomipramine, and various antipsychotics, as well as prolonged and intensive CBT. The fact that two-thirds of these severely disabled and highly resistant patients improve on DBS supports the efficacy of direct electrical modulation of hypothesized dysfunctional circuits in OCD. Along these lines, recent proposals to individualize anatomical targets by brain connectivity findings or symptoms hold out promise for future improvements[32].

The results of published studies are limited to adult patients with OCD. Candidates for DBS must meet strict criteria in order to be considered for electrode implantation: their Y-BOCS scores must indicate severe to extreme OCD and they must present serious impairment in daily functioning lasting more than five years despite a minimum of three adequate pharmacological trials and cognitive-behavioral therapy. Even for patients with early-onset OCD in childhood or adolescence, it takes years to meet these criteria. In fact, in the studies assessed here mean illness duration before DBS implantation was around 24 years. It is unknown at this time if younger patients or patients with shorter disease progression might be better candidates for DBS.

What can be offered to patients with treatment resistance or limited/fluctuating response to DBS? Several studies indicate the usefulness of retrying CBT after implanting electrodes in order to target rituals that persist even though patients experience fewer intrusive thoughts or less associated emotional distress[19]. In these cases, the rituals may have been a part of their lives for years and may have become habitual. For subjects resistant to DBS, especially those in whom suboptimal electrode placement is confirmed, reimplantation of the electrodes at different targets may be appropriate. There are some reports of cases that have been successfully managed in this way, in spite of the surgical risks [19]. Studies in which more than two electrodes are implanted in the same patient, allowing the stimulation of limbic and non-limbic areas, suggest that some subjects respond to the stimulation of certain anatomical targets but not others, even though these features share the cortico-striato-thalamo-cortical pathway. Finally, subjects who exhaust all DBS options should still be considered for stereotactic surgery. Neuroablative surgical techniques have improved dramatically in recent years, showing optimized results and reduced side effects[72]. In a recent meta-analysis, ablative neurosurgery for OCD obtained a greater reduction in Y-BOCS scores than DBS (50.4% *vs* 40.9% reductions) and also produced fewer adverse effects (in 43.6% *vs* 64.6% of patients)[73].

DBS is not without adverse effects. Although most are mild and transient, and can usually be resolved by modifying the stimulation parameters, some serious adverse effects are possible. Among the psychiatric effects, hypomania was the most commonly identified in the present review, but it remains unclear whether this is a predictor of DBS response or an inevitable consequence of the treatment's mechanism of action. Another topic that deserves special attention is the risk of suicide and death by suicide among patients with OCD who are treated with DBS. Most studies relate this risk to the presence of comorbid major depressive disorder or the absence of an adequate response to DBS[19,29]. The presence of excessive and unrealistic expectations of improvement after stimulation also seems to increase the risk of suicidality [13]. It is therefore essential that patients receive clear and realistic information about their expected response to DBS and are aware that several months of treatment and multiple adjustments are often necessary before an adequate response is achieved. Careful ongoing assessment of suicide risk is required, especially in the presence of comorbid major depressive disorder and nonresponse.

To date, it has not been possible to establish clear predictors of response to DBS that might help to improve patient selection or treatment application. In fact, the significant heterogeneity in the targets proposed for stimulation and the absence of standardized programming settings have meant that DBS has remained an experimental therapeutic

option for OCD, with limited scientific proof of its efficacy. Recent efforts to develop measurable biomarkers using fMRI, tractography, or electroencephalography may help to develop a more personalized approach to DBS, and thus identify more accurately the patients most likely to benefit from a treatment with a very high economic cost and significant risks.

Our review has several limitations. We decided not to restrict our search to RCTs and included open studies, series, and published clinical cases, which represented 79% of ST studies and 91% of LT studies. Although this makes our results more representative, it also limits their methodological validity because we were unable to adequately control for biases and for the risk of a placebo response. The marked heterogeneity among the studies reviewed, including sample size, study design, stimulation parameters, anatomical targets, and psychometric tools for defining primary and secondary outcomes, also makes any meaningful comparison difficult. Finally, many groups use other therapeutic approaches (*e.g.*, CBT) concurrently with DBS or do not define whether pharmacological treatments are interrupted after DBS implantation. Therefore, we cannot be sure that the beneficial effects attributed to DBS were not in fact due to a multimodal treatment approach.

CONCLUSION

In conclusion, the present review confirms that DBS is a promising therapy for patients with severe resistant OCD, with evidence of efficacy in the short and long term. There remain many unknowns, including the optimal anatomical targets, the criteria for standardized stimulation protocols, and the identification of biomarkers or factors that predict outcomes and allow treatment individualization. To achieve a progressive improvement of DBS outcomes, we strongly recommend that this approach be applied only at centers that can guarantee access to multidisciplinary teams comprising not just neurosurgeons with experience in functional surgery but also psychiatrists and behavioral therapists with adequate expertise in the pharmacological and psychotherapeutic management of severe OCD. This strategy will ensure the selection of suitable potential candidates, the timely implementation of advances in surgical techniques, improved postoperative management, optimization of stimulation parameters, and the concomitant use of other therapies like CBT. The development of an international registry with clinical, programming, and neuroimaging data on all patients undergoing DBS for treatment-resistant OCD would also contribute to expanding our knowledge of this technique, which constitutes the last therapeutic option for many patients with severe OCD.

ARTICLE HIGHLIGHTS

Research background

Twenty years after the first deep brain stimulation (DBS) implantation in a patient with obsessive-compulsive disorder (OCD), we review all the information published to date regarding the efficacy and tolerability of this therapeutic option for severe obsessive patients resistant to pharmacological approaches and behavioral therapy.

Research motivation

There are still many unknowns regarding the benefits and risks of using DBS in OCD. The main ones are the optimal anatomical targets, the best stimulation parameters, the long-term effects of the therapy or the possibility of establishing clinical or biological factors associated with response. Responding to them would allow optimizing the results of this therapeutic alternative, with a high economic and human resources cost, and not without potentially serious risks.

Research objectives

The main objectives of this systematic review were to summarize existing knowledge regarding efficacy and tolerability of DBS in treatment-resistant OCD as well as to analyze the possible existence of response predictors that allow improving the selection of candidates. We confirmed that DBS proved to be an effective and safe alternative for two out of three severe and resistant OCD patients who received it. Although we did not detect any clear predictor of response, there are promising proposals based on the use of neuroimaging tools to individualize treatment that

should be analyzed in depth in future research.

Research methods

We performed a comprehensive search in the PubMed, Cochrane, Scopus, and ClinicalTrials.gov databases from inception to December 31, 2020 with “(Obsessive-compulsive disorder OR OCD) AND (deep brain stimulation OR DBS)” as searching strategy. Inclusion criteria were a main diagnosis of OCD, DBS conducted for therapeutic purposes in humans and variation in symptoms of OCD measured by the Yale-Brown Obsessive-Compulsive scale (Y-BOCS) as primary outcome. Data was recorded using a standardized collection tool and analyzed with descriptive statistics. Risk of bias was assessed using the Cochrane Handbook for Systematic Reviews of Interventions for randomized controlled trials and the Newcastle-Ottawa Scale for observational studies.

Research results

Our systematic review detected 40 studies fulfilling inclusion criteria. 29 of them reported results on short-term response to DBS in 230 patients (follow-up: 18.5 ± 8 mo, range: 7-36) and eleven on long-term response in 155 subjects (63.7 ± 20.7 mo, range: 38-96). Mean Y-BOCS reduction reported on short-term studies was $47.4\% \pm 21\%$ and on long-term studies $47.2\% \pm 9.9\%$, confirming the long-term stability of the response. A significantly greater number of patients fulfilled criteria for response (Y-BOCS reduction $> 35\%$) on the long-term studies (70.7%) than in the short-term ones (60.6%), although the maximum symptom reduction was achieved in general in the first 12-14 mo after DBS implantation. Comorbid depressive symptoms tend to improve in parallel to obsessive symptoms, although this correlation was not observed in all patients. DBS was well-tolerated by most OCD patients, with reversible hypomania as the most frequently reported side effect associated to stimulation. No clear clinical or biological predictors of response emerged from our data, probably due to the high heterogeneity on DBS application conditions in OCD patients.

Research conclusions

Our results underscore the importance of exploring new strategies that allow individualizing the conditions of application of DBS in OCD, combining neuroimaging data and a detailed analysis of the patient's symptoms.

Research perspectives

Future directions on research on DBS application in OCD should focus on establishing which individual factors at the clinical and/or neuroimaging level can allow us to establish which will be the target and the optimal stimulation conditions for each patient, since the results show that although the standard application of the technique is effective and safe for 2 out of 3 operated patients, there are still patients who do not benefit from the treatment.

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