Dorsal anterior cingulotomy and anterior capsulotomy for severe, refractory obsessive-compulsive disorder: a systematic review of observational studies

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OBJECTIVE The object of this study was to perform a systematic review, according to Preferred Reporting Items of Systematic reviews and Meta-Analyses (PRISMA) and Agency for Healthcare Research and Quality (AHRQ) guidelines, of the clinical efficacy and adverse effect profile of dorsal anterior cingulotomy compared with anterior capsulotomy for the treatment of severe, refractory obsessive-compulsive disorder (OCD).

METHODS The authors included studies comparing objective clinical measures before and after cingulotomy or capsulotomy (surgical and radiosurgical) in patients with OCD. Only papers reporting the most current follow-up data for each group of investigators were included. Studies reporting results on patients undergoing one or more procedures other than cingulotomy or capsulotomy were excluded. Case reports and studies with a mean follow-up shorter than 12 months were excluded. Clinical response was defined in terms of a change in the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score. The authors searched MEDLINE, PubMed, PsycINFO, Scopus, and Web of Knowledge through October 2013. English and non-English articles and abstracts were reviewed.

RESULTS Ten studies involving 193 participants evaluated the length of follow-up, change in the Y-BOCS score, and postoperative adverse events (AEs) after cingulotomy (n = 2 studies, n = 81 participants) or capsulotomy (n = 8 studies, n = 112 participants). The average time to the last follow-up was 47 months for cingulotomy and 60 months for capsulotomy. The mean reduction in the Y-BOCS score at 12 months' follow-up was 37% for cingulotomy and 55% for capsulotomy. At the last follow-up, the mean reduction in Y-BOCS score was 37% for cingulotomy and 57% for capsulotomy. The average full response rate to cingulotomy at the last follow-up was 41% (range 38%–47%, n = 2 studies, n = 51 participants), and to capsulotomy was 54% (range 37%–80%, n = 5 studies, n = 50 participants). The rate of transient AEs was 14.3% across cingulotomy studies (n = 116 procedures) and 56.2% across capsulotomy studies (n = 112 procedures). The rate of serious or permanent AEs was 5.2% across cingulotomy studies and 21.4% across capsulotomy studies.

CONCLUSIONS This systematic review of the literature supports the efficacy of both dorsal anterior cingulotomy and anterior capsulotomy in this highly treatment-refractory population. The observational nature of available data limits the ability to directly compare these procedures. Controlled or head-to-head studies are necessary to identify differences in efficacy or AEs and may lead to the individualization of treatment recommendations.

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KEY WORDS obsessive-compulsive disorder; cingulotomy; capsulotomy; stereotactic lesions; psychiatric neurosurgery; functional neurosurgery

OBSESSIVE-compulsive disorder (OCD) is characterized by repetitive and intrusive thoughts and behaviors that cause clinically significant distress or impairment.² The estimated prevalence of OCD in the US is 2.3%, making it one of the most common psychiatric

disorders in the US.²⁷ In 2002, the World Health Organization reported that OCD was responsible for nearly 1% of global years lost due to disability.²³ Approximately 40%–60% of patients with OCD fail to satisfactorily respond to standard treatments, including serotonin reuptake inhibi-

ABBREVIATIONS AE = adverse event; AHRQ = Agency for Healthcare Research and Quality; CBTC = cortico-basal ganglia-thalamocortical; dACC = dorsal anterior cingulate cortex; DBS = deep brain stimulation; LL = limbic leucotomy; MeSH = Medical Subject Headings; OCD = obsessive-compulsive disorder; OFC = orbitofrontal cortex; PRISMA = Preferred Reporting Items for Systematic reviews and Meta-Analyses; SCT = subcaudate tractotomy; Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

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tors and cognitive behavioral therapy. These patients are potential candidates for neurosurgical intervention.

The advent of stereotaxy in the mid-20th century led to the development of precise and reproducible lesion procedures for psychiatric indications, including dorsal anterior cingulotomy and anterior capsulotomy.^{3,18,22} The mechanism of action for both of these procedures is typically framed in relation to aberrancies in the affective cortico-basal ganglia-thalamocortical (CBTC) circuit.^{1,5} Dorsal anterior cingulotomy, a lesion in the dorsal anterior cingulate cortex (dACC) and cingulum bundle, disrupts bidirectional signaling between the dACC and the orbitofrontal cortex (OFC), ventral striatum, and limbic structures. Anterior capsulotomy, which targets the anterior limb of the internal capsule, is thought to disrupt communication among the OFC, dACC, ventral striatum, and thalamus.

Independent bodies of evidence support the efficacy of cingulotomy and capsulotomy in the management of treatment-refractory OCD. However, we are aware of only 2 studies that directly compared the 2 procedures, and the most recent was conducted in 1982.^{9,17} Given the potential benefit of neuromodulatory procedures for intractable psychiatric and neurological disorders, it is critical to understand the evidence supporting these procedures, as well as their adverse effect profiles.

The primary objective of this study was to evaluate and compare the clinical efficacy and adverse effect profiles of dorsal anterior cingulotomy and anterior capsulotomy for the treatment of severe, refractory OCD. This systematic review was conducted in compliance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)²⁴ as well as the Agency for Healthcare Research and Quality (AHRQ) recommendations (www.effectivehealthcare.ahrq.gov) for comparative effectiveness reviews, where appropriate.

Methods

Literature Search Strategy and Data Sources

The following electronic databases were searched for primary studies through October 2013: MEDLINE, PubMed, PsycINFO, Scopus, and Web of Knowledge. The search strategy used index terms, such as Medical Subject Headings (MeSH), and key words, as applicable. There were no language restrictions. Conference proceedings were included. Table 1 provides a representative example of the database search strategy implemented in MEDLINE.

In an effort to reduce publication bias, gray literature (for example, unpublished data) was obtained by searching clinical trial registries including ClinicalTrials.gov, National Research Register, and metaRegister of Controlled Trials. Additional information was gathered by hand searching bibliographies from selected papers as well as collections of articles known to the study authors.

Eligibility Criteria

Study Selection

The search results were compiled, and duplicate citations were deleted. One reviewer assessed the titles and abstracts of these studies for potential relevance. Full text

articles were identified for the potentially relevant citations. These articles were examined, and study eligibility was determined in an unblinded fashion. Only papers with the most current follow-up data for each group of investigators were included. Case studies were excluded from review. All other study designs were considered for inclusion. Selection criteria are summarized in Table 2.

Participants

The target study population constituted adults (age ≥ 18 years old) with severe, refractory OCD and no history of surgery for a psychiatric indication. We excluded studies with patients whose history included psychiatric neurosurgery to reduce the risk of attributing clinical outcome to the cumulative effect of multiple surgeries. However, many of the studies meeting all other selection criteria included results from 1 or more patients who had undergone repeat surgery. Fortunately, many of these studies provided individual patient results, allowing for the exclusion of participants who had undergone more than 1 procedure. Individual participants were included if both of the following criteria were met: 1) the second procedure was a reoperation of the same type as the first (for example, cingulotomy followed by cingulotomy was included, whereas cingulotomy followed by subcaudate tractotomy was excluded); and 2) reoperation took place within a few months of the initial procedure because of the insufficiency of the first procedure, as indicated by postoperative neuroimaging or clinical assessment.

Studies that did not provide sufficient detail to exclude individual participants were selected if they met the following conditions: 1) less than a quarter of the participants underwent a second procedure; 2) the second procedure was a reoperation of the same type as the first (as explained above); and 3) reoperation took place within a few months of the initial procedure because of the insufficiency of the first procedure, as indicated by postoperative neuroimaging or clinical assessment.

Interventions

Bilateral cingulotomy and capsulotomy for the primary indication of OCD were the exclusive interventions of interest. Surgical and radiosurgical techniques were included. Stereotactic guidance with MRI was required for inclusion as this technique is most relevant to current practice. Studies that used other methods (that is, CT only or ventriculography) were excluded. Variations in lesion technique with regard to lesion location or radiation dose were noted, although these did not influence study eligibility. Studies comparing the interventions to each other or to placebo, as well as noncomparative studies, were considered for inclusion. Studies combining either procedure of interest with an adjunct lesion procedure were excluded (for example, limbic leucotomy).

Outcomes

The primary outcome was clinical improvement of OCD symptoms, as measured by a change in the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score,¹¹ after undergoing either capsulotomy or cingulotomy. Secondary outcomes included changes in depression and

TABLE 1. Search term combinations for MEDLINE database accessed on October 28, 2013

Question Components & Selection of Relevant Terms	Type of Term		Boolean Operator
	Free	MeSH	
Population: adults w/ treatment-refractory OCD			
1 exp Obsessive Compulsive Disorder/		x	OR (captures population)
2 OCD.mp.	x		
3 obsessive compulsive disorder.mp.	x		
4 Obsessive-Compulsive Disorder.mp.	x		
5 or (1-4)			
Interventions: cingulotomy, capsulotomy			
6 exp Psychosurgery/		x	OR (captures intervention)
7 exp Stereotaxic Techniques/		x	
8 exp Gyrus Cinguli/		x	
9 cingulotomy.mp.	x		
10 capsulotomy.mp.	x		
11 anterior capsulotomy.mp.	x		
12 or (6-11)			
Outcomes			
No search			
Study Designs			
No search			
13 5 and 12			AND (combines population and interventions)

anxiety rating scale scores and adverse events (AEs), with a separate category for those causing permanent or serious morbidity (for example, hemiplegia, intracranial hemorrhage, seizure disorder, cognitive deficits, personality change, weight gain) or mortality. Studies were excluded for a lack of documentation on primary outcome and for a mean follow-up shorter than 12 months. Depression, anxiety, and AE reporting did not impact study eligibility.

Data Extraction and Data Items

Data were obtained from eligible studies using a pre-specified electronic data collection form.¹² Collected data included the following: characteristics of study participants, study design and location, definition of treatment-refractory OCD, study eligibility criteria, details of surgical and medical treatment, change in therapeutic regimen during the study period, length of follow-up, method of data collection at each time point, Y-BOCS scores at baseline and available follow-ups, depression and anxiety scores at baseline and subsequent follow-ups, and AEs.

Quality Assessment

Risk of bias for the primary efficacy outcome was assessed for each individual study using a study design-specific tool developed by the AHRQ.³¹ Assessment of the risk of bias did not play a role in data synthesis.

Synthesis of Results

The primary outcome was pooled across studies by calculating the weighted mean Y-BOCS score at baseline, 12 months' follow-up, and last follow-up for cingulotomy and capsulotomy groups. The weight was based on the relative

proportion of participants from each study that met our inclusion criteria. Adverse event rates were quantified as the percentage of procedures that had complications. Repeat procedures were taken into account. Pooled AEs were calculated using a weighted average within each intervention group. The weight was based on the number of procedures that met inclusion criteria.

Results

Study Selection

A total of 1921 references were retrieved from electronic database searches, gray literature, and hand searches. After excluding 654 duplicates, 1267 references were

TABLE 2. Study selection criteria

Inclusion
Adult (age ≥18 yrs)
OCD Dx
Bilat cingulotomy or bilateral capsulotomy
Y-BOCS before & after intervention
Exclusion
Case report
Previous psychosurgery*
Lack of stereotactic MRI guidance
Cingulotomy or capsulotomy combined w/ other intervention
Mean FU <12 mos

Dx = diagnosis; FU = follow-up.

* See text for exceptions.

FIG. 1. PRISMA study selection flowchart. The selection process moves from top to bottom, starting with the electronic database search results and ending with the 10 studies included in this review. Exclusions are enumerated at each step in the selection process. Reasons for study exclusion are provided on the right side of the figure.

screened for potential eligibility, of which 1167 were excluded. The remaining 100 references underwent full text review (Fig. 1).

Study Characteristics

The characteristics of included studies are summarized in Table 3. Two cingulotomy and 8 capsulotomy studies were included in the review.

Study Design

The majority of included study designs were single-arm prospective cohort observational studies with the following exceptions: 1 retrospective cohort study²⁶ and 1 prospective controlled cohort study.⁶

Participants

All study participants were adults meeting the criteria for OCD in the Diagnostic and Statistical Manual of Mental Disorders. The studies included a total of 193 partici-

pants—81 who underwent cingulotomy and 112 who underwent capsulotomy. Most of the studies required treatment refractoriness as part of the inclusion criteria.^{6,7,19,21,25,26,28,29} One cingulotomy study¹⁴ and 4 capsulotomy studies^{15,19,21,28} specified exclusion criteria in the participant selection process. Only 5 studies, all capsulotomy studies,^{7,19,21,26,28} reported on the prevalence of psychiatric comorbidities.

Interventions

Surgical techniques included both open and radiosurgical methods. Each study reported unique parameters for temperature or radiation dose, number of lesion isocenters, or tracks per side. Rück et al. is notable among the stereotactic radiosurgery capsulotomy studies for using the largest radiation dose and number of isocenters.²⁶ Three capsulotomy studies pooled data from patients who had undergone reoperation with those who had undergone a single procedure,^{7,19,25} and 1 study included 1 patient with a history of deep brain stimulation (DBS) for OCD.²⁶ The majority of studies did not report co-interventions or ad-

TABLE 3. Characteristics of included studies

Source	Population			Intervention		Outcomes			
	Authors & Year (n, setting, study design)	Selection Criteria	Exclusion Criteria	Comorbid Psychiatric Disorders, Prevalence	Mean Age in Yrs, % Females, Baseline Severity	Surgery Details	Co-Interventions; Repeat Procedures	Efficacy Measures; AEs	Notes
Cingulotomy									
Jung et al., 2006 (n = 17, Korea, single-arm prospective cohort)	Duration: >3 yrs; severity: clinical assessment	Substance abuse, delusional disorders, Axis II (clusters A, B), Axis III Dx w/ brain pathology	None	None	36.1 (SD 9.4), 41.2%, Y-BOCS: 35 (SD 3.9), extreme	Bilat RF: 85°C for 90 sec, 4 isocenters along 2 tracks per side	NR; no repeat procedures	Y-BOCS, HAM-D, HAM-A	No TxR selection criteria; excluded patients w/ certain comorbid psychiatric disorders
Sheth et al., 2013 (n = 64, USA, single-arm prospective cohort)	Severity: clinical assessment; TxR: ≥3 SRIs, 2 aug, & >20 hrs behavioral therapy	None	None	None	34.7 (SEM 1.4), 34%, Y-BOCS: 30.9 (SEM 1.3), severe	Bilat RF: 85°C for 60 sec, 1 isocenter per side (before yr 2000), 3 isocenters per side (after yr 2000)	NR; 30 repeat procedures, results not pooled	Y-BOCS, BDI; passive surveillance	Demographic data for entire study population; rigorous TxR criteria
Capsulotomy									
Oliver et al., 2003 (n = 15, Spain, single-arm prospective cohort)	TxR: exhausted nonop options	None	None	None	34.2 (SD 8.2), 40%, Y-BOCS: 29.7, severe	Bilat RF: 75° C for 75 sec, 2 isocenters per side	NR; 3 repeat procedures, pooled results	Y-BOCS, BDI, HAM-D; passive surveillance	
Liu et al., 2008 (n = 35, China, single-arm prospective cohort)	TxR: pharmaco therapy, psychotherapy, or CBT ≥5 yrs	Cognitive deficits, severe heart disease, clotting disorders	Anxiety 60%, mood 37.1%, Tourette's 8.6%, behavioral 22.9%	Anxiety 60%, mood 37.1%, Y-BOCS: 21.2 (SD 4), moderate	29.6 (SD 10.6), 37.1%, Y-BOCS: 21.2 (SD 4), moderate	Bilat RF: 70°C & 80°C for 60 sec, 3 isocenters per side	Anti-OCD meds w/drawn; 2 repeat procedures, pooled results	Y-BOCS, HAM-A, HAM-D; passive surveillance	Baseline Y-BOCS indicates less severe OCD symptoms than other studies; discontinuation of anti-OCD meds
Rück et al., 2008 (n = 25, Sweden, single-arm retrospective cohort)	Duration: ≥5 yrs, severity: clinical assessment; TxR: systematic pharmaco- & psychotherapy trials	None	Mood 20%, anxiety 36%, tic 12%, personality 32%, suicide attempt 36%	Mood 20%, anxiety 36%, tic 12%, personality 32%, suicide attempt 36%	41 (SD 11), 56%, Y-BOCS: 33.5 (SD 3.4), extreme	Bilat & unilat RF: 60°C; bilat & unilat GK: 180 Gy at 1 isocenter or 200 Gy at 3 isocenters	NR; 8 repeat procedures, results not pooled for 7/8	Y-BOCS, MADRS, BSA; active surveillance (EAD)	High radiation doses
(continued)									

(continued)

TABLE 3. Characteristics of included studies (continued)

Source	Population			Intervention		Outcomes			
	Authors & Year (n, setting, study design)	Selection Criteria	Exclusion Criteria	Comorbid Psychiatric Disorders, Prevalence	Mean Age in Yrs, % Females, Baseline Severity	Surgery Details	Co-Interventions; Repeat Procedures	Efficacy Measures; AEs	Notes
Capsulotomy (continued)									
Lopes et al., 2009 (n = 5, Brazil & USA, single-arm prospective cohort)	Duration: ≥5 yrs, severity: Y-BOCS >26, TxR: ≥3 SSRIs/SRIs, 2 aug, & >20 hrs CBT w/o improvement in Y-BOCS & CGI scores	<18 or >55 yrs old, history of posttraumatic amnesia, OCD due to effects of a substance, pregnancy or lactation, mental retardation	Mood 80%, anxiety 60%, alcohol abuse 20%, personality 120%	35 (SD 11), 60%, Y-BOCS: 32.2 (SD 1.48), extreme	Bilat VC/VS GK: 180 Gy, 2 isocenters per side	Medical regimen unchanged; no repeat procedures	Y-BOCS, BDI, BAI; active surveillance (SAFTEE scale)	Rigorous TxR criteria; lesion location more ventral compared to those for other traditional anterior capsulotomy; only study w/ multi-center setting	
Csigó et al., 2010 (n = 5, Hungary, prospective controlled cohort)	TxR: not specified	None	None	32.2 (SD 6.3), 40%, Y-BOCS: 38.2 (SD 1.78), extreme	Bilat RF	Intensive rehab program; no repeat procedures	Y-BOCS, HAM-D, HAM-A; passive surveillance	Intensive rehabilitation co-intervention; only controlled study	
Kondziolka et al., 2011 (n = 3, USA, single-arm prospective cohort & case series)	Surgery requested by participant, severity: Y-BOCS >24	Abnormal brain MRI	None	43.7 (SD 9.9), 66.7%, Y-BOCS: 37.3 (SD 2.9), extreme	Bilat GK: 140 or 150 Gy	NR; no repeat procedures	Y-BOCS, clinical narrative; passive surveillance	No TxR selection criteria; patients had to request surgery	
D'Astous et al. 2013 (n = 19, Canada, single-arm prospective cohort)	Duration: ≥5 yrs, severity: Y-BOCS >24, GAF <50, TxR: ≥3 SRIs & psychotherapy ≥30 hrs	None	Mood 57.9%, anxiety 15.8%, psychotic 5.3%, adjustment 5.3%, personality 26.3%, mental retardation 5.3%, suicide attempt/ideation 31.6%	40.8 (SD 11.6), 63.2%, Y-BOCS: 34.9 (SD 4.8), extreme	Bilat leucotomy: 4 isocenters per side	NR; 2 repeat procedures, results pooled	Y-BOCS; passive surveillance	Rigorous TxR criteria, only study that used leucotomy	
Sheehan et al., 2013 (n = 5, USA, single-arm prospective cohort & case series)	Severity: Y-BOCS ≥24, TxR: treating psychiatrist clinical judgment	Brain MRI showing tumor, stroke, or vascular malformation	Mood 20%, suicide attempt/ideation 40%	37.8 (SD 8.8), 40%, Y-BOCS: 32.3 (SD 1.3), extreme	Bilat GK: 140–160 Gy, 1 isocenter per side	NR; no repeat procedures	Y-BOCS; passive surveillance		

aug = augmentation medication; BAI = Beck Anxiety Inventory; BSA = Beck Depression Inventory; BDI = Brief Scale of Anxiety; CBT = cognitive behavioral therapy; CGI = Clinical Global Impression; EAD = Execution, Apathy, and Disinhibition Scale; GAF = Global Assessment of Functioning; GK = Gamma Knife; HAM-A = Hamilton Anxiety Scale; HAM-D = Hamilton Depression Scale; MADRS = Montgomery-Asberg Depression Scale; meds = medications; none = none reported; NR = not reported; rehab = rehabilitation; RF = radiofrequency thermolesion; SAFTEE = Systematic Assessment for Treatment Emergent Events; SD = standard deviation; SEM = standard error of the mean; SRI = serotonin reuptake inhibitor; SSRI = selective SRI; TxR = treatment refractoriness; VC/VS = ventral capsular/ventral striatal capsulotomy.

dress potential therapeutic confounders, such as a change in medication regimen at the time of intervention. One study withdrew all anti-OCD medications at the time of capsulotomy,¹⁹ and another enrolled participants in an intensive rehabilitation program consisting of pharmacological and psychotherapy after surgery.⁶

Outcomes

Each study quantified OCD symptom severity using the Y-BOCS before and after the procedure and at the long-term follow-up. Nearly all of the studies also provided Y-BOCS data at the 12-month follow-up.^{6,7,14,19,21,25,26,29} Seven studies quantified depression before and after surgery,^{6,14,19,21,25,26,29} and 5 studies scored anxiety symptoms.^{6,14,19,21,26} All studies reported AEs. Two capsulotomy groups employed active surveillance of AEs through the use of a standardized inventory.^{21,26}

Quality Assessment

The assessment of risk of bias for the efficacy outcome is summarized in Table 4.

Individual Study Results

The Y-BOCS–based efficacy results of the individual studies are summarized in Table 5. Depression and anxiety outcomes are summarized in Table 6. Adverse events for each study are summarized in Table 7.

Synthesis of Results

Given that the majority of studies were observational and noncomparative, we were unable to perform statistical comparisons between or within cingulotomy and capsulotomy groups. However, individual study results were combined within their respective groups where appropriate.

Characteristics of Participants

The average age of participants at the time of surgery was 35.3 ± 10.7 (mean $\pm$ standard deviation), 35.0 ± 10.9 , and 35.6 ± 10.6 years across all studies, cingulotomy studies, and capsulotomy studies, respectively. The majority of participants were male, comprising 57% of participants across all studies. The average time to the last follow-up was 55 months (range 22–84 months) for all studies, 47 months (range 24–59 months) for cingulotomy, and 60 months (range 22–84 months) for capsulotomy.

Efficacy

The Y-BOCS–based efficacy results of individual studies are summarized in Table 5. The mean baseline Y-BOCS score was 32.3 (range 30.9–35) in the cingulotomy group and 29.3 (range 21.2–38.2) in the capsulotomy group. These scores fall within the extreme and severe ranges, respectively. The mean reduction in the Y-BOCS score at 12 months' follow-up was 37% (range 36%–37%) for cingulotomy and 55% (range 36%–75%) for capsulotomy. At the last follow-up, the mean reduction in the Y-BOCS score was 37% (range 31%–48%) for cingulotomy and 57% (range 32%–79%) for capsulotomy. In keeping with traditional thresholds used in pharmacology trials, full response was defined as a Y-BOCS score reduction $\geq$

TABLE 4. Risk of bias assessment

Authors & Year	Selection		Performance		Attrition	Detection	Interventions Defined Using Valid/Reliable Measures?	Outcomes Defined Using Valid/Reliable Measures?	Confounding Variables Assessed Using Valid/Reliable Measures?	Reporting
	Design or Analysis Accounts for Confounding?		Accounted for Concurrent Intervention/Unintended Exposure?	Fidelity to Intervention Protocol?						
Cingulotomy										
Jung et al., 2006	Yes		Unclear	Yes	NA	Unclear	Yes	Yes	Yes	Yes
Sheth et al., 2013	No		Unclear	No	Yes	Unclear	Yes	Yes	Unclear	Yes
Capsulotomy										
Oliver et al., 2003	No		Unclear	Yes	Unclear	Unclear	Yes	Yes	Unclear	Yes
Liu et al., 2008	No		No	Yes	NA	Yes	Yes	Yes	Yes	Yes
Rück et al., 2008	Yes		Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
Lopes et al., 2009	Yes		Yes	Yes	NA	Unclear	Yes	Yes	Yes	Yes
Csigó et al., 2010	Yes		No	Yes	NA	Unclear	Yes	Yes	Unclear	Yes
Kondziolka et al., 2011	Yes		Yes	No	NA	Unclear	Yes	Yes	Unclear	Unclear
D'Astous et al., 2013	No		Unclear	Yes	NA	Yes	Yes	Yes	Yes	Yes
Sheehan et al., 2013	Yes		Unclear	No	NA	No	Yes	Yes	Unclear	No

NA = not available.

TABLE 5. Outcomes per the Y-BOCS

Authors & Year	No.*	Mean		Preop Severity	Mean 12-Mo		12-Mo Severity	12-Mo Change in		12-Mo %		Mean LFU		LFU Severity	LFU		LFU % Change in Y-BOCS Score	LFU % Change in Y-BOCS Score	LFU % w/ Full Response	LFU % w/ Partial Response
		LFU in Mos (SD)	Preop Y-BOCS Score (SD)		Y-BOCS Score (SD)	12-Mo Y-BOCS Score (SD)		Y-BOCS Score	Y-BOCS Score	Y-BOCS Score (SD)	Y-BOCS Score (SD)	Y-BOCS Score	Y-BOCS Score							
		Cingulotomy																		
Jung et al., 2006	17	24†	35 (3.9)	Extreme	22.4 (6.5)		Mod	-12.6	-36			18.2 (4.4)	Mod	-16.8	-48	47‡		—		
Sheth et al., 2013	34	59 (61)	30.9 (7.6)	Severe	19.5 (10.4)§		Mod	-11.4	-37			21.3 (1.5)¶	Mod	-9.6	-31	38		25		
Capsulotomy																				
Oliver et al., 2003	15	24†	29.7**††	Severe	17.3**§§		Mod	-12.4	-42			18.2**¶¶	Mod	-11.5	-39	—		—		
Liu et al., 2008	35	36†	21.2 (4)	Mod	5.4 (2.1)		Sub	-15.8	-75			4.4 (4.4)	Sub	-16.8	-79	—		—		
Rück et al., 2008	18	135 (49)	33.5 (3.4)	Extreme	16.3 (11.8)***		Mod	-17.2	-51			15.9 (11.4)	Mod	-17.6	-53	61		28		
Lopes et al., 2009	5	48†	32.2 (1.5)	Extreme	20.2 (10.4)		Mod	-12	-37			20.6 (12.3)	Mod	-11.6	-36	60		20		
Csigo et al., 2010	5	24†	38.2 (1.8)	Extreme	19.6 (8.6)		Mod	-18.6	-49			18.2 (10)	Mod	-20	-52	—		—		
Kondziolka et al., 2011	3	42 (14)	37.3 (2.9)	Extreme	—		—	—	—			16.7 (8.1)	Mod	-20.6	-55	67		33		
D'Astous et al., 2013	19	84**	34.9 (4.8)	Extreme	22.2 (5)		Mod	-12.7	-36			23.8†††	Mod	-11.1	-32	37		10		
Sheehan et al., 2013	5	22 (12)	32.3 (1.3)	Extreme	—		—	—	—			16.2 (8.3)	Mod	-16.1	-50	80		0		

LFU = last follow-up; mod = moderate; sub = subclinical.

* Number of participants after exclusions.

† Prospective study with uniform LFU.

‡ Criteria includes CGI = 1 (very much improved) or CGI = 2 (much improved).

§ First postoperative follow-up was approximately 9–12 months; n = 30.

¶ n = 32.

** Standard deviation not reported.

†† n = 18, based on the number of procedures.

§§ n = 10.

¶¶ n = 5.

*** n = 16.

††† Variance represented in original graph in cited study.

35% at the last follow-up, and partial response was defined as a Y-BOCS score reduction $\geq 25\%$ and $< 35\%$. The mean full response rate for cingulotomy at the last follow-up was 41% (range 38%–47%, $n = 2$ studies, $n = 51$ participants), and the partial response rate was 25% ($n = 1$ study, $n = 34$ participants). For capsulotomy, the mean full response rate at the last follow-up was 54% (range 37%–80%, $n = 5$ studies, $n = 50$ participants) and the partial response rate was 18% (range 0%–33%, $n = 5$ studies, $n = 50$ participants).

Depression and anxiety outcomes for available studies are presented in Table 6. We were unable to combine results across studies given that the scales used to assess depression and anxiety differed between studies.

Adverse Events

Adverse events were characterized as the number of events per procedure (Table 7). The rate of transient AEs was 14.3% (range 13.7%–17.6%) across cingulotomy studies ($n = 116$ procedures) and 56.2% (range 0–260%) across capsulotomy studies ($n = 112$ procedures). The rate of serious or permanent AEs was 5.2% (range 0–6%) across cingulotomy studies and 21.4% (range 0–66.7%) across capsulotomy studies. It should be noted that the AE rate across cingulotomy studies may be overly elevated as 1 study includes complications from all procedures, including repeat cingulotomy and limbic leucotomy procedures.²⁷ In addition, nearly all of the serious or permanent AEs reported by Rück et al. are attributable to 3 patients who had received 200 Gy at 3 isocenters, and thus receiving the greatest radiation exposure of all participants in the reviewed studies.²⁶ Excluding this study from the pooled results nearly halves the rate of serious complications in the capsulotomy group to 12.8% (range 0–40%).

Discussion

Summary of Evidence

The reviewed literature supports the assertion that dorsal anterior cingulotomy and anterior capsulotomy are effective interventions in the management of severe, refractory OCD. The pooled mean reduction in baseline Y-BOCS score meets the criteria for treatment response following both capsulotomy and cingulotomy at the 12 months' and the long-term follow-ups. In both intervention groups, the Y-BOCS scores appear to change very little between 12 months and the last follow-up, indicating a stable treatment response over time. More than half of the participants who underwent capsulotomy met the criteria for treatment response at the last follow-up (54%, range 37%–80%) as well as nearly half of those who underwent cingulotomy (41%, range 38%–47%). Both procedures carry the risk of AEs. Capsulotomy was associated with 56.2% transient and/or mild AEs and 21.4% permanent and/or serious AEs. Excluding Rück et al. from the pooled results yields a 12.8% serious complication rate for capsulotomy.²⁶ Cingulotomy was associated with 14.3% transient and/or mild AEs and 5.2% permanent and/or serious AEs. Lastly, both cingulotomy and capsulotomy appear to be efficacious in addressing comorbid depression and anxiety symptoms, as evidenced by a significant reduction in the respective inventory scores following both procedures.

TABLE 6. Depression and anxiety scale outcomes

Authors & Year	No.*	Mean LFU in Mos	Depression				Anxiety					
			Scale	Mean Baseline Score	Mean LFU Score	% Change	p Value	Scale	Mean Baseline Score	Mean LFU Score	% Change	p Value
Cingulotomy												
Jung et al., 2006	17	24†	HAM-D	23.9 (SD 11.5)	12 (SD 7.4)	-50	0.003	HAM-A	16.8 (SD 8)	7.2 (SD 6.1)	-57.1	0.005
Sheth et al., 2013	34	59 (SEM 11)	BDI	24.3 (SEM 1.8)	21.3 (SEM 2.6)‡	2§	—	—	—	—	—	—
Capsulotomy												
Oliver et al., 2003	15	24†	HAM-D	NR	NR	NR	0.415	—	—	—	—	—
			BDI	20.1	11	-45.3	0.038	—	—	—	—	—
Liu et al., 2008	35	36†	HAM-D	7.4 (SD 3.4)	2.4 (SD 2.1)	-67.6	<0.001	HAM-A	17.4 (SD 3.1)	4 (SD 2.4)	-77	<0.001
Rück et al., 2008	18	135 (SD 49)	MADRS	20.1 (SD 7.9)	8.8 (SD 5.4)	-56.2	<0.001	BSA	16.7 (SD 6.3)	9.9 (SD 5.6)	-40.7	<0.05
Lopes et al., 2009	5	36†	BDI	25.2 (SD 10)	16.6 (SD 13.2)	-23.4§	—	BAI	27.6 (SD 11.5)	12.6 (SD 8.1)	-51.2§	—
Csigó et al., 2010	5	24†	HAM-D	22.6 (SD 13.7)	7.2 (SD 4.7)	-68.1	NS¶	HAM-A	21.2 (SD 7.15)	11 (SD 7.9)	-48.1	0.001¶

NS = not significant.

* Number of participants after exclusions.

† Prospective study with uniform LFU.

‡ $n = 32$.

§ Significance not reported.

¶ Friedman's ANOVA testing significance of time.

TABLE 7. Adverse events

Authors & Year	No. of Procedures*	Transient AEs			Permanent/Serious AEs			
		Event	Time to Resolution	No. of Events	%	Event	No. of Events	%
Cingulotomy								
Jung et al., 2006	17	Immediate memory dysfunction	<2 mos	3	17.6	None	—	—
Sheth et al., 2013	99†	Postop memory difficulty	Days to mos	5	5.1	Seizure disorder requiring AED	1‡	1
		Urinary retention	Days	2	2	Subdural empyema requiring surgical evacuation	1	1
		Worsened preexisting urinary incontinence	—	1	1	Pulmonary embolus	1§	1
		Abulia after initial cingulotomy	Days	1	1.6¶	Suicide	2**	2
		Intraop seizure	<1 min	3	3	Ventriculostomy to rule out hydrocephalus	1††	1
		Postop seizure	—	1‡	1	ICH	0	0
Capsulotomy								
Oliver et al., 2003	18	Hallucinations	Transient	1	5.6	Postop brain edema w/ permanent sequela	1	5.6
		Single seizure	—	1	5.6	Behavior disorder	1‡‡	5.6
						Cognitive impairment	0	0
Liu et al., 2008	37	Urinary incontinence	3–5 days	3	8.1	ICH requiring ventricular drainage	1	2.7
		Acute confusion	3–5 days	3	8.1	Personality change (apathy, abulia, loss of interest)	2	5.4
		Mild cognitive deficits	3–10 days	9	24.3	Weight loss	1	2.7
		Transient dementia	3–10 days	9	24.3	Severe personality change	0	0
						Cognitive impairment	0	0
						Hemiparesis	0	0
						Aphasia	0	0
Rück et al., 2008	18	None	—	—	—	EAD ≥3 at LFU§§	7	38.9
						Chronic brain edema	1	5.6
						Radiation necrosis w/ permanent sequelae	1	5.6
						Memory problems	1¶¶	5.6
						Urinary incontinence	1***	5.6
						Seizures requiring hospitalization	1***	5.6
						Long-term mean weight gain†††	—	—
Lopes et al., 2009	5	Headaches, NSAID responsive	Days to weeks	3	60	Considerable weight gain	1	20
		Lightheadedness/vertigo	Days to weeks	4	80	Episodic headaches, requiring steroids	1	20
		Weight changes	Days to weeks	4	80			
		Episodic N/V	Days to weeks	2	40			
Csigó et al., 2010	5	Urinary incontinence	Temporary	2	40	Weight gain	2	40
		Periorbital tumescence	—	2	40			
		Fever	Several days	3	80			
		Sleepiness	4 days	1	20			
		Mod depressive episode	10 days	2	40			

(continued)

TABLE 7. Adverse events (*continued*)

Authors & Year	No. of Procedures*	Transient AEs			Permanent/Serious AEs			
		Event	Time to Resolution	No. of Events	%	Event	No. of Events	%
Capsulotomy (<i>continued</i>)								
Kondziolka et al., 2011	3	No adverse outcomes		0	0	No adverse outcomes	0	0
D'Astous et al., 2013	21	Asymptomatic hemorrhage		3	14.3	Hemiplegia due to perioperative hemorrhage	1	4.8
		Frontal syndrome		5	23.8	Cognitive deficit	1	4.8
		Urinary incontinence		1	4.76			
		Pneumonia		1	4.76			
		Urinary infection		1	4.76			
		DVT		3	14.3			
Sheehan et al., 2013	5	No adverse outcomes	NA	0	0	No adverse outcomes	0	0

DVT = deep vein thrombosis; ICH = intracerebral hemorrhage; N/V = nausea/vomiting.

* Number of procedures after exclusions.

† Includes all procedures for all included subjects (that is, 34 single cingulotomies, 30 second procedures, 35 third procedures).

‡ One of the patients that had an intraoperative seizure.

§ In the setting of a long plane trip home.

¶ n = 64, number of initial cingulotomies.

** One patient: history of major depressive disorder (preoperative BDI 41, severe depression) and Y-BOCS score unchanged at 7 months' follow-up; suicide at 10 months postoperatively. Other patient: history bipolar and severe depression (preoperative BDI 39); stable on discharge at postoperative Day 2; committed suicide 8 days later.

†† In setting of postoperative abulia and slightly enlarged ventricles.

††† Permanent sequela of postoperative brain edema.

§§ Represents clinically significant dysfunction in areas of executive function, apathy, and disinhibition.

¶¶ Secondary to radiation necrosis.

*** Secondary to chronic postoperative brain edema.

††† 81.0 kg (SD 25.0; range 50–140 kg); n = 22.

Study Limitations

Overall, the included studies reflect the population, interventions, and outcomes of interest. Treatment refractoriness and disease severity were important population descriptors for the purposes of this review. Nearly all of the included studies satisfied these 2 criteria. Nevertheless, inconsistent comorbidity reporting across studies makes generalization difficult given the significant impact of psychiatric comorbidity, specifically depression, on quality of life measures in OCD.^{8,13}

Interinstitutional heterogeneity in surgical technique was evident in both cingulotomy and capsulotomy studies. Variation in radiation dosage, number of radiosurgical isocenters, thermolesion temperature dosage, and lesion location must be taken into account when generalizing to current neurosurgical practice. This heterogeneity is of particular relevance to AEs. Rück et al. illustrate an association between excessive radiation exposure and risk of permanent AEs.²⁶ In their report, the authors conceded that the dose was too high and probably accounted for the complications observed in those patients. Removing this outlier study from our analysis greatly reduced the AE rate for capsulotomy, thereby highlighting the need for careful consideration of individual technique and event reporting before casting broad generalizations on the safety of either capsulotomy or cingulotomy. Active surveillance of AEs in future studies would facilitate comparison within and across intervention groups.

All included studies used the Y-BOCS to assess symptom severity prior to surgery and at follow-up. The validity and reliability of the Y-BOCS for measuring OCD symptom severity has been well established; however, the relationship between Y-BOCS scores and quality of life measures is less well characterized. A number of studies have found that OCD symptoms have a significant effect on quality of life, but this relationship is not as well established as that between depressive symptoms and quality of life.^{10,13,16,30} Fortunately, the reviewed literature supports the role of cingulotomy and capsulotomy in treating comorbid depressive symptoms as well.

A major limitation of this study is its composition of solely observational studies without controls. The nature of these study designs increases the risk of bias due to compromised internal validity (Table 4). Furthermore, the lack of comparison in the designs of the included studies does not support the direct or indirect comparison of outcomes between cingulotomy and capsulotomy. Controlled trials are necessary to determine the relative efficacy between the 2 procedures. The results of this systematic review must be interpreted within the context of the strengths and weaknesses of the included studies.

Currently, the choice of which lesion procedure to offer is largely based on historic institutional practice. As highlighted in this systematic review, no data support the application of one procedure over the other in terms of efficacy or safety profile. Future studies should strive for homogeneity of technique and careful documentation of OCD subtype and neuropsychological profile. Head-to-head comparisons, even in a blinded fashion potentially, would be ethically feasible given current clinical equipoise. Because the procedures target different regions of the same CBTC

circuit, it is quite possible that such comparisons would reveal subtle differences in response, allowing tailoring of recommendations based on individual symptoms.

We did not include DBS studies in this systematic review for a number of reasons. First, a recent article has thoroughly reviewed the literature of DBS for OCD.⁴ Whereas that article is not a “systematic review,” we believe that the information presented in our current paper can be easily compared with the information presented in that article and that further recapitulation of the same information would be redundant. Second, there is significant heterogeneity in the DBS literature (summarized in Blomstedt et al.⁴) in terms of study design and reporting. Given the limitations mentioned above within just the lesion literature, we believe that inclusion of the DBS literature would further limit the utility of a systematic review. Third, DBS has been available for a comparably shorter period of time; therefore, the duration of follow-up is less than that for lesions. For example, the last follow-up intervals in the lesion studies included in the present review ranged from 22 to 135 months, whereas those in some of the DBS studies were as short as 3 months.

We also chose not to include subcaudate tractotomy (SCT) and limbic leucotomy (LL) in this systematic review. A dearth of studies report OCD outcomes for SCT and LL in the literature. Search protocols similar to the ones used for cingulotomy and capsulotomy were used to query PubMed for articles published within the past 10 years that reported LL or SCT outcomes for OCD. The initial search yielded 21 articles for SCT and 34 articles for LL, published since January 1, 2003. After applying our study inclusion criteria, only 1 of the articles covering SCT or LL would have been included. Therefore, SCT and LL were not included in the current systematic review.

Despite the limitations of this study, cingulotomy and capsulotomy remain important parts of the neurosurgical armamentarium for the treatment of severe, refractory OCD. These procedures are quite relevant in contemporary practice, as evidenced by the fact that 3 of the 10 studies were published in 2013. Lopes and colleagues recently published the results of a randomized controlled trial of gamma ventral capsulotomy for OCD, the first such study to evaluate lesion outcomes for OCD.²⁰ This study further supports the modern relevance of lesion studies as well as the feasibility of employing a randomized blinded study design to measure clinical outcomes. With the advent of newer methods of lesioning (laser ablation, focused ultrasound), it is likely that stereotactic lesions will continue to play an important role in functional neurosurgery.

Conclusions

The available clinical evidence supports the efficacy of both cingulotomy and capsulotomy in treating severe, refractory OCD, as well as comorbid depressive and anxiety symptoms. Current evidence is insufficient to directly compare cingulotomy and capsulotomy, and recommendations on when to choose one procedure over the other cannot be made. Active AE surveillance is necessary to compare negative outcomes between the 2 interventions. Future controlled comparative studies are necessary to

accurately compare responses to cingulotomy and capsulotomy and may shed light on subtle differences in patient response that can be used to provide individualized treatment recommendations.

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