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CME Objective

After studying this article, you should be able to:

- Consider the use of deep brain stimulation for patients with severe, refractory obsessive-compulsive disorder and depressive symptoms

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Release, Expiration, and Review Dates

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Efficacy, Effect on Mood Symptoms, and Safety of Deep Brain Stimulation in Refractory Obsessive-Compulsive Disorder: A Systematic Review and Meta-Analysis

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and Frederico Simões do Couto, MD, PhD[d]

ABSTRACT

Objective: To evaluate efficacy, effect on mood, and safety of deep brain stimulation (DBS) for obsessive-compulsive disorder (OCD) at different target sites.

Data Sources: Electronic records from databases MEDLINE, EMBASE, and CENTRAL up to November 2019 were searched. Search terms included *OCD, depression,* and *DBS*.

Study Selection: Eight randomized controlled trials (RCTs) (n = 85) and 38 observational studies (case reports and case series) (n = 225) were included.

Data Extraction: In RCTs, the differences in outcomes between sham and active stimulation for OCD and depression were evaluated and the proportion of responders was determined. In all included studies, at last follow-up, the improvement from baseline in OCD (Yale-Brown Obsessive Compulsive Scale [Y-BOCS score]) and a scale of weighted depression scores (WDS) were determined. Predictors of response (age, illness duration and severity, frequency parameters, and response in depression) were evaluated. The proportions of adverse events and dropouts were calculated.

Results: In RCTs, mean differences between sham and active stimulation in Y-BOCS and Hamilton Depression Rating Scale (HDRS) scores were −7.8 (95% CI = −11.2 to −4.3, $I^2 = 40\%$, $P = .0001$) and −7.3 (95% CI = −11.5 to −3.0, $I^2 = 0\%$, $P = .0009$), respectively. No differences between limbic and non-limbic targets were identified ($\chi^2 = 0.21$, $I^2 = 0\%$, $P = .0006$). At last follow-up, improvements in Y-BOCS and WDS were −15.0 (95% CI = −18.3 to −11.7, $I^2 = 90\%$, $P < .001$) and −13.7 (95% CI = −20.1 to −7.3, $I^2 = 76\%$, $P < .001$), respectively. No consistent predictors of response were found. There were 0.68 adverse events (95% CI = 0.59 to 0.78, $I^2 = 88\%$), 0.32 serious adverse events (95% CI = 0.12 to 0.62, $I^2 = 96\%$), and 0.13 dropouts (95% CI = 0.07 to 0.16, $I^2 = 16\%$) per treated patient.

Conclusions: DBS can significantly decrease Y-BOCS score and depressive symptoms in refractory OCD.

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Clinical Points

- Deep brain stimulation has been shown to be effective for the treatment of patients with severe and refractory OCD. However, its costs, adverse events, diversity of targets, and limited use demand a clear analysis of efficacy.
- For a patient with severe and refractory OCD, DBS can significantly decrease depression and OCD symptoms.

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Obsessive-compulsive disorder (OCD) is characterized by the presence of obsessions (persistent and intrusive thoughts, urges, or impulses that cause marked anxiety and that the individual attempts to ignore, suppress, or neutralize) or compulsions (behaviors or mental acts that the individual feels driven to perform in response to an obsession in order to reduce anxiety).[1] OCD has a lifetime prevalence of 2.3%.[2]

First-line therapeutic options for OCD include selective serotonin reuptake inhibitors (SSRIs) and cognitive-behavioral therapy (CBT) with exposure and response prevention, alone or in combination. Second-line options are heterogeneous but may include antidepressants or antipsychotics, among others.[3,4] However, a fraction of people are refractory to all such options.[5] Ablative neurosurgical procedures such as anterior capsulotomy, anterior cingulotomy, subcaudate tractotomy, and limbic leucotomy were developed in response to treatment-resistant disease, with promising results.[6–8] These procedures are irreversible, which dissuades some patients. However, other patients also actually prefer the "one and done" approach of the ablative procedures as opposed to implanted hardware and clinical appointments for the rest of their lives with DBS.

Deep brain stimulation (DBS), a reversible and adaptable procedure that uses high frequency electrodes implanted in specific areas of the brain to promote electric and chemical changes,[9,10] was initially used for the treatment of Parkinson's disease. Its use in OCD patients was first published in 1999.[11] DBS targets were chosen according to the knowledge of neural OCD basis, including results from lesions studies. Functionally, convergent findings implicate the cortico-striato-thalamo-cortical system (CSTC)[12,13] in the pathophysiology of the disease. CSTC includes limbic structures such as the anterior limb of the internal capsule (ALIC),[11] the nucleus accumbens (NAcc),[14,15] the middle forebrain bundle,[16] and the ventral capsule and ventral striatum (VC/VS, which includes the ventral portion of the internal capsule, the NAcc, the anteroventral portion of the putamen, and the transition between the NAcc and the head of the caudate nucleus),[17,18] as well as non-limbic structures such as the medial dorsal and ventral anterior nuclei of the thalamus (MD/VA),[19] the inferior thalamic peduncle (ITP),[20–22] and the subthalamic nucleus (STN).[23,24] The mechanism seems to be far more complex than initially thought, probably due to the integration of the loops, to the role of the amygdala and hippocampus, and to the distinct and disparate roles of the lateral and medial orbitofrontal cortices.[25,26] Most targets belong to the CSTC pathway, and other targets, although not belonging to the CSTC, have intimate connections to it, such as the bed nucleus of stria terminalis (BST).[27,28] The efficacy of DBS for refractory OCD has been shown in several studies.[15,19–22,24,25,28–32] However, the magnitude of the effect, the different targets, and some studies with negative results highlight the need for further study. Of people who meet the criteria for OCD, 63.3% also meet criteria for a mood disorder, and 40.7% meet criteria for major depressive disorder (MDD).[2] Multiple accounts of DBS for OCD have reported an improvement in mood symptoms.[27,29,30,33–35] It is known that mood symptoms in patients with OCD may differ from those in patients with MDD,[36] and neurobiological data seem to confirm that there are pathophysiologic differences between primary MDD and secondary depressive symptoms in OCD patients.[37]

The two meta-analyses performed so far[38,39] have shown that there is a decrease in OCD symptoms with DBS but have not addressed mood. Furthermore, the last meta-analysis performed dates back to 2014 and does not include the largest randomized controlled trial (RCT) published to date.[27] Although globally safe, DBS can have significant adverse events and is extremely expensive. Stronger evidence of its efficacy could help the involved subjects in the decision to choose DBS as a treatment, which provided encouragement to perform this study.

METHODS

This systematic review and meta-analysis was conducted according to the PRISMA guidelines.[40]

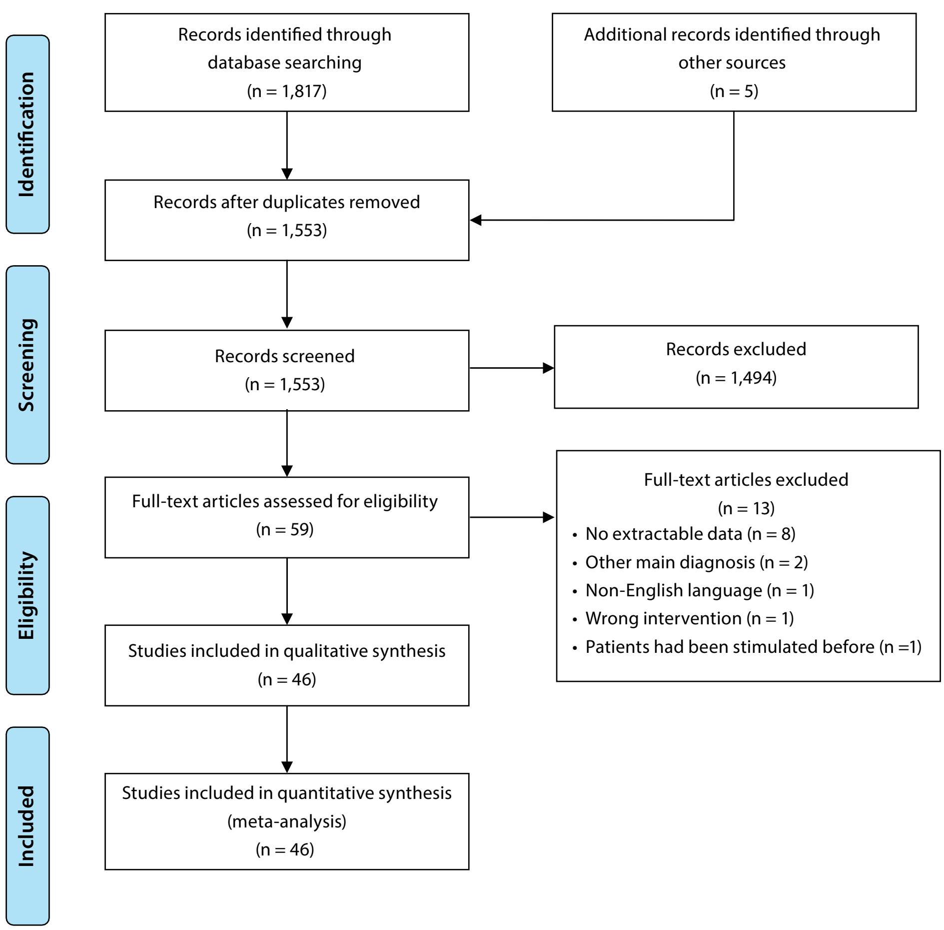
Eligibility Criteria

RCTs, either parallel or crossover, and observational studies that enrolled people with OCD treated with DBS were included. Only studies published in English were included. Patients required a main diagnosis of OCD of disabling severity, according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition or Fifth Edition.[1,41] Studies were accepted regardless of participants' comorbid conditions or age and publication year or publication status of the study.

Studies were required to report data on at least 1 of the following outcomes:

- Primary efficacy outcome: variation of obsessive and/or compulsive symptoms, measured by the Yale-Brown Obsessive Compulsive Scale (Y-BOCS).[42]
- Primary safety outcome: proportion of participants with serious adverse events.

Figure 1. Flowchart PRISMA of Study Selection



- Secondary outcomes: proportion of patients with complete response (Y-BOCS improvement > 35%); proportion of patients in remission (Y-BOCS score < 6); variation of mood symptoms, measured by any validated instruments; proportion of participants with any adverse event; proportion of dropouts; and predictors of response.

Narrative or systematic reviews; articles on neurophysiological, neuropsychological, or functional imaging effects of DBS; or articles focused solely on acute effects were excluded.

Information Sources

MEDLINE, EMBASE, and CENTRAL were searched from inception to November 2019, as were WHO International Clinical Trials Registry Platform and ClinicalTrials.gov. Reference lists were cross-checked for additional references. Principal investigators of clinical trials with unpublished data were contacted for additional data.

Study Selection

Titles, abstracts, and full texts were screened independently by 2 reviewers. Disagreements were solved by consensus.

Data Collection Process

One reviewer extracted individual study data onto a piloted extraction sheet. Another reviewer confirmed the extracted data.

Data Items

The following data items were collected, when available: study design, duration, and country; inclusion and exclusion criteria; patient age and sex, duration of illness, and follow-up time; stimulation parameters (site, laterality, frequency, pulse width and voltage); (*a*) baseline, (*b*) ON-period and OFF-period outcomes (if RCT), and (*c*) longest follow-up outcomes (RCTs with open-label phase and non-RCTs) for (1) Y-BOCS and (2) depression score measured by the Hamilton Depression Rating Scale (HDRS), the Beck Depression Inventory (BDI), the Montgomery-Asberg Rating Scale (MADRS) and the Depression Anxiety Stress Scales-Depression (DASS-D); total and serious adverse events; and dropout rates. When possible, items were collected on an individual patient level. Included studies were cross-checked for duplicate patients (using available epidemiologic data such as age, gender, and OCD age at onset) and the latest and most detailed information was collected. When 2 or more studies reported

Table 1. Study Characteristics

		N	New Patients, n	% Female	Average Age (y)	Average Duration of Illness (y)	Stimulation Site	Side	Average Frequency (Hz)	Average Pulse Width	Average Voltage	Average Follow-up (mo)	Depression (HDRS, BDI, MADRS, DASS-D)
RCTs	Abelson 2005[33]	4	4	50	40.3	22.5	ALIC	Bilateral	125	172.5	7.4	12.9	Yes, HDRS
	Denys 2010[31]	16	1	44	43	28.4	NAcc	Bilateral	123	180	4.7	21	Yes, HDRS
	Goodman 2010[49]	6	1	50	35.2	16.8	VC/VS	Bilateral	133	165	5.1	11.4	Yes, HDRS
	Huff 2010[34]	10	2	40	36.3	22.2	ALIC/NAcc	Right	145	90	5.5	12	Yes, HDRS and BDI
	Luyten 2016[27]	24	1	12	40.6	NR	ALIC/BST	Bilateral	115	270	6.4	77	Yes, HDRS
	Mallet 2008[24]	17	2	41	43.1	29.5	STN	Bilateral	130	60	NR	10	Yes, MADRS
	Nuttin 2003[11]	8	7	NR	NR	NR	ALIC	Bilateral	100	247	6.1	18.8	Yes, BDI
	Schuurman 2011[65]	16	1	NR	NR	NR	NAcc	Bilateral	NR	NR	NR	21	Yes, HDRS
Non-RCTs[a]	Anderson 2003[15]	1	2	100	35	10	ALIC	Bilateral	100	210	2	10	No
	Aouizerate 2004[50]	1	1	0	56	40	VC/VS	Bilateral	120	90	4	15	Yes, HDRS
	Aouizerate 2009[67]	2	1	0	51	33.5	NAcc/CN	Bilateral	130	120	4	15	Yes, HDRS
	Azriel 2019[75]	1	2	100	67	44	GPi	Bilateral	NR	NR	NR	16	No
	Barcia 2014[76]	2	16	50	32.5	14.5	NAcc/STN	Left	130	60	3.75	25.5	Yes, HDRS
	Barcia 2018[68]	7	1	57	36.3	25.3	NAcc/CN	Bilateral	130	60	4.5	3	Yes, HDRS and BDI
	Burdick 2010[57]	1	7	0	33	24	ALIC/NAcc	Bilateral	135	90	6.5	30	No
	Chabardès 2013[23]	4	0	50	38.3	17.8	STN	Bilateral	130	60	2.5	6	No
	Chang 2017[51]	1	2	0	28	8	VC/VS	Bilateral	130	210	3	24	Yes, HDRS
	Choudhury 2017[54]	1	3	100	45	21	ALIC	Bilateral	100	210	2	51	Yes, BDI
	Coenen 2017[16]	2	1	0	41.5	29	MFB	Bilateral	130	60	NR	12	No
	Doshi 2019[62]	1	1	100	42		NAcc	Bilateral	130	60	2.6	12	Yes, HDRS
	Farrand 2018[66]	7	10	NR	46.6	NR	NAcc/BST	Bilateral	NR	NR	NR	30.9	Yes, DASS-D
	Fayad 2016[52]	6	13	67	44.5	NR	VC/VS	Bilateral	133	165	5.1	NR	Yes, HDRS
	Franzini 2010[35]	2	2	0	37	21.5	NAcc	Bilateral	130	90	5.3	25.5	Yes, HDRS
	Gabriels 2003[58]	3	10	67	41.7	24.3	ALIC/NAcc	Bilateral	NR	NR	NR	12	Yes, HDRS
	Grant 2016[63]	1	20	0	30	5	NAcc	Bilateral	NR	NR	NR	36	No
	Greenberg 2006[17]	10	6	40	35.3	22.5	VC/VS	Bilateral	115	150	NR	30.6	Yes, HDRS
	Greenberg 2010[59]	26	1	46	36.5	21.9	ALIC/NAcc	Bilateral	NR	NR	NR	24	Yes, HDRS
	Gupta 2019[69]	2	5	100	46.5	23	VC/VS/ALIC	Bilateral	NR	NR	NR	42	Yes, BDI
	Huys 2019[60]	20	1	50	43.2	26.1	ALIC/NAcc	Bilateral	134	131.2	4.9	12	Yes, BDI
	Islam 2015[28]	6	5	17	45.8	30.2	NAcc/BST	Bilateral	138	NR	4.7	25	No
	Jiménez 2007[21]	1	13	0	21	9	ITP	Left	130	450	4.5	18	Yes, HDRS
	Jiménez-Ponce 2009[20]	5	4	40	36.8	17.4	ITP	Bilateral	130	450	5	12	No
	Jiménez 2013[22]	6	17	50	34.7	16.2	ITP	Bilateral	NR	NR	NR	24	No
	Lee 2019[74]	5	0	60	32.4	116.2	ITP	Bilateral	130	90.4	6.76	49.8	Yes, HDRS
	Maarouf[19]	4	30	75	39.3	23.5	MD/VA	Bilateral	130	105	3.1	11.5	Yes, BDI
	Mallet 2019[70]	14	1	43	43.6	31.1	STN	Bilateral	NR	NR	NR	46	No
	Menchón 2019[55]	30	0	52	41	24.5	ALIC	Bilateral	130	221	4.7	12	No
	Mulders 2017[71]	1	5	100	49	34	STN	Bilateral	130	90	4.5	24	No
	Munckhof 2013[56]	16	1	44	43	28.4	ALIC	Bilateral	103	145	4.7	50	No

(continued)

Table 1 (continued).

	N	New Patients, n	% Female	Average Age (y)	Average Duration of Illness (y)	Stimulation Site	Side	Average Frequency (Hz)	Average Pulse Width	Average Voltage	Average Follow-up (mo)	Depression (HDRS, BDI, MADRS, DASS-D)
Plewnia 2008[61]	1	9	100	51	NR	ALIC/NAcc	Right	130	60	4.5	24	No
Polosan 2019[72]	12	4	67	38.3	18.8	STN	Bilateral	NR	NR	NR	37.9	No
Roh 2012[29]	4	1	25	33.8	16.8	VC/VS	Bilateral	120	165	3.9	24	Yes, HDRS
Sachdev 2012[64]	1	0	100	32	28	NAcc	Bilateral	130	60	3	7	No
Senova 2019[73]	1	1	100	72	52	STN	Bilateral	130	60	2.35	36	Yes, MADRS
Tsai 2012[30]	4	4	0	25.5	8.3	VC/VS	Bilateral	130	210	3.6	15	Yes, HDRS
Tyagi 2019[77]	6	6	17	45.5	24.2	VC/VS/STN	Bilateral	130	60	3.7	9	Yes, MADRS

[a]Non-RCTs = case series and case reports.
Abbreviations: ALIC = anterior limb of internal capsule, BDI = Beck Depression Inventory, BST = bed nucleus of stria terminalis, CN = caudate nucleus, DASS-D = Depression Anxiety Stress Scales—Depression, GPe = external globus pallidus, GPi = internal globus pallidus, HDRS = Hamilton Depression Rating Scale, ITP = inferior thalamic peduncle, MADRS = Montgomery-Asberg Depression Rating Scale, MD/VA = medial-dorsal and ventral anterior nuclei of the thalamus, MFB = middle forebrain bundle, NAcc = nucleus accumbens, NR = not reported, PRZ = pre-reticular zone, RCT = randomized controlled trial, STN = subthalamic nucleus, VC/VS = ventral caudate/ventral striatum.

on the same cohort of patients, the data from these studies were analyzed together on a single cohort.

Risk of Bias in Individual Studies

The Cochrane risk of bias tool[43] was used to classify RCTs as being at low, high, or unclear risk of bias in the standard domains. Risk of bias in observational studies was evaluated with the Newcastle-Ottawa Scale,[44] which awards 4 stars for selection of exposure and control groups, 2 stars for compatibility between exposure and control groups, and 3 stars for outcome evaluation. Two authors independently assessed risk of bias. Disagreements were solved by consensus.

Summary Measures and Planned Method of Analysis

Because different depression instruments were used, depression scores were standardized by calculating the percentage of each patient's score from the maximum score of the instrument used, and subsequent statistical analysis was performed with this value, which was named weighted depression score (WDS). Analyses of active vs sham stimulation data were performed using Review Manager 5.3 and SPSS v.23.[45,46] Mean differences (MDs) and corresponding 95% confidence intervals (CIs) were calculated for Y-BOCS and WDS. Differences between active and sham stimulation were analyzed. A subgroup analysis for limbic versus non-limbic stimulation sites was conducted. Risk ratios (RRs) and number needed to treat (NNT) were calculated for dichotomous outcomes.

Analyses of last follow-up vs baseline data were performed with OpenMetaAnalyst[47] and SPSS v.23. The Paule-Mandel random-effects method was used. MD from baseline was calculated for Y-BOCS and WDS. A Spearman rank-order correlation was used to study the correlation between decrease in Y-BOCS during RCT and patient age, duration of illness, stimulation frequency, pulse width and voltage, baseline Y-BOCS, and WDS improvement. Bonferroni correction was applied to all correlations. Heterogeneity was quantified using the I^2 statistic.[48] Safety outcomes were analyzed in OpenMetaAnalyst, by pooling Freeman-Tukey transformed proportions using Paule-Mandel random-effects model.

Analyses of epidemiologic data and stimulation parameters were performed on an individual patient level. Otherwise, cohort level analyses were performed, using the latest and most detailed information from each cohort.

Ethics

Because this research used anonymized data previously published in the literature, it is exempt from institutional review board approval.

RESULTS

Study Selection

Of the 1,817 articles whose abstracts were reviewed, 59 were selected for full-text assessment. Of these, 46 met eligibility criteria and were included in the meta-analysis (see Figure 1).

Study Characteristics

Eight studies were RCTs (2 of them reporting on the same cohort), and 38 were observational studies (13 case reports and 25 case series). Eighty-five patients were included in RCTs and 225 were included overall. The average patient age was 40 years (from 18 to 72 years), and 46% were female. The average duration of illness was 24 years (from 5 to 52 years). The average time of follow-up was 33 months (0.3 to 171 months). The most frequent

Table 2. Risk of Bias Across RCTs

	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Participants and Personnel (Performance Bias)	Blinding of Outcome Assessment (Performance Bias)	Incomplete Outcome Data (Attrition Bias)	Selective Reporting (Reporting Bias)	Other Bias
Abelson 2005[35]			−	−	+		
Denys 2010[31]	+		−	−	+	+	
Goodman 2010[33]			−	−	+		
Huff 2010[37]					+		
Luyten 2016[27]	+		−	−			
Mallet 2008[24]		+			+	+	
Nuttin 2003[36]	+		−	−			
Schuurman 2011[65]					+		

Abbreviation: RCT = randomized controlled trial.
Symbols: + = low risk of bias, − = high risk of bias. (No signal = uncertain risk of bias.)

Table 3. Risk of Bias Across Non-RCTs[a]

Author	Selection	Comparability	Outcome
Anderson 2003[15]	★★	★	★★
Aouizerate 2004[50]	★★	★	★★★
Aouizerate 2009[67]	★★	★	★★★
Azriel 2019[75]	★★	★	★★★
Barcia 2014[76]	★★	★	★★★
Barcia 2019[68]	★★	★	★★
Burdick 2010[57]	★★	★	★★
Chabardès 2013[23]	★★	★	★
Chang 2017[51]	★★	★	★★★
Choudhury 2017[54]	★★	★	★★★
Coenen 2017[16]	★★	★	★★★
Doshi 2019[62]	★★	★	★★★
Farrand 2018[66]	★★	★	★★★
Fayad 2016[52]	★★	★	★★★
Franzini 2010[35]	★★★	★	★★★
Gabriëls 2003[58]	★★	★	★★★
Grant 2016[63]	★★	★	★★★
Greenberg 2006[17]	★★	★	★★★
Greenberg 2010[59]	★★	★	★★★
Gupta 2019[69]	★★	★	★★★
Huys 2019[60]	★★	★	★★★
Islam 2015[28]	★★	★	★★★
Jiménez 2007[21]	★★	★	★★
Jiménez-Ponce 2009[20]	★★	★	★★★
Jiménez 2013[22]	★★	★	★★★
Lee 2019[74]	★★	★	★★★
Maarouf 2016[19]	★★★	★	★★
Mallet 2019[24]	★★	★	★★★
Menchón 2019[55]	★★	★	★★★
Mulders 2017[71]	★★	★	★★★
Munckhof 2013[56]	★★	★	★★★
Plewnia 2008[61]	★★	★	★★★
Polosan 2019[72]	★★	★	★★★
Roh 2012[29]	★★	★	★★★
Sachdev 2012[64]	★★	★	★★
Senova 2019[73]	★★	★	★★★
Tsai 2012[30]	★★	★	★★
Tyagi 2019[77]	★★	★	★★★

[a]Non-RCTs = case series and case reports. Each star indicates a positive reply for an item; the more stars in each domain, the lower the risk of bias.
Abbreviation: RCT = randomized controlled trial.

stimulation sites were limbic (33 studies in total, 7 studies in VC/VS,[17,29,30,49–52] 6 studies in ALIC,[15,33,53–56] 6 studies in ALIC/NAcc,[34,57–61] 6 studies in NAcc,[31,35,62–65] 2 studies in NAcc/BST,[28,66] 2 studies in NAcc/CN,[67,68] 1 study in ALIC/BST,[27] 1 study in MFB,[16] and 1 in VC/VS/ALIC[69]). Six studies reported stimulation in the STN,[23,24,70–73] 4 in ITP,[20–22,74] 1 in GPi,[75] and 1 in MD/VA.[19] Two studies reported mixed stimulation in limbic and non-limbic sites, 1 in NAcc/STN,[76] and 1 in VC/VS/STN.[77] Two studies reported stimulation in the left side and 2 in the right side, and the remainder 42 were bilateral. The average stimulation frequency used was 132 Hz (85 to 280 Hz), average pulse width was 143 ms (60 to 450 ms), and average voltage was 4.9 V (1.5 to 10.5 V). All studies collected Y-BOCS scores. Thirty-one collected data on depression (20 used HDRS, 5 BDI, 3 MADRS, 2 HDRS and BDI, and 1 DASS-D). A summary of study characteristics may be found in Table 1.

Risk of Bias Within Studies

In RCTs, risk of bias for selection, attrition, and reporting was considered low or uncertain in all studies. Risk bias in the performance and detection parameters was considered high in all but 2 studies, in which it was uncertain.[24,34] Most non-RCTs were attributed 2 or 3 stars in patient selection and outcome assessment. Since no study had a comparison arm, comparability domain questions were not applicable, so all studies were awarded 1 star by default. Risk of bias within RCTs and non-RCTs may be found in Tables 2 and 3, respectively.

Synthesis of Results

Analyses were performed on 2 aggregates of studies: (*a*) RCTs only for On and Off stimulation results and (*b*) all selected studies for baseline and last follow-up results. Analyses of absolute and percentage data were conducted and had similar results. Data from duplicate patients were merged, and of the 46 included studies, 39 cohorts were analyzed.

Efficacy

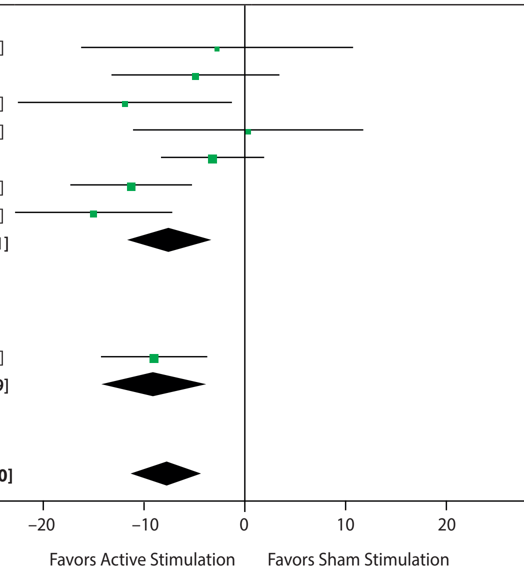
Baseline scores. The average Y-BOCS score at baseline was 33.8 (SD = 4.2) in RCTs and 33.7 (SD = 3.8) overall.

Decrease in Y-BOCS score. In RCTs, MD in Y-BOCS in sham versus active stimulation was −7.8 (95% CI = −11.2 to −4.3, $I^2 = 40\%$, $P < .0001$) (see Figure 2).

Complete response to treatment. Complete response to treatment (as defined by a decrease of > 35% in Y-BOCS score from sham to active stimulation) was analyzed. In

Figure 2. Forest Plot for Y-BOCS Mean Difference Between Active and Sham Stimulation in RCTs

Study or Subgroup	Active Stimulation Mean	SD	Total	Sham Stimulation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Limbic								
Abelson 2005[33]	26.5	11.81	4	29.25	6.95	4	5.5%	−2.75 [−16.18 to 10.68]
Denys 2010[31] Group 1	25.8	9.3	6	30.7	4.5	6	11.4%	−4.90 [−13.17 to 3.37]
Denys 2010[31] Group 2	17.6	10.1	8	29.5	11.4	8	8.1%	−11.90 [−22.45 to −1.35]
Goodman 2010[49]	27	6.42	6	26.67	12.66	6	7.2%	0.33 [−11.03 to 11.69]
Huff 2010[34]	27.9	6.44	10	31.1	5	10	19.5%	−3.20 [−8.25 to 1.85]
Luyten 2015[27]	17.5	9.92	18	28.78	8.29	18	16.7%	−11.28 [−17.25 to −5.31]
Nuttin 2003[11]	19.67	6.81	3	34.67	0.58	3	12.5%	−15.00 [−22.73 to −7.27]
Subtotal [95% CI]			**55**			**55**	**81.0%**	**−7.43 [−11.66 to −3.21]**
Heterogeneity: $\tau^2 = 14.27$; $\chi^2 = 11.27$, $df = 6$ ($P = .08$); $I^2 = 47\%$								
Test for overall effect: $Z = 3.45$ ($P = .0006$)								
STN								
Mallet 2008[24]	19	8	16	28	7	16	19.0%	−9.00 [−14.21 to −3.79]
Subtotal [95% CI]			**16**			**16**	**19.0%**	**−9.00 [−14.21 to −3.79]**
Heterogeneity: Not applicable								
Test for overall effect: $Z = 3.39$ ($P = .0007$)								
Total [95%] CI			**71**			**71**	**100.0%**	**−7.75 [−11.19 to −4.30]**
Heterogeneity: $\tau^2 = 9.16$; $\chi^2 = 11.58$, $df = 7$ ($P = .12$); $I^2 = 40\%$								
Test for overall effect: $Z = 4.41$ ($P < .0001$)								
Test for subgroup differences: $\chi^2 = 0.21$, $df = 1$ ($P = .65$); $I^2 = 0\%$								



Abbreviations: CI = confidence interval, IV = inverse variance, RCT = randomized controlled trial, SD = standard deviation, STN = subthalamic nucleus, Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

RCTs, the percentage of patients that reached complete response to treatment during active stimulation was 51%, as opposed to 18% during sham stimulation (RR = 2.4 [95% CI = 1.3 to 4.3, $I^2 = 0\%$, $P = .003$], risk difference = 0.33 [95% CI = 0.16 to 0.49, $I^2 = 37\%$, $P = .0001$], NNT = 3.03). In all included studies, the percentage of patients that reached complete response to treatment at last follow-up was 57.9% (95% CI = 49.7 to 69.9%, $I^2 = 62\%$, $P < .001$).

Remission. Remission (as defined by Y-BOCS score < 6) was analyzed. In RCTs, the percentage of patients that reached remission was 8% during active stimulation and 5% during sham stimulation, but was not statistically significant (RR = 1.3 [95% CI = 0.2% to 10.55%, $I^2 = 26\%$, $P = .80$], NNT = 33.3). In all included studies, the percentage of patients that reached remission at last follow-up was 5.4% (95% CI = 2.4% to 8.4%, $I^2 = 0\%$, $P = .92$).

Subgroup analysis. Only 2 subgroups were included in subgroup analyses: the overall aggregate of limbic targets and STN (limbic targets subgroup: MD = −7.4, 95% CI = −11.7 to −3.2, $I^2 = 47\%$, $P = .0006$; STN subgroup: MD = −9.0, 95% CI = −14.2 to −3.8, $P = .0007$; test for subgroup differences: $\chi^2 = 0.21$, I^2 for subgroup differences = 0%, $P = .65$). The STN subgroup included only 1 study. In all included studies, improvement in Y-BOCS from baseline was −15.0 (95% CI = −18.3 to −11.7, $I^2 = 90\%$, $P < .001$). Due to the fact that some RCTs optimized stimulation parameters before the RCT period[24,34] and others did not, a post hoc subgroup sensitivity analysis was conducted, comparing efficacy between these two groups, and yielded no subgroup difference between the two groups of trials ($P = .21$).

Predictors of response. Age, duration of illness, stimulation frequency, pulse width and voltage, basal Y-BOCS, and depression response were evaluated, both in RCT data and at last follow-up, totaling 14 correlations. The most consistent correlation found was between response in Y-BOCS and response in depression, both in RCT data and at last follow-up (respectively, Spearman $\rho = 0.989$, $P = .006$ and Spearman $\rho = 0.454$, $P = .000$). Age was not a predictor of response either in RCTs or at last follow-up. Duration of illness was a positive predictor of response in RCT data (Spearman $\rho = 0.377$, $P = .02$) but not at last follow-up. Stimulation frequency was a negative predictor of response in RCT data (Spearman $\rho = 0.416$, $P = .005$) but a positive predictive factor at last follow-up (Spearman $\rho = 0.195$, $P = .026$). In RCT data, pulse width was a positive predictor of response (Spearman $\rho = 0.416$, $P = .005$), but not at last follow-up. Voltage was not a predictor of response at either stage. Illness severity at baseline as measured by Y-BOCS was not a predictor of response at baseline but was a negative predictor of response at last follow-up (Spearman $\rho = -0.271$, $P = .001$). However, since 14 correlations were performed, only the negative correlation between Y-BOCS response and baseline Y-BOCS and the positive correlation between Y-BOCS response and depression response would hold up to a Bonferroni correction.

Effect on mood. Effect of DBS on mood symptoms was reported in 31 studies. The average WDS basal score was 33.7 (SD = 39.8) in RCTs and 36.6 (SD = 17.0) overall.

Two studies were included in the analyses for RCTs. In RCTs, MD in the HDRS between sham and active stimulation was −7.3 (95% CI = −11.5 to −3.0, $I^2 = 0\%$, $P = .0009$). At last follow-up, absolute decrease of the average weighted depression score from baseline was −13.7 (95% CI = −20.1 to −7.3, $I^2 = 76\%$, $P < .001$).

There was a correlation between response in Y-BOCS and response in WDS, both in RCTs and at last follow-up (Spearman $\rho = 0.989$, $P = .006$ and Spearman $\rho = 0.454$, $P = .000$).

Safety

A total of 814 adverse events were reported: 289 psychiatric adverse events (most commonly hypomania, sleep complaints, irritability, apathy, and depression), 215 medical adverse events (most commonly weight change, sexual complaints, infections, gastrointestinal symptoms, and orthopedic/musculoskeletal symptoms), 202 neurologic symptoms (most commonly paresthesias, cognitive complaints, headache, and sensorial complaints), 41 device-related symptoms (most commonly sensations with extension leads or stimulation), and 67 other. Of these, 66 adverse events were considered serious, of which 24 were medical, 19 neurologic, 13 psychiatric, and 10 device-related. There were 4 reported deaths; 1 due to breast cancer, 1 due to overdose, 1 due to tuberculosis, and 1 due to suicide. There were 0.68 adverse events per participant (95% CI = 0.59 to 0.78, $I^2 = 88\%$, cohort-level analysis, 30 included cohorts, 195 patients). There were 0.32 serious adverse events per participant (95% CI = 0.12 to 0.52, $I^2 = 96\%$, cohort-level analysis, 27 included cohorts, 158 included patients). There were 0.13 dropouts per participant (95% = CI 0.07 to 0.16, $I^2 = 16\%$, cohort-level analysis, 30 included cohorts, 175 included patients). There were no correlations between total adverse events, serious adverse events, or dropout rate and stimulation site or time of follow-up.

DISCUSSION

Efficacy

In this meta-analysis, we found a statistically significant decrease in Y-BOCS score of 7.8 from sham to active stimulation and a complete response probability 2.4 times higher in active vs sham stimulation, with an NNT of 3. At last follow-up, there was a decrease in Y-BOCS from basal of 15.0, and 57.9% reached complete response. These data are comparable to those of previous meta-analyses of DBS, in which the decrease in Y-BOCS score was 8.93 between active and sham stimulation[39] and complete response rate was 60%.[38] In comparison to surgical approaches, these results are slightly better than those of capsulotomy (52.9% of patients had complete response)[78] and cingulotomy (47% of patients had complete response).[79] Despite this, a recent meta-analysis[80] found capsulotomy to have a greater utility than DBS; however, it used a measure of utility, which was different from the methodology used here.

In subgroup analysis for efficacy in different targets, there were no differences between limbic and non-limbic sites. A possible explanation for this is that OCD is due to a dysfunction of the CSTC network, and not of a specific nucleus or region, so the intervention over any part of the network will have some effect on symptoms. However, this analysis was limited because it was not possible to compare efficacy in different limbic sites, due to high variability in limbic stimulation targets between and within studies and considerable overlap in their stimulation, and only 1 non-limbic target RCT[24] was included. A recent RCT[77] comparing stimulation of VC/VS and STN showed that Y-BOCS improved similarly between the STN and the VC/VS group, confirming the data from this meta-analysis. On the other hand, stimulation of the STN (but not of VC/VS) improved cognitive flexibility, and stimulation of the VC/VS improved mood (to a greater degree than STN stimulation). This, along with tractography data from that trial showing connection of VC/VS and STN to different brain regions, suggests that despite both structures belonging to the CSTC pathway, stimulation of VC/VS and STN may affect different functional networks.

The most consistent results in the search for predictors of response were that decrease in depression symptoms correlated with Y-BOCS decrease and that age and voltage did not, contradicting a previous meta-analysis that found that older age at onset was a predictor of response.[38] The remainder of analyses had inconsistent statistically significant results that lost significance after a Bonferroni correction.

Testing stimulation occurred prior to the blinding phase in most RCTs, in order to identify maximum efficacy and increase the study's detection power. However, that may have led to the unblinding of the trial due to the patients' knowledge of stimulation effects. So, in most RCTs there was almost certainly a high risk of detection bias. Despite this, most included studies reported symptom increase when the device battery became depleted, which was in effect a triple blinding situation, which favors therapeutic efficacy of the method. On the other hand, in order to avoid detection bias, 2 RCTs[24,34] used low voltages during the pre-blinding phase, which might have decreased the detection power of the trials. For that reason, a post hoc analysis was conducted in order to compare efficacy between these two approaches, and no difference was detected.

A limiting factor in this review might have been the Y-BOCS itself. Because the scale attributes maximum score to obsessions that last for 8 hours a day, and any patients included in the review had very serious OCD with obsessions longer than 8 hours, this scale is not very sensitive to symptomatic improvement in the very severe extreme of the OCD symptom spectrum, even if that improvement is very significant. Additionally, the remission threshold was a Y-BOCS of 6, which is rather conservative. So, considering these aspects, the Y-BOCS improvement reported can be considered clinically significant.

Effect on Mood

There was a decrease in HDRS score of 7.3 between active and sham stimulation. At last follow-up, DBS led to a decrease of 13.7 in WDS. These results may have been limited by the fact that many reports excluded patients with a diagnosis of major depressive disorder, many reported this parameter incompletely or not at all, and different reports used different mood scales, which had to be standardized, possibly decreasing the quality of the analysis. There was a statistically significant correlation between Y-BOCS and WDS decreases. However, it is not possible with this review to determine whether this decrease indicates that (1) clinically severe OCD leads to depressive symptoms that remit once illness is treated or (2) there are pathological mechanisms of depression underpinning OCD, and the interference of OCD on these mechanisms leads to symptom improvement. Two reports[31,51] suggest that symptomatic improvement happens sequentially: first, mood and anxiety within hours; next, obsessions within days; and finally, compulsions within weeks or months. This sequence appears to be in accordance with the hypothesis that there are pathological mechanisms of depression underpinning OCD.

Safety

There are significant proportions of adverse events and dropouts. This is consistent with previous reports[38,39] and appears to be similar to adverse event rates in capsulotomy.[81] A recent meta-analysis, however, found capsulotomy to have less adverse events than DBS.[80] The high rate of adverse events found here may be due to overrepresentation of transient events, which were not possible to exclude. Furthermore, there were significant differences in adverse event reporting in the included reports. There was no association between adverse events and stimulation site or time of follow-up, which may be a suggestion that their incidence is limited to the perioperative time.

CONCLUSIONS

Our results showed that, including recent trials performed, DBS can significantly decrease YBOCS score and depressive symptoms in refractory OCD.

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Posttest

To obtain credit, go to PSYCHIATRIST.COM **(Keyword: June CME) to take this Posttest and complete the Evaluation.** A $10 processing fee is required.

1. **Diego is a 38-year-old man with severe obsessive-compulsive disorder (OCD). At the present visit, his score on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) is 34, and every time you evaluate him, it is always over 30. Diego has also had subsyndromal-to-moderate depressive symptoms for most of the course of the OCD and currently meets criteria for major depressive disorder. He has been approved by a multidisciplinary team for deep brain stimulation (DBS). According to this meta-analysis, what is the most probable change for Diego's symptoms after DBS?**
   a. Improvement in OCD symptoms and in depressive symptoms
   b. Improvement in OCD symptoms but not in depressive symptoms
   c. Improvement in depressive symptoms but not in OCD symptoms
   d. No improvement in OCD or depressive symptoms

2. **Charlotte is a 52-year-old woman with OCD. Several months ago, she received an implanted bilateral DBS device in the nucleus accumbens (NAcc), and she has been regularly followed for improvement. Her Y-BOCS score indicates only partial response. The DBS parameters are the following: voltage 2.5 V, pulse width 130 ms, and frequency 160 Hz. According to this meta-analysis, which change in parameters would improve DBS efficacy for Charlotte?**
   a. Increase voltage
   b. Increase pulse width
   c. Increase frequency
   d. Data do not support an expected improvement with any of the above changes when compared to each other

3. **Violet is a 32-year-old woman with severe OCD. At the present visit, her score on the Y-BOCS is 37, and every time you evaluate her, it is always over 28. She has been approved by a multidisciplinary team for DBS. According to this meta-analysis, which of the following statements is most accurate regarding the preferred stimulation site for Violet?**
   a. Stimulation in the NAcc has a higher probability of reducing Y-BOCS scores than stimulation in the subthalamic nucleus (STN)
   b. Stimulation in the STN has a higher probability of reducing Y-BOCS scores than stimulation in the NAcc
   c. Neither NAcc nor STN stimulation has a significant effect on Y-BOCS scores
   d. Data do not support an increased effect on Y-BOCS scores for stimulation in limbic and non-limbic sites compared with each other