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Deep brain stimulation for obsessive compulsive disorder: A review of results by anatomical target

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Abstract

Studies suggest deep brain stimulation (DBS) as a treatment modality for the refractory obsessive-compulsive disorder (OCD). It is unclear where to place the DBS. Various sites are proposed for placement with the ventral capsule/ventral striatum (VC/VS) among the most studied. Herein, we aim to summarize both quantitative Yale-Brown Obsessive-Compulsive Scale (YBOCS) data and qualitative descriptions of the participants' symptoms when given. A literature search conducted via PubMed yielded 32 articles. We sought to apply a standard based on the utilization of YBOCS. This yielded 153 distinct patients. The outcome measure we focused on in this review is the latest YBOCS score reported for each patient/cohort in comparison to the location of the DBS. A total of 32 articles were found in the search results. In total, 153 distinct patients' results were reported in these studies. Across this collection of papers, a total of 9 anatomic structures were targeted. The majority of studies showed a better response at the last time point as compared to the first time point. Most patients had DBS at nucleus accumbens followed by VC/VS and the least patients had DBS at the bilateral superolateral branch of the median forebrain bundle and the bilateral basolateral amygdala. The average YBOCS improvement did not seem to directly correlate with the percentile of patients responding to the intervention.

Well-controlled, randomized studies with larger sample sizes with close follow up are needed to provide a more accurate determination for placement of DBS for OCD.

Introduction

OCD is a disabling psychiatric disorder with a lifetime prevalence of 2.3%. OCD patients spend an average of nearly 6 hours per day occupied with intrusive obsessions and performing compulsions or rituals.[1] Few OCD patients achieve full remission of symptoms. Even in patients receiving a combination of clomipramine, exposure therapy, and ritual prevention therapy, approximately one third do not respond to treatment.[2,3]

Many recent studies suggest stereotactic DBS as a promising treatment modality that may address OCD refractory to current therapies. DBS has been approved by the FDA for treatment of movement disorders; notably, Weaver et. al. demonstrated that DBS led to superior six-month outcomes compared to best medical therapy in advanced Parkinson disease.[4] DBS remains an investigational treatment for the indication of OCD, but may be used in accordance with a Humanitarian Device Exemption.[5]

Once implanted, the parameters of the electrodes in a DBS device can be adjusted according to a patient's response to treatment. This affords a customizability that makes DBS more likely to be effective in each individual patient. By activating or deactivating specific electrodes in the implanted device, even the location of neuro-stimulation can be slightly adjusted without requiring repeat surgical intervention and re-implantation.

Meta-analysis of the many studies of OCD treatment with DBS remains limited by small sample sizes for each anatomic location, varying psychiatric and medical comorbidities of participants, and the heterogeneous approaches used to report results.[6] Most of these cases and studies use the Yale-Brown Obsessive-Compulsive Scale (YBOCS) to quantify the severity of patients' symptoms before and after treatment; as such, this is the best metric with which to analyze the compiled results. However, the time points at which these scores are collected vary, and they might be reported for each individual patient or in the aggregate. Moreover, the YBOCS is not sensitive to some changes in symptoms. A decrease in the number of hours spent per day on compulsions from 8 hours to 3 hours would not yield a change in score. Therefore, we aim to summarize per each location both quantitative YBOCS data and qualitative descriptions of the participants' symptoms.

Materials and Methods

PubMed was used to search for relevant literature using the terms: "obsessive compulsive disorder," "OCD," "deep brain stimulation," "DBS," and "electrical stimulation." Only studies in humans were considered. No patients were eliminated from the review on the basis of comorbid psychiatric or medical conditions. Studies not using the YBOCS as an outcome measure were not included. Cohorts of patients whose results were reported in multiple articles were counted once.

In some patients, DBS was not an effective treatment for their OCD symptoms at the first implanted location and the device was surgically removed and re-implanted elsewhere. In these situations, patients were counted as two separate trials. Patients whose devices stimulated two anatomic regions simultaneously were counted once.

Patients for whom an individual post-treatment YBOCS score was given were combined to give an overall mean reduction in YBOCS score. In order to include studies which only reported the number of patients responding to treatment (with a response being a reduction in YBOCS of 35% or more), rather than a degree of response for each individual, the percentage responders were also calculated where applicable. This threshold for determination of responders versus non-responders was the most commonly used in the literature, and is therefore used here; however, we aim to identify and qualitatively discuss non-responders with clinically relevant improvements in their symptoms of OCD.

Follow-up times among these studies varied from one month to nine years, with some patients being re-tested on the YBOCS very frequently and some only once. Therefore, the outcome measure we

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Table 1. Studies by anatomic site.

B VC/VS	NA	ST	BN ST	BAIC	AM GP	ITP	B SL MFB	MD/V ANT	BLA
**Greenberg 2006[12] & 2010[13]	*Sturm 2003[21]	Mallet 2002[29] & 2008[30]	*Luyten 201633, some patients	Anderson 2003[35]	*Nair 2014[38]	**Jimenez 2009[39] & 2013[40]	Coenen 2017[41]	Maarouf 2016[28] *** (1st and 2nd trial)	Maarouf 2016[28] *** (3rd trial)
Goodman 2010[14], **Vora 2012[15], **Fayad 2016[16] Tsai 2010[17] & 2012[18]	Guehl 2008[22]	Fontaine 2004[31]	(includes	Abelson 2005[36]					
Real 2016[19] *** (2nd trial)	Plewnia 2008[23]	*Piallat 2011[32]	**Nuttin 2013[34])	Chang 2010[37]					
Williams 2016[20] *** (2nd trial)	Denys 2010[24]	Williams 2016[20] *** (1st trial)		Maarouf 2016[28] (with NAcc)					
	Huff 2010[25]	Wojtecki 2016		***(1st trial)					
	Franzini 2010[26]			Luyten 201633, some patients					
	Grant 2016[27]								
	Real 2016[19] ***(1st trial)								
	Kohl 2016								
	Maarouf 2016[28] (with ALIC)								
	***(1st trial)								

*Study did not use YBOCS, eliminated; **duplicate patients; ***more than one anatomic location tried per patient. B VC/VS- Bilateral ventral capsule/ventral striatum; NA- Nucleus accumbens (bilateral and unilateral); ST- Subthalamic nucleus (bilateral); BN ST- Bed nucleus of stria terminalis; BAIC- Bilateral anterior internal capsule; AM GP- Anteromedial globus pallidus interna; ITP- Inferior thalamic peduncle; B SL MFB- Bilateral superolateral branch of the median forebrain bundle; MD/V ANT- Bilateral medial dorsal and ventral anterior nucleus of the thalamus; BLA- Bilateral basolateral amygdala.

focus on in this review is the latest YBOCS score reported for each patient/cohort. The latest time point was not used if a significant number of patients dropped out of the study before that point. YBOCS score at earliest post-op time point tested was included when given.

Results

A total of 32 articles were found in the search results. Four were eliminated from consideration due to the absence of YBOCS scores. Three papers reported on the same cohort of six patients; two papers used data

Table 2. Ventral capsule/ventral striatum.

Study	N.	Average YBOCS reduction at first time point	Responders at first time point	Average YBOCS reduction at latest time point	Responders at last time point
Greenberg 2006[12] and 2010[13]	26	not given at 1 month	7/25	38% at >3 months	16/26
Tsai 2010[17] and 2012[18]	4	n/a	n/a	35% at x months	2/4
Goodman[14], Vora[15], Fayad[16]	6	12 months	4/6	6-9 years	4/6
Real, trial 2[19]	1	32% at 16 wks	0/1	42% at 1 yr	1/1
Williams[20], trial 2	1	n/a	n/a	69% at 9 months	1/1

Table 3. Nucleus accumbens.

Study	N.	Average YBOCS reduction at first time point	Responders at first time point	Average YBOCS reduction at latest time point	Responders at last time point
Guehl, bilateral[22]	3	not given	n/a	35-60% at one year. No average given	3/3
Plewnia, unilateral[23]	1	25% at 4 wks	0/1	21.9% at 2 years	0/1
Denys, bilateral[24]	16	46% at 32 weeks, open	9/16	52% at 21 months	?/14
Huff, unilateral[25]	10	not given	n/a	21% at 1 year	1/10
Franzini, bilateral[26]	2	not given	n/a	38% at 24-27 months	2/2
Grant, bilateral[27]	1	69% at 8 months	1/1	69-75% at 3 years	1/1
Real, bilateral, trial 1[19]	1	not given	n/a	7.9% at 2 years	0/1
Maarouf[28], bilateral, patient 3, trial 1	1	not given	n/a	not given	0/1
Kohl, bilateral	18	not given	4/18	not given	6/12

Table 4. Anterior limb of the internal capsule.

Study	N.	Average YBOCS reduction at first time point	Responders at first time point	Average YBOCS reduction at latest time point	Responders at last time point
Anderson[35]	1	79.4%	1/1	97.1%	1/1
Abelson[36]	4	20.0% (double blind)	1/4 (double blind)	30.25% (open)	2/4 (open)
Chang[37]	1	0%	0/1	11.1%	0/1
Luyten[33], bilateral	4	not given	n/a	20% at >4 years	0/4
Luyten[33], bilateral, adjacent to NAcc	2	not given	n/a	26% at >4 years	1/2
Luyten[33], bilateral, adjacent to BST	1	not given	n/a	76% at >4 years	1/1
Luyten[33], bilateral ALIC, left adjacent to BST and right in BST	1	not given	n/a	57% at >4 years	1/1
Luyten[33], right in ALIC, left in BST	1	not given	n/a	67% at >4 years	1/1
Maarouf[28], patients 1 and 2 (with NAcc), trial 1	2	not given	n/a	not given	0/2

from the same cohort of eight, and; another two reported on the same five patients. One additional paper was a case study of a patient included in another cohort. In total, 153 distinct patients' results were reported in these studies. Across this collection of papers, a total of nine anatomic structures were targeted (Table 1). Patients in whom the device was re-implanted in a different location had each of their trials counted separately. There was a total of 158 trials for these 153 patients.

The majority of studies showed a better response at the last time point as compared to the first time point (Tables 2-7).[7-41]

Most patients had DBS at nucleus accumbens followed by VC/VS and the least patients had DBS at the bilateral superolateral branch of the median forebrain bundle and the bilateral basolateral amygdala (Table 8). The average YBOCS improvement did not seem to directly correlate with the percentile of patients responding to the intervention.

Discussion

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. But we also must consider that patients with clinical benefit who did not always meet the "responder" threshold.

Studies with fewer than 4 participants were generally more likely to have positive findings, likely due to publishing bias; we are able to see results of negative case studies in situations where stimulators were eventually re-implanted in a location that produced better results.

The question remains the same, what is the best location to implant the device? Several anatomic locations have been targeted in DBS for the indication of OCD. The VC/VS is among the most studied, followed by the nucleus accumbens.[7-9] Data is amassing for these few aforementioned locations and fortunately, new locations are being explored with both positive and negative results. Less-studied locations include the subthalamic nucleus, inferior thalamic peduncle, anterior limb of the internal capsule, anteromedial globus pallidus, superolateral branch of the median forebrain bundle, medial dorsal and ventral anterior nucleus of the thalamus, and bed nucleus of the stria terminalis.[10 11]

Furthermore, the studies that measured YBOCS score at multiple time points demonstrate that response to stimulation does not all occur at the beginning of thera-

Table 5. Subthalamic nucleus.

Study	N.	Average YBOCS reduction at first time point	Responders at first time point	Average YBOCS reduction at latest time point	Responders at last time point
Mallet *et al.* 2002[29]	2	81.6% at 2 weeks or 1-6 month, can't tell from table	2/2	n/a	n/a
Mallet *et al.* 2008[30]	16	32.1% compared to sham stimulation, 40.6% compared to baseline	not given, but guessing from graph, 10/16	n/a	n/a
Fontaine *et al.* 2004[31]	1	96.9% at 1 year	1/1	n/a	n/a
Williams, trial 1[20]	1				
Wojtecki	1	92.3% at 3 years	1/1	n/a	n/a

Table 6. Bilateral medial dorsal and ventral anterior nucleus of the thalamus; bilateral superolateral branch of the median forebrain bundle; inferior thalamic peduncle; bilateral basolateral amygdala.

Study	N.	Average YBOCS reduction at first time point	Responders at first time point	Average YBOCS reduction at latest time point	Responders at last time point
Bilateral medial dorsal and ventral anterior nucleus of the thalamus					
Maarouf[28], pts 1-3 trial 2, pt 4 trial 1	4		0/4	not given	0/4
Bilateral superolateral branch of the median forebrain bundle					
Coenen[41]	2	31.5% at 1 month	1/2	41.7% at 12 months	1/2
Inferior thalamic peduncle					
Jimenez 2013[40]	6	8.4% at 1 month	0/6	49% at 12 months	6/6
Bilateral basolateral amygdala					
Maarouf[28], patient 3, 3rd trial	1	not given	n/a	not given	0/1

Table 7. Bed nucleus of stria terminalis (BST).

Study	N.	Average YBOCS reduction at first time point	Responders at first time point	Average YBOCS reduction at latest time point	Responders at last time point
Bilateral medial dorsal and ventral anterior nucleus of the thalamus					
Luyten[33], bilateral	9	not given	n/a	42% at >4 years	6/9
Luyten[33], unilateral right	1	not given	n/a	77% at >4 years	1/1
Luyten[33], left in BST, right in IC adjacent to BST	2	not given	n/a	51% at >4 years	2/2
Luyten[33], right in BST, left in IC adjacent to BST	1	not given	n/a	58% at >4 years	1/1
Luyten[33], bilateral in prereticular zone, BST adjacent	1	not given	n/a	35% at >4 years	1/1
Luyten[33], bilateral in IC, BST adjacent	1	not given	n/a	95% at >4 years	1/1

Table 8. Response per location.

Location	N.	Average YBOCS reduction at first time point	Responders at first time point	Average YBOCS reduction at latest time point	Responders at last time point
VC/VS	38	32%	11/32	35-69%	24/38
Nucleus Accumbens	53	25 to 69%	14/36	7.9 to 75%	13/31
Anterior limb of the internal capsule	14	20 to 79%	2/6	11 to 97%	7/17
Subthalamic nucleus	21	32 to 96%	14/20	n/a	n/a
Bilateral medial dorsal and ventral anterior nucleus of the thalamus	4	not given	0/4	Not given	0/4
Bilateral superolateral branch of the median forebrain bundle	2	31%	1 /2	41%	1/2
Inferior thalamic peduncle	6	8%	0/6	49%	6/6
Bilateral basolateral amygdala	1	Not given	n/a	Not given	0/1
Bed nucleus of stria terminalis	15	Not given	n/a	35 to 95%	12/15

py; rather, there is an accumulation of the effect. The percent YBOCS increase and the number of patients responding within a study tend to increase with time. In studies where the average YBOCS score did not continue to increase with time, patients still experienced clinical benefit.

Conclusions

Well-controlled, randomized studies with larger sample sizes with close follow up are needed to provide a more accurate determination for placement of DBS for OCD.

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