Psychiatr. Pol. 2022; 56(5): 1093–1108
PL ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE)
www.psychiatriapolska.pl
DOI: https://doi.org/10.12740/PP/141150

Deep brain stimulation in the treatment of refractory obsessive-compulsive disorder: A systematic literature review

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Summary

Aim. The aim of this review is to present the overview of deep brain stimulation (DBS) outcomes for obsessive – compulsive disorder (OCD). We have discussed the current OCD pathophysiology with its implications for DBS. We have also presented the current indications and contraindications for DBS in OCD patients as well as still existing limitations in neuromodulation for OCD.

Method. The literature was reviewed using two medical databases: Medical Literature, Analysis and Retrieval System on-line (MEDLINE) and Cochrane Central Register of Controlled Trials (CEN-TRAL) on DBS research in OCD with the use of the following key words: "deep brain stimulation", "refractory obsessive-compulsive disorder", "anterior limb of the inner capsule". We have found 9 well-conducted trials or open label trials with at least 6 individuals in each trial. Other reports present the data on the case series or single case reports of OCD treated with DBS.

Results. A number of well-conducted trials have demonstrated that the response rates (more than 35% YBOCS score reduction) of OCD symptomatology remain in 50% to 80% range. The study individuals in these trials have proven refractoriness and severity of OCD. The most common adverse events related to DBS include hypomanic episodes, suicidal ideation and other mood changes.

Conclusions. Our review suggests that DBS for OCD cannot be regarded as an established therapy for OCD. DBS for OCD should be regarded as palliative treatment, but it is not curative. DBS should be considered if available non-operative forms of OCD treatment have failed.

Key words: obsessive-compulsive disorder, deep brain stimulation, neuromodulation

Introduction

Obsessive-compulsive disorder (OCD) is a psychiatric illness that involves anxiety-provoking thoughts and simple time-consuming behaviors [1, 2]. OCD is the fourth most common mental disorder after depression, alcohol/substance misuse and social phobia [3]. This debilitating psychiatric disorder is associated with significant disruptions in functioning across multiple settings such as home, work and social life [4]. It is an illness characterized by a great impact not only on interpersonal relationships and job, but also on the participation in all activities normally concerning social aspects of life. People are often able to hide their OCD symptoms, even from their own family [3]. OCD is relatively common in the United States, with a lifetime prevalence of 2–3% [5]. When the disorder starts in the childhood or adolescence, young people may avoid socializing with other people or become unable to live independently. A sex ratio in epidemiological surveys across the world is equal. However, more women have compulsive washing, while more men have sexual obsessions, obsessive slowness or magical numbers obsessions [6]. The mean age of onset is late puberty for men and 20s for women [3].

The most common comorbid diagnoses in the surveys of people with OCD are depression, social phobia, alcohol misuse, specific phobias, and generalized anxiety disorder [7]. OCD is more common than it would be expected in people with bipolar disorder (in about 10%), schizophrenia (in about 10%), Tourette's disorder (in about 20%), anorexia nervosa and bulimia nervosa (in about 20%) [7–10]. Research shows that people can spend 10 years or sometimes even more struggling with OCD symptoms before they get the appropriate help [11].

Nonsurgical treatment for OCD

Two nonsurgical treatment modalities are currently available for patients with OCD: psychotherapy and pharmacotherapy. Although there are a lot of forms of psychotherapy, the cognitive behavioral therapy (CBT) has had the most success in the treatment of OCD. The follow-up studies of CBT show that about 30% of people refuse treatment, leave the therapy early or do not respond [12]. Other studies have shown that up to 50% of people have residual symptoms after CBT [13]. Numerous studies have highlighted the benefit of selective serotonin reuptake inhibitors (SSRIs) and the tricyclic antidepressant clomipramine, supporting the use of these medications [14].

Despite the beneficial effect of SSRIs and clomipramine in some patients with OCD, 40% to 60% of patients remain refractory to treatment [14]. However, the best effectiveness is the combination of CBT therapy with pharmacotherapy. Nevertheless, 10% of OCD patients are considered drug-resistant cases.

OCD pathophysiology and its implications for DBS targets

Currently, it is believed that movement disorders (Parkinson's disease, dystonia) as well as psychiatric disorders (OCD) are caused by the abnormalities of individual somatosensory and limbic neural areas connecting the cortico-striato-thalamo-cortical (CSTC) loops [15]. The somatosensory CSTC loop integrates primary somatosensory cortex, dorsal striatum, dorsal pallidum, anterior nuclei of the thalamus, and ventrolateral thalamic nuclei complex. The limbic CSTC loops connect the following structures: limbic cortical areas, ventral striatum, including its main part – nucleus accumbens, ventral pallidum, nucleus parafascicularis and nucleus dorsalis medialis of the thalamus [15]. The motor and limbic loops have direct and indirect pathways influencing their appropriate functioning. Neuromodulation (DBS) of somatosensory areas of CSTC loop has turned out to be very efficacious treatment for advanced PD as well as dystonia. By analogy, neuromodulation of limbic areas of CSTC loop should normalize the symptoms of OCD.

The main cortical areas involved in limbic circuits include the orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (dlPFC) and dorsal anterior cingulate cortex (dACC). A currently prevailing model regarding the pathophysiology of OCD is based on this CSTC loop and dysfunction within prefrontal circuits [16]. The limbic cortical areas send glutaminergic projections through the ventral capsule/ventral striatum to the basal ganglia. The direct pathway connects the ventral striatum through GABA-ergic neurons with the output structures of the extrapyramidal system, mainly the globus pallidus pars interna (GPi) and substantia nigra pars reticulata (SNr). The indirect pathway connects the ventral striatum through the globus pallidus pars externa (GPe) and subthalamic nucleus (STN) with the output structures (GPi/SNr) of the extrapyramidal system. The information from the limbic output structures (GPi/SNr) of the extrapyramidal system travels through GABA-ergic neurons to the nucleus parafascicularis and nucleus dorsalismedialis as well as to the anterior nucleus anterior of the thalamus. The thalamic limbic loop relay nuclei send glutaminergic excitatory connections to the limbic cortical areas (OFC, dlPFC and ACC), therefore, closing the limbic CSTC loop [17, 18].

Brain-imaging reports have provided the accumulating evidence that the hyperactivity is observed, especially in the OFC and caudate nucleus in OCD patients [19]. The hyperactivity of the OFC exerts the excitation of the direct pathway, which inhibits the output structures (GPi/SNpr) of the extrapyramidal system and provokes the disinhibition of thalamic limbic relay nuclei and contributes to excessively increased glutamatergic activity and additional excitation of the OFC. The disruption of this pathological hyperactive activity in the neuronal loop at the ventral capsule/nucleus accumbens region may normalize the activity in a limbic loop with subsequent clinical improvement in OCD symptomatology [20]. DBS electrodes are placed in the region of an anterior limb of internal capsule (ALIC), especially its ventral territory, in close

vicinity to the NAc, in order to disrupt an overactive flow from limbic cortices to the limbic parts of the basal ganglia [21].

The ALIC contains prefrontal corticopontine tracts, anterior thalamic radiation (connecting the limbic cortex of the frontal lobes with the dorsal and medial thalamic nuclei). Anterior thalamic radiation integrates the nucleus dorsalis medialis of the thalamus and prefrontal cortices as well as the anterior thalamic nuclei and the dorsal anterior cingulate cortex (dACC). The adjacent structures to the ALIC include the stria terminalis and bed nucleus of stria terminalis (BNST) that are responsible for anxiety and fear in OCD patients [22]. The stria terminalis and bed nucleus of stria terminalis are a part of the extended amygdala. The extended amygdala is directly connected to the NAc and both these structures establish neuronal circuits with the prefrontal cortex, especially with the medial prefrontal cortex (mPFC) and orbitofrontal cortex (OFC). The amygdala and BNST are involved in mediation of a stimulus specific to fear and anxiety and revealed dysfunction in OCD patients [23].

The commonly used targets for DBS in the treatment of OCD are derived from neurosurgical ablative procedures for OCD, i.e., capsulotomy and cingulotomy [24]. The improvements achieved by anterior capsulotomy (ablation of the anterior limb of capsula interna – ALIC) or cingulotomy (ablation of the anterior cingulate cortex – ACC) provide evidence that the ALIC stimulation could efficiently replace ablative techniques [24, 25]. The targets within the vicinity of this region have been defined with different names. Capsulotomy refers to the entire white matter structure, namely the ALIC. The ventral capsule/ventral striatum (VC/VS) refers to the most ventral part of the inner capsule and the underlying gray matter of the ventral striatum, including the nucleus accumbens (NAc). Placing the DBS electrode in the ALIC indicates that the target is within white matter tracts, and the goal of the stimulation is to influence the fibers coursing through this region [24, 26]. Placing the electrode in the gray matter of the VC, i.e., in the NAc, modulates the relay structures in the limbic loop.

The NAc is a key brain region that plays a significant role in the cognitive processing of motivation, aversion and reward. This nucleus is considered as a limbic-motor interface, where associations of motivational significance are converted into goal-directed behavior [27]. The NAc has reciprocal connections with the basal ganglia, amygdala, mediodorsal thalamic nucleus, and prefrontal cortex, i.e., the structures that are all involved in the processing and control of the level of anxiety in patients with OCD [28]. It was suggested that the beneficial effects of ventral striatum DBS are primary derived from blocking the NAc rather than the white fiber tracks in the ALIC. Moreover, the NAc seems to be a promising target for DBS because there is evidence for the dysfunction of the reward system in OCD [28].

In close proximity to the ventral striatum there is the bed nucleus of the stria terminalis, through this nucleus and the stria terminalis runs the largest projection from the amygdala. Clinical studies suggest that stimulation of these structures is more ef-

fective than stimulation of the anterior limb of internal capsule in treating symptoms of OCD. This was confirmed by two clinical trials with a long postoperative follow-up [29, 30]. The role of the bed nucleus of stria terminalis in the pathophysiology of OCD is known to be the structure connecting the amygdala to the frontal-striatal-thalamo-cortical limbic loop. Moreover, the activity of the BNST is modulated directly by the orbitofrontal cortex, which is involved in many aspects of the regulation of the level of anxiety, adequate behavior and hypervigilance, i.e., symptoms occurring in OCD patients [31]. The orbitofrontal cortex is overactive in patients with OCD, thus stimulation of the bed nucleus of stria terminalis may reduce the level of anxiety in patients with OCD.

The subthalamic nucleus (STN) is also the stereotactic target used in the treatment of OCD [32, 33]. The limbic region of this nucleus has numerous neuronal connections with the limbic cortices (OFC, dlPFC and dACC) creating the so-called hyperdirect limbic pathway [33]. STN neuromodulation is believed to exert a therapeutic effect on the entire limbic loop in patients with OCD, reducing the severity of obsessive-compulsive disorder.

In summary, the goal of neuromodulation in OCD is to modulate excessive signaling in the limbic cortical-striatal-thalamo-cortical loop by implanting electrodes into its various areas. Excessive pulsation from the limbic cortex can be inhibited at the level of the anterior limb of internal capsule (ALIC), the ventral striatum – mainly the nucleus accumbens (NAc), as well as the limbic region of the subthalamic nucleus (STN). An interesting target is the bed nucleus of stia terminalis (BNST), which modulates the level of anxiety by affecting the limbic loop being closely related to the amygdala and the orbitofrontal cortex.

Criteria for candidacy for DBS in OCD

It should be noted that most of the international learned societies in psychiatry consider DBS as the treatment of last resort. The main criteria for considering DBS for OCD are correct diagnosis, chronicity, severity, and refractoriness of OCD. In 2013, the American Psychiatric Association recommended DBS or transcranial magnetic stimulation (sTMS) only after failed pharmacotherapy and CBT. In 2017, the National Institutes of Mental Health and Neurosciences proposed a decision tree in which rTMS should be proposed before DBS [34]. In 2014, a *Consensus on guidelines for stereotactic neurosurgery for psychiatric disorders* was published by the World Society for Stereotactic and Functional Neurosurgery (WSSFN) [35].

According to the recommendations of the WSSFN, patients with psychiatric disorders qualified for neuromodulation procedures should meet the following requirements. Patients should meet the OCD diagnostic criteria according to the International Classification of Diseases (ICD). A diagnosis of OCD should be made by a psychiatrist. Additional comorbid psychiatric disorders may include mood dis-

orders, anxiety and eating disorders. These psychiatric conditions should not be used as basic diagnoses [35]. Patients must sign an informed consent for DBS treatment after receiving comprehensive information on its effectiveness and possible complications. Patients should be assessed for their ability to give informed consent to surgery. Patients must be of legal age. The prognosis without surgery must be unfavorable. Preoperative evaluation using a standardized OCD rating scale should be performed by a multidisciplinary team. Patients are referred to surgical treatment by a psychiatrist who provides treatment documentation, and are qualified by a council consisting of psychiatrists, neuropsychologists from the team for obsessive-compulsive disorders and neurosurgeons. Patients should be assessed using an objective scale, the most common is the *Yale-Brown Obsessive Compulsive Scale* (Y-BOCS). The qualification criterion for the DBS procedure according to the OCD score is at least 28.5 points on the Y-BOCS. Chronicity is defined as having the illness at least 5 years from diagnosis. Resistance to drug treatment is defined as at least 3 pharmacological trials of more than 12 weeks duration using maximum tolerated doses of serotonin reuptake inhibitors (SSRIs), including one pharmacological trial with clomipramine. Treatment resistance is also considered when appropriate cognitive behavioral therapy and rTMS have been unsuccessful.

The exclusion criteria include significant comorbid psychiatric diagnoses with the potential to interfere with DBS treatment such as a psychotic disorder, manic episodes, active substance abuse disorder, severe personality disorder, imminent risk of suicide or formed suicidal ideation. Other contraindications include underage, pregnancy, unstable neurological or medical illness.

Methods for search of clinical studies on DBS for OCD

We used the following key words when searching for clinical studies on DBS in treatment-resistant obsessive-compulsive disorder: “deep brain stimulation”, “refractory Obsessive-Compulsive Disorder”, “anterior limb of internal capsule”. Due to the fact that DBS for refractory OCD was initiated in 1998 by Nuttin et al., we examined the period from 1998 to February 2021. The following electronic databases were consulted: Medical Literature, Analysis, and Retrieval System on-line (MEDLINE) and Cochrane Central Register of Controlled Trials (CEN-TRAL).

We have chosen the following inclusion criteria for our search. DBS studies were included with at least 6 people diagnosed with refractory OCD. This limit was set because studies with fewer than 6 patients often reported individual patient outcomes, rather than looking at whole population data. Moreover, with small sample sizes, the presence of outliers can significantly affect data analysis. The placebo effect is very strong for all functional neurosurgical procedures, and to minimize its impact on the final clinical outcomes, a minimum postoperative follow-up period of 6 months was chosen. Only research published in English was considered.

Exclusion criteria included: animal studies, studies that included treatment of refractory OCD without DBS and studies that included ablative methods, preclinical studies, review articles, letters to the editor, and duplicate studies. Clinical studies with less than 6 patients and less than 6 months follow-up were excluded. The exclusion criteria included articles describing patient populations other than those with OCD and reports that mainly dealt with aspects related to the surgical technique.

The search using two databases and above mentioned key words has yielded 833 articles. Three hundred and seven articles mentioned the use of DBS in the treatment of refractory OCD. Using the inclusion and exclusion criteria listed above, we identified 9 articles suitable for further analysis included and discussed below.

Clinical outcomes of DBS in the treatment of OCD

In 1999, Nuttin et al. [24] reported the first cases of DBS in the treatment of OCD. The stereotactic target was derived from the experiences of capsulotomy for intractable OCD patients [24]. The chosen target was the ALIC, with two proximal contacts implanted in the ALIC, while more distal contacts of the DBS electrodes were in the ventral striatum, reproducing the trajectory and lesion of stereotactic capsulotomy. The obtained results were promising in 3 out of 4 patients, but high voltages were needed to induce OCD symptoms relief. The reported results in the group of 4 patients were descriptive, but this first study has shown the safety and efficacy of DBS in alleviating OCD symptoms [24]. All studies reporting the outcomes of DBS in six or more OCD patients are presented in chronological order in Table 1. In order to avoid duplication, we excluded the reports whose results are included in a later publication.

The first multicenter study involving 16 individuals was presented by Mallet at el. in 2008 [32]. The stereotactic target was limbic territory of the STN. The Y-BOCS score was reduced by 41% after 3 months of active stimulation. Huff et al. [36] reported the outcomes in 10 patients after unilateral right-sided ALIC/NAc DBS in a single institution in the double-blind study. The primary outcome measure was Y-BOCS change at 12 months. Only one patient met a full response criteria, using Y-BOCS reduction of more than 35% as an indicator of clinical response [36]. Four patients had a partial response (Y-BOCS score reduction between 25% and 34%). In 2010, three large DBS studies regarding OCD were published [29, 37, 38]. Denys et al. [38] in 16 OCD patients implanted electrodes bilaterally in the NAc achieving 46% Y-BOCS score reduction during an open-label phase. A multicenter, double-blind study reported by Goodman et al. [37] targeting the VC/VS in 6 patients found that 4 out of 6 patients were responders at 12 months (Y-BOCS score reduction of more than 35%) with subsequent depression improvement.

Greenberg et al. [29] found that in a group of 26 OCD patients with VC/VS DBS, 61.5% of patients achieved Y-BOCS score reduction of more than 35% in the mean follow-up lasting 31.4 months postoperatively. This was a multicenter study and covered

the 10-years period. During the course of this study the anatomical target, set primary anteriorly to the anterior commissure (AC), including the anterior limb of internal capsule and the ventral striatum, was altered. These researchers observed that placing the electrode posteriorly and medially to the anterior commissure was more effective, with a significant reduction in the voltage of the stimulating current. This new location of the stereotactic target may be the optimal target for DBS in OCD [29]. Anatomically, this region is related to the bed nucleus of stria terminalis. In 2013, Jiménez et al. [39] presented the results of inferior thalamic peduncle bilateral DBS in 6 OCD patients. At 12 months, the mean reduction in Y-BOCS score in 6 patients was 49 %.

Luyten et al. [30], the first authors who introduced DBS for OCD, conducted a larger trial in 24 patients reporting in 2015 the results that covered the period from 1998 to 2010. Initially they placed DBS electrodes in the ALIC, approximately 15 mm anterior to the AC, but over the course of their clinical outcomes the target was moved posteriorly and medially to the AC, as in the study by Greenberg et al. [29]. This new location was more effective in treating OCD symptoms [29, 30]. In the last group of patients DBS electrodes were placed in this new localization, i.e., in the BNST [30]. Placing DBS electrodes within the BNST resulted in an increased responder rate. This long-term trial confirmed the evidence that DBS in the region of the BNST is effective for OCD.

The trial published in 2019 combined two stereotactic targets VC/VS and STN [40]. Each patient received four electrodes – two in the STN and two in the VC/VS. The mean Y-BOCS reduction in the STN stimulation group was 42% (3 patients with Y-BOCS score reduction of more than 35%), compared to 53% Y-BOCS reduction in patients with VC/VS DBS (5 patients with Y-BOCS score reduction of more than 35%). Simultaneous STN and VC/VS DBS resulted in 62% Y-BOCS reduction with 5 patients with Y-BOCS score reduction of more than 35% [40]. The authors concluded that DBS of the VC/VS and STN resulted in the reduction in Y-BOCS score and the results did not differ. However, there were differences in mood and cognition between two targets. STN DBS significantly improved cognitive flexibility. VC/VS DBS improved the mood rather than cognitive functions. The authors of this report stated that different effects reflected DBS modulation of distinct brain areas [40].

In a recent study published in 2020, Winter et al. [41] assessed long-term DBS in the treatment of refractory OCD 4–8 years after surgery. In this prospective follow-up study, six patients underwent BNST/ALIC DBS. Four of the six patients had sustained improvement over long term follow-up. According to these authors, targeting the bed nucleus of stria terminalis (BNST) was not particularly efficient as no patient benefited from direct stimulation of this target. These authors observed that DBS ALIC provided long-term benefits in the treatment of refractory OCD [41].

Adverse events related to DBS procedures for treatment-refractory OCD

The DBS procedure begins with application of a stereotactic frame. Patients with OCD are operated under local or general anesthesia. Once a stereotactic target is selected, a stereotactic trajectory is planned from the entry point (in cerebral surface) to the target (ALIC, VC/VS, NAc, BNST), where the electrode for permanent stimulation is inserted. The second part of the procedure consists in placing a wire connecting the intracerebral electrode with the pulse generator implanted in the chest wall or in the abdominal wall.

Adverse events related to the DBS procedure can be divided into 3 categories: (1) surgery-related ones, i.e., hemorrhagic complications (intracerebral bleeding, venous infarction), (2) hardware-related complications (infection, erosions, fracture of a DBS lead) and (3) stimulation-induced complications (worsening of comorbid psychiatric symptoms or occurrence of new psychiatric symptoms). DBS procedures for neuropsychiatric indications are performed in the centers with experience in DBS for movement disorders. This situation explains a low number of complications associated with DBS surgery for OCD. Among the patients reported in well-controlled studies on DBS for OCD 5 asymptomatic hemorrhages occurred [21, 24, 29]. No patients in the world literature suffered immediate neurological deficit or death related to DBS procedure [29, 30, 32, 37, 38]. The hardware-related adverse events included cases of broken DBS leads [29, 30, 32, 37]. All of them were successfully managed by revision surgeries [21, 29, 30, 32, 37, 38].

The most common adverse events in OCD patients are stimulation-related in regard to the mood changes, especially the mood decline [41–45]. Some stimulation-related adverse events are related to the stimulation of individual structures of the limbic loop. During the VC/VS stimulation the patients experienced increased depression and episodes of suicidal ideation [29, 30]. The stimulation of the BNST may be related to the increase in suicidal thoughts [30]. The stimulation of the NAc may elicit transient agitation or hypomania [38]. The limbic STN stimulation was also associated with increased hypomanic episodes [32].

In the recent meta-analysis of DBS adverse events in OCD patients, the main adverse events were as follows: increased anxiety (21.6% of the OCD patients), hypomania (19.8%) [42]. Other less common stimulation-related adverse events include disinhibition (6%), depressive mood (4.3%), weight gain (4.3%), suicidal ideation (3.4%), paresthesia and olfactory disorder (3.4%), and insomnia (3.4%) [42]. The above-mentioned adverse events are stimulation-related and resolve after the readjustment of stimulation settings. Generally, a safety profile of DBS in OCD patients is considered good with a very low rate of adverse events related to surgery or hardware with reversibility of the stimulation-related adverse events.

Limitations of current studies on DBS in OCD

Although DBS for OCD was first performed in 1998, till now there have been very few randomized clinical trials and open-label studies in this field [29, 30, 32, 37–40]. The studies with fewer than 6 patients often reported the outcomes of individual patients rather than the clinical data for the whole population. In addition, small sample sizes may significantly influence data analysis. The largest studies of DBS in OCD to-date are not without limitations. Even randomized clinical trials have different designs with possible variables affecting the reported final outcomes [29, 30, 32, 37–40]. A strong confounding effect is the presence of an insertional effect that may last up to several months in movement disorders and especially in epilepsy patients after a DBS procedure [46]. This insertional effect is defined as improvement in clinical scores due to the implantation of DBS electrodes and not the stimulation per se. The final confounder is a very strong placebo effect seen in functional neurosurgery, this effect wanes with time but may have a profound impact on the short-term outcomes in OCD patients. In order to reduce the placebo effect of DBS procedure on OCD symptoms, these studies should last at least 6 months. In contrast to Parkinson's disease (PD) or essential tremor (ET), where the symptomatic feedback after turning on the stimulation is fairly immediate, in the case of OCD the symptomatic improvement may last from several weeks to several months and only after this period manifest fully. This time lag presents a challenge to pulse generator programmers and obviously affects treatment evaluation.

Additional external factors may profoundly affect the temporal OCD symptoms severity such as medication adjustments, life events, or waxing and waning of OCD symptoms over time. These confounding factors cannot be easily controlled. Moreover, these factors may significantly distort the assessment of patients in the case of changes in the stimulation parameters.

Another limitation of studies on DBS in OCD is the lack of a control group. The above-mentioned limitations and the small number of randomized clinical trials using DBS in OCD can be explained by many problems resulting from the assessment of patients and many variables having a significant impact on the final results of the presented studies.

Conclusions

Although DBS for OCD has been done for two decades, only a few clinical trials have demonstrated the benefit of the stimulation. Most studies report small case series or are single case reports [47–50]. A remarkable response rate is achieved in about 60% of patients, i.e., they present Y-BOCS score reduction of more than 35%, with a mean of 45.1% Y-BOCS score reduction [29, 42].

The DBS in OCD has several limitations. The studies targeted different structures of the limbic CSTC loop with various not standardized set of stimulation param-

eters [29, 30, 32, 37–40]. The postoperative episodes of suicidal ideation, attempted suicides and often reported hypomanic episodes raise some concerns [42, 43, 45]. The stimulation-related adverse events are transient due to the stimulation parameters readjustment. Therefore, DBS for OCD should only be administered in clinical studies driven by multidisciplinary teams.

Table 1. **Randomized clinical trials and open-label trials reporting DBS outcomes for treatment-refractory OCD**

Authors and year of publication	N	Stereotactic target	Study design	Conclusions	Patients qualified as responders (with Y-BOCS score reduction of more than 35%)
Mallet et al. (2008)	17	STN	Randomized, double-blind, multicenter trial	Stimulation resulted in a reduction in symptoms on the Y-BOCS scale from 29 to 18 points	The exact number of patients is not shown, only the overall mean Y-BOCS improvement
Huff et al. (2010)	10	ALIC/ NAc	Randomized, double-blinded, single institution trial	At 1 year, the Y-BOCS was reduced on average by 7 points	Only 1 patient demonstrated Y-BOCS score reduction of more than 35%)
Denys et al. (2010)	16	NAc	Open phase with optimization followed by double-blind randomized phase trial	Mean Y-BOCS reduced by 47% after 1 year, 52% after 21 months	9 patients with mean Y-BOCS reduction from 33.2 +/-4 to 25.4 +/-6.7
Goodman et al. (2010)	6	IC	Randomized, double-blind trial	YBOCS decreased significantly at 1 year	4 out of 6 patients with Y-BOCS score reduction of more than 35% at 12 months
Greenberg et al. (2010)	26	VC/VS	Open label, multicenter, international trial (case series)	In the last 17 patients Y–BOCS was reduced by 54%. In the last follow-up (mean 31.4 months) the response rate was 61.5 %	16 of 26 patients with Y-BOCS score reduction of more than 35%
Jimènez et al. (2013)	6	ITP	Open-label study, single center	Y-BOCS reduced by 49% after 12 months	6 patients were responders

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Luyten et al. (2015)	24	ALIC/ BNST	Open-label, optimization followed by double-blind trial	At 4 years postimplantation 15 of 24 patients were responders, with median of 66% reduction in Y-BOCS	15 of 24 patients were responders – Y-BOCS score reduction of more than 35%
Tyagi et al. (2019)	6	STN + VC/VS	Randomized, double-blind trial	Both targets revealed effective for Y-BOCS reduction. Simultaneous stimulation slightly better effective than single target stimulation	5 patients out of 6 responders – Y-BOCS score reduction of more than 35%
Denys et al. (2020)	70	vALIC	Open-label study, single center	ALIC proved effective in the treatment of refractory OCD. At 12 months follow-up Y-BOCS score decreased by 40 %	36 patients out of 70 were classified as responders with Y-BOCS reduction of more than 35%
Winter et al. (2020)	6	BNST/ALIC	Open-label study, single center	ALIC proved to be superior for the treatment of OCD. BNST was not particularly relevant since no patient benefited from direct stimulation of this target.	4 patients out of 6 had sustained improvement in Y-BOCS
Menchon et al. (2021)	30	ALIC/BNST	Open label, multicenter study	ALIC/BNST proved effective. At 12 months follow-up Y-BOCS score was reduced by 42%	Responder rate was 60%, 18 patients were responders

Abbreviations: ALIC – anterior limb of internal capsule; vALIC – ventral part of the anterior limb of internal capsule; VC/VS – ventral capsule/ventral striatum; NAc – nucleus accumbens; STN – subthalamic nucleus; ITP – interior thalamic peduncle; BNST – Bed nucleus of stria terminalis; Y-BOCS – Yale-Brown Obsessive-Compulsive Scale.

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