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Deep Brain Stimulation for Psychiatric Diseases: What Are the Risks?

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Abstract Despite the application of deep brain stimulation (DBS) as an efficient treatment modality for psychiatric disorders, such as obsessive-compulsive disorder (OCD), Gilles de la Tourette Syndrome (GTS), and treatment refractory major depression (TRD), few patients are operated or included in clinical trials, often for fear of the potential risks of an approach deemed too dangerous. To assess the surgical risks, we conducted an analysis of publications on DBS for psychiatric disorders. A PubMed search was conducted on reports on DBS for OCD, GTS, and TRD. Forty-nine articles were included. Only reports on complications related to DBS were selected and analyzed. Two hundred seventy-two patients with a mean follow-up of 22 months were included in our analysis. Surgical mortality was nil. The overall mortality was 1.1 %: two suicides were unrelated to DBS and one death was reported to be unlikely due to DBS. The majority of complications were transient and related to stimulation. Long-term morbidity occurred in 16.5 % of cases. Three patients had permanent neurological complications due to intracerebral hemorrhage (2.2 %). Complications reported in DBS for psychiatric diseases appear to be similar to those reported for DBS in movement disorders. But class I evidence is lacking. Our analysis was based mainly on small non-randomized studies. A significant number of patients (approximately 150 patients) who were treated with DBS for psychiatric diseases had to be excluded from our analysis as no data on complications was available. The exact prevalence of complications of DBS in psychiatric diseases could not be established. DBS for psychiatric diseases is promising, but remains an experimental technique in need of further evaluation. A close surveillance of patients undergoing DBS for psychiatric diseases is mandatory.

Keywords Deep brain stimulation · Obsessive-compulsive disorder · Gilles de la Tourette syndrome · Treatment-resistant depression · Lesion therapy

Abbreviations

AE	Adverse events
ALIC	Anterior limb of the internal capsules
BA	Brodmann area
DBS	Deep brain stimulation
GTS	Gilles de la Tourette Syndrome
ECT	Electroconvulsive therapy
HW	Hardware
ICH	Intracranial hemorrhage
MER	Microelectrode recordings
NA	Nucleus accumbens
OCD	Obsessive-compulsive disorder
PD	Parkinson's disease
SCG	Subgenual cingulated gyrus
STN	Subthalamic nucleus
TRD	Treatment refractory major depression
VC/VS	Ventral capsule/ventral striatum

Introduction

Despite progresses in conventional therapy for psychiatric diseases, as obsessive-compulsive disorder (OCD), Gilles de la Tourette syndrome (GTS), and depression, an estimated

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10–30 % of patients fail to respond to medical treatment [1–3] and continue to suffer from these very disabling psychiatric conditions. Moreover, pharmacological treatment and electroconvulsive therapy (ECT) expose the patients to various complications [4–8].

For decades, neurosurgery has represented an alternative option for refractory psychiatric diseases [9]. Lesion therapy, such as anterior cingulotomy, capsulotomy, subcaudate tractotomy, and limbic leucotomy were and continue to be used effectively for severe psychiatric illness [10–13]. However, these techniques, consisting of performing an irreversible brain lesion, were questioned for ethical reasons [14, 15]. Deep brain stimulation (DBS), nowadays considered as a standard technique in medically refractory movement disorders, has the presumed advantage to be a non-destructive, reversible, and adjustable surgical technique. DBS has been proposed for psychiatric diseases in the last decade, mainly in pilot studies based on the results of previous lesion studies, serendipity, and the knowledge of the neuronal networks underlying psychiatric diseases physiopathology.

Vandewalle and colleagues pioneered in 1999 DBS for refractory GTS [16] targeting the same thalamic nuclei lesioned decades earlier by Hassler and Dieckmann [17]. Since that, several DBS studies, targeting various deep nuclei, reported a 25–90 % tic reduction in patients with severe GTS [18].

Nuttin and colleagues [19] proposed DBS for refractory OCD, by stimulating the anterior limb of the internal capsules (ALIC), a target previously used for lesion. In small series, DBS targeting the ALIC, the nucleus accumbens (NA) or the subthalamic nucleus (STN) led to a mean 35 % decrease of the obsessive-compulsive symptoms severity in most of the patients [11]. Efficacy of DBS in OCD has been strongly suggested in two small-sized cross-over randomized studies [20, 21].

In 2005, Mayberg and colleagues [22] pioneered DBS for treatment refractory depression (TRD), by implanting the subgenual cingulated region (BA 25), based on their observation that the Brodmann area 25 (BA 25) metabolism was increased in TRD patients and decreased after remission. TRD patients treated by DBS targeting the BA25, nucleus accumbens, or ventral striatum demonstrated an overall response rate of 30–50 % in open studies [3].

Despite these encouraging results, there is a lack of class I evidence and DBS for psychiatric disorders still remains at an investigational stage [23•]. Psychiatrists facing severe and medically refractory OCD, GTS, or TRD patients, have to consider the risk/benefit ratio of DBS before to refer their patients to the neurosurgeon or include them in clinical studies. However, although approximately 420 patients underwent DBS for psychiatric disorders over the last decade, little is known on the safety profile of DBS for psychiatric diseases. Most of the publications focused mainly on clinical outcome and less on complications. Our study aimed, therefore, to analyze the reported complications and to allow a comprehensive assessment of the benefits and risks in DBS for psychiatric diseases. However, one should mind that the benefit-risk ratio of DBS must be considered in light of the severity of this group of patients and the adverse effects of the alternative treatments.

Methods

We conducted a PubMed search selecting original studies in English language reporting on DBS for psychiatric diseases, limited to GTS, OCD, and TRD, which represent the main psychiatric indications for DBS treatment in recent years. Articles that did not disclose the information related to complications were excluded. The assumption that complications were not reported because they did not occur was not made. Consequently, only 49 out of the initial 82 studies were included: 21 GTS [24•, 25•, 26–29, 30•, 31•, 32, 33•, 34–40, 41•, 42, 43•, 44], 18 OCD [19–21, 45, 46•, 47–57, 58•], and 10 TRD studies [59–61, 62•, 63–67]. When the precise degree of overlap of cohorts reported in serial papers was not specified, the authors were contacted and, if provided, the information was integrated in our analysis.

To present the highly heterogeneous data in a comprehensive way, we extracted for each psychiatric indication the reported adverse events (AE) (Tables 1, 2, and 3). Only AE specified by the authors to be secondary to DBS were tabulated, except death (other than suicide), suicide, and suicidality (that included "suicide attempts," "suicide plans," and "suicide ideation"). AE were classified into surgical-, device-, and stimulation-related ones. We chose to analyze separately hardware-related complications and hardware infections, but some authors did not report them separately. Consequently, the rate of infections might be slightly underestimated in our analysis. We did not consider battery replacement as a complication. Complications were regrouped subsequently into 11 main AE: death (other than suicide), suicide, suicidality, intracranial hemorrhage (ICH), device-related complications, infection, anxiety, mood changes (these, although not always specified, included unwanted increase or decrease in mood, hypomania, mania, depression), psychosis, apathy, and alterations in sexual function. These AE were analyzed separately per disease (Table 4) and per target (Table 5). Results were indicated in percentages. The analysis of AEs per target (Table 5) excluded the multiple targets DBS studies, because they did not report the respective AEs of each target separately.

We did not compare the rates of AE between targets and diseases because the small size of the samples made the statistical analysis poorly relevant.

Table 1 GTS DBS

Authors (year)	Ref.	Target, laterality, (*n*° pts)	Sample size	Age (yrs)	FU (mo)	YGTSS % reduction	YBOCS % reduction	Transient AE surgical HWR (*n*° pts)	Long-term AE surgical HWR (*n*° pts)	Transient AE (*n*° pts)	Long-term AE (*n*° pts)
Cannon (2012)	[24•]	mGPi, bl	11	33	3	49	56		HWR→Rpl (3), lead infections→Rpl (1)	Anxiety, (panic attacks), V ↑ (2)	
Martinez-Fernandez (2011)	[25•]	mGPi, bil (3); pvGPi, bil (2)	5	38	24	31	28		Infection→Rpl of battery and extension cables (1)	Capsular effects (V ↑), anxiety >100 Hz (1), weight ↑ (1)	Anxiety, agitation, tiredness; (1) weight ↑ (1)
Dueck (2009)	[26]	mGPi, bl	1	16	12	0	N/A			Nausea, dizziness, anxiety, visual sensations (1)	
Dehning (2008)	[27]	mGPi, bl	1	44	12	88	N/A	No	No	Depressive moods, vertigo, stomach aches (1)	
Gallagher (2006)	[28]	GPi, bl	1	26	NM	NM	NM		Lead infection→Rpl (1)		
Diederich (2005)	[29]	mGPi, bl	1	27	14	47			ICH→bradykinesia left hand (1)	Fatigue; (1)	
Duits (2012)	[30•]	Voi-Cm-Spv, bl	1	20	36	N/A	N/A				Death (unrelated to DBS? Patient in off stimulation for the last 18 months)
Servello (2010)[a]	[31•]	Voi-Cm-Pf, bl (34), Voi-Cm-Pf uni (1), GPi (1), AIC-NA R (4)	36	32	51	47	20	Infection (5), revision of surgical wounds along extension wires (2)			
Servello (2008)	[32]	Voi-Cm-Pf, bl	18	28	19	64	NM		1. Scalp scar healing ↓→plastic surgery (1) 2. Hematoma, IPG area (1)	>4 V: Subjective vertigo (18), blurring of vision (4), abdominal discomfort (2), upward ocular deviation (1)	
Ackermans (2011)	[33•]	Voi-Cm-Spv, bl	6	40	12	49	63	Infection (1)	ICH→vertical gaze palsy (1)	Apathy ↓ (6), nystagmus (1), visual disturbances (6)	Lethargy, binge eating, dysarthria, apathy, gait disturbance, falls (1)
Ackermans (2010)[b]	[34]	Voi-Cm-Spv, bl	2	44	120	86	N/A	HWR (2)		Disturbance of sexual function (2), disturbance of visual adaption, vertigo (1)	
Ackermans (2006)[c]	[35]	1. Voi-Cm-Spv, bl; 2. Voi-Cm-Spv+GPi, bl	2	36	12	89	N/A			Libido ↓ (1), dystonic jerk (1)	Energy ↓ (2)
V-Vandewalle (2003)	[36]	Voi-Cm-Pf, bl	3	38	60	82	N/A	Traction pain→revision of pulse generator/ extension cables (2)		Apathy (3), disturbance of sexual function (2)	
Kaido (2010)	[37]	Voi-Cm-Pfc, bl	3	20	12	36	0			Vision Δ, V ↑ (3)	
Idris (2010)	[38]	Cm-Pfc, bl	1	24	18	NM	N/A	ICH→headache (1)			
Maciunas (2007)	[39]	Voi-Cm-Pf, bl	5	28	3	44	46	No		Acute psychosis (1), spontaneous recurrence of tics (2)	
Bajwa (2007)	[40]	Voi-Cm-Spv, bl	1	50	24	66	75	No		Woozy feeling, V ↑ (1)	
Welter[d] (2008)	[41•]	Cm, Pf, bl+vm GPi, bl	3	32	20	TA: 64, 30, 40; GPi: 65, 96, 74; TA+GPi:60, 43, 76	N/A			Cheiro-oral/arm paresthesias, lethargy (N/A), nausea, vertigo (2); anxiety (1); libido ↓ (1)	
Houeto (2005)	[42]	Cm-Pfc+amGPi, bl	1	36	24		N/A				

Table 1 (continued)

Authors (year)	Ref.	Target, laterality, (*n*° pts)	Sample size	Age (yrs)	FU (mo)	YGTSS % reduction	YBOCS % reduction	Transient AE surgical HWR (*n*° pts)	Long-term AE surgical HWR (*n*° pts)	Transient AE (*n*° pts)	Long-term AE (*n*° pts)
						TA: 64, GPi: 65, TA+GPi: 60, sham: 8 (inc.)				TA: contraction of c/l half of body (c2, 3), paresthesia (V ↑); GPi: nausea, hypotonia, anxiety (V ↑)(1)	
Neuner (2010)	[43•]	Nac, AIC	1	42	58	40	38			Suicide attempt (reported unrelated to DBS) (1)	
Flaherty (2005)	[44]	ALIC	1	37	18	25	N/A	No		Subjective dysarthria, rhythmic jaw clenching, apathy, depression (c 0, 4); hypomania (c 3, 7); stable euthymic state (c 2, 6)(1)	
		Total[e]	82								
		Mean	5.3	32.9	27.6						
		SD	4.1	8.9	27.2						

TA thalamus, *voi* ventro-oralis internus, *cm-pf* centromedian-parafascicular complex, *spv* substantia periventricularis, *pv* posteroventral, *m* medial, *GPi* globus pallidus internus, *yrs* years, *mo* months, *YGTSS* Yale Global Tic Severity Scale, *YBOCS* Yale Brown Obsessive-Compulsive Scale, *FU* follow-up, *AE* adverse effects, *HWR* hardware related, *Rpl* replacement, *n*° number, *pts* patients, *V* voltage, *NM* not mentioned, *IPG* internal pulse generator, *ICH* intracranial hemorrhage, *ALIC-NA* anterior limb of internal capsule-nucleus accumbens, *c/l* controlateral, ↑ increased, → leading to, ↓ decreased

[a] Eighteen patients previously reported by Servello et al. 2008

[b] Ackermans et al. 2010 = two patients from Visser-Vandewalle et al. 2003

[c] Ackermans et al., 2006 = one patient from Visser-Vandewalle et al. 2003

[d] One patient previously reported by Houeto et al.

[e] Total number of patients considered overlap of patients in serial reports

Table 2 OCD DBS

Authors (year)	Ref.	Target, laterality	Size	Age (yrs)	FU (mo)	YBOCS (% decrease)	Transient AE surgery/ HWR (*n*° pts)	Long-term AE surgery/ HWR (*n*° pts)	Transient AE stimulation (*n*° pts)	Long-term AE stimulation (*n*° pts)	Status unspecified: AE stimulation Transient? Long term? (*n*° pts)
Haq (2011)[a]	[45]	ALIC-NA bl	6	36	24	36			Laughter (5)		
Greenberg (2010)[b]	[46•]	ALIC-NA bl	26	37	36	38	ICH (2), tonic clonic seizure (1), infection (1)		Suicidality (3), mood Δ (NA), anxiety (NA), panic attack (NA), cognitive changes (NA), olfactory, gustatory sensations (NA), smile (NA)		
Goodman (2010)[c]	[47]	ALIC-NA bl	6	36	12	35	1. Incision pain (NA), 2. Headache (NA), 3. Scalp tingling/ numbness (NA)		Emotional, perceptual, somatic experiences (NA), mood changes (NA), c/l smile (5), insomnia (1), mood improvement/OCD worsening (NM), battery depletion→mood↓ (NM)	Hypomania (4)	
Haq (2010)	[48]	ALIC-NA bl	1	29	6	94	No		Mania (1)		
Greenberg (2006)	[49]	ALIC-NA bl	10	35	36	35	ICH→resolved on repeat CT within days (1), seizure (1), wound infection (1)		Unilateral smile (1), jaw muscle tightness/ dysarthria (1), epigastric, physical sensation of sadness (1), olfactory/ gustatory sensations (1), mood elevations (5), memory experiences (1), battery depletion→-depressed mood (6), flushing (1)		
Okun (2006)[d]	[50]	ALIC-NA bl	5	38	0	N/A			Sensory hallucinations, V ↑ (NA) mood ↓, anxiety, V ↑ (NM)		
Shapira (2005)	[51]	ALIC-NA bl	1	52	18	N/A			Panic attack (1)		
Okun (2004)	[52]	ALIC-NA bl	1	34	0	NM			Unilateral smile; gustatory, olfactory hallucinations; nausea (1)		
Nuttin (2003)	[19]	ALIC-NA bl	6	NM	31	38					Unpleasant thought of electrodes in head (1), weight ↑ (1), weight ↓ (1), cognitive/behavioral disinhibition, V ↑ (2), fatique (1)
Roh (2012)	[53]	ALIC-NA bl	4	34	24	59	No				Anxiety, V ↑ (1), Hypomania, V ↑ (1)
Tsai (2012)	[54]	ALIC-NA bl	4	26	15	33			Hypomania, anxiety, allergy to battery (1); vertigo, olfactory hallucination (1); hypomania (1)		

Table 2 (continued)

Authors (year)	Ref.	Target, laterality	Size	Age (yrs)	FU (mo)	YBOCS (% decrease)	Transient AE surgery/ HWR (*n*° pts)	Long-term AE surgery/ HWR (*n*° pts)	Transient AE stimulation (*n*° pts)	Long-term AE stimulation (*n*° pts)	Status unspecified: AE stimulation Transient? Long term? (*n*° pts)
Abelson (2004)	[55]	ALIC-NA bl	4	40	23	23			Mood elevation, >7 V (1)		
Luigjes (2011)	[56]	NA, bl	2	49	3	50			Hypomania, V ↑ (2); impulsivity, V ↑ (2)		
Denys (2010)	[20]	NA, bl	16[e]	43	12	46	Wound infection (1), feeling of numbness at incision site (7), feeling of extension leads (7), feeling of electric current around neurostimulator (3)	Feeling of neurostimulator in chest (3), feeling of extension leads (1)	Hypomania (8), headache (3), feeling face asymmetric (1), menstruation 1 y post-menopause (1), allergy ↑ (1), insomnia (3), forgetfulness (1)	Libido ↑ (7); micturition problems, enuresis, polyuria (2); difficulty findings words (3); forgetfulness (5)	
Huff (2010)	[57]	NA r	10	36	12	31	Dysesthesia in s/c region post IPG implantation (1)		Agitation, anxiety (4), hypomania (2), concentration δ (1), suicidal ideations (1), sleep ↓/inner tension ↑ (1), weight ↑ (2), headache-frequency ↑ (1)		
Chabardès (2012)	[58•]	STN, bl	4	38	6	65			Mania, anxiety (1); enuresis, anxiety (1); hemibalissism, impulsivity, aggressivity (1); hypomania, infection (1)	Weight gain (2)	
Mallet (2008)	[21]	STN, bl	17	43	10	36		ICH (1), diplopia, perielectrode edema (1), infection→IPG (1)	Hypomania (3); anxiety (3); disabling dyskinesias with impulsivity (1); facial asymmetry, dysarthria, dysphagia, walking difficulties (1); depressive symptoms with suicidal ideas (2)		
		Total	89[e]	38.6	15.8						
		Mean	7.2	6.7	11.6						
		SD	6.7								

ALIC-NA anterior limb of internal capsule-nucleus accumbens, *HWR* hardware related, *NM* not mentioned, *N/A* not applicable, *n*° number, *pts* patients, *AE* adverse effects, *yrs* years, *FU* follow-up, *mo* months, *V* voltage, *ICH* intracranial hemorrhage, *c/l* controlateral, *OCD* obsessive-compulsive disorder, *s/c* subcutaneous, *IPG* internal pulse generator, *bl* bilateral, *r* right, ↑ increased, → leading to, ↓ decreased, > more than

[a] One pt possibly from Haq 2010

[b] Includes 10 pts from Greenberg et al. 2006, 5 pts from Goodman et al. 2010, 5 patients from Okun et al. 2006, 1 pt from Shapira et al. 2006

[c] Includes 5 pts from Okun et al. 2006, 1 pt from Shapira et al. 2006

[d] One pt from Shapira et al. 2006

[e] Total number of patients considered overlap of patients in serial reports

Table 3 DBS TRD

Authors (year)	Ref.	Target, laterality	Sample size	Age (yrs)	FU (mo)	Response /remission rate	Transient AE surgery/ HWR (*n*° pts)	Long-term AE Surgery/ HWR (*n*° pts)	Transient AE-stimulation (*n*° pts)	Long-term AE stimulation (*n*° pts)
Ramasubbu (2013)	[59]	SCG, bl	4	17	6	50 % response			Anxiety (2), insomnia (1)	
Puigdemont (2012)	[60]	SCG, bl	8	47	12	62.5 % response/50 % remission	Cephalalgia (2)		Suicidality (1), severe depressive recurrence (2)	
Lozano (2012)	[61]	SCG, bl	21	47	12	29 % response	HWR (2), skin erosion (1)	Suicide/reported unrelated to DBS (1)	Suicidality/reported unrelated to DBS (1); nausea, vomiting (7); agitation, V ↑ (3)	
Holtzheimer (2012)[a]	[62•]	SCG, bl	17	42	24	92 % response/58 % remission	Infection (2), HWR (4)		Suicidality/reported unrelated to DBS (2)	
Holtzheimer (2010)	[63]	SCG, bl	1	27	24	50-60 % symptom reduction	No		IPG battery depletion→ symptoms ↑ (1)	
Lozano (2008)[b]	[64]	SCG, bl	20	47	12	55 % response/35 % remission	Infection (4), HWR (4)		Mental slowing (2)	
Mayberg (2005)	[22]	SCG, bl	6	46	6	66 % response/50 % remission	Skin erosion (1)	Infection→device explantation (2)		
Malone Jr (2008)	[65]	VC/VS, bl	15	46	48	53 % response/40 % remission	HWR (1)		Suicidality/DBS-R unknown (4), syncope/DBS-R unknown (2), hypomania (in bipolar patient) (1), mixed bipolar state/DBS-R unknown (1)	
Bewernick (2010)	[66]	NA, bl	10	48	24	50 % response	Dysphagia (3), swollen eye (6), pain (3)	Suicide/reported unrelated to DBS (1)	Suicidality/reported unrelated to DBS (1), erythema (4), anxiety increase (3), sweating (3), disequilibrium (2), hypomania (2), paresthesia (2), agitation (2), headache (1), lead-dislodgement (1), psychosis (1)	
Jiménez (2005)	[67]	ITP, bl	1	49	24	81 % ↓ (HDRS/at 8 month)			Anxiety, vertical nystagmus/ c1, 2 at 2 V; anxiety, dyspnea, TC, HT/c2 at 4 V (1)	
		Total	96[c]							
		Mean	10.3	41.6	19.2					
		SD	7.5	10.8	12.6					

Yrs years, *FU* follow-up, *mo* months, *AE* adverse effects, *n*° number, *pts* patients, *SCG* subcallosal cingulate gyrus, *IPG* internal pulse generator, *bl* bilateral, *VC/VS* ventral capsule/ventral striatum, *ITP* inferior thalamic peduncle, *NA* nucleus accumbens, *c* contact, *TC* tachycardia, *HT* hypertension, ↑ increase, → leading to

[a] Includes one patient from Holtzheimer et al. 2010

[b] Includes 6 pts from Mayberg et al. 2005

[c] Total number of patients considered overlap of patients in serial reports

Table 4 Prevalence (in percentage) of complications per disease

Complications	OCD (n=94 patients)	GTS (n=82 patients)	TRD (n=96 patients)	Total (n=272 patients)	Total rate of AE (%)
Death (other than suicide)	0	1	0	1	0.37
Suicide	0	0	2	2	0.74
Suicidality	6	1	9	16	5.9
ICH	3	3	0	6	2.2
HWR	21	7	11	39	14.3
Infection	4	9	8	21	7.7
Anxiety	10	7	6	23	8.5
Mood	36	2	6	44	16.2
Psychosis	2	1	1	4	1.5
Apathy	0	13	0	13	4.8
Sexual function alteration	7	6	0	13	4.8
Total number of AE	89	50	43	182	

OCD obsessive-compulsive disorder, *GTS* Gilles de la Tourette, *TRD* treatment-resistant depression, *n°* number, *pts* patients, *ICH* intracranial hemorrhage, *HWR* hardware related, *NSR* not suicide related

Results

Two hundred seventy-two patients were included: 94 OCD patients, 82 GTS patients, and 96 TRD patients (Tables 1, 2, and 3).

The mean age of all patients was 40 years (SD=9.0). The mean sample-size was six subjects (SD=7.6) per study and the mean follow-up was 22 months (SD=21.4). A total of 182 AE were reported across all the studies. Mortality directly related to surgery was zero. Overall mortality was 1.1 % (3 cases): 2 suicides (0.7 %) were reported and one additional death, which according to the authors was unlikely related to DBS (26). Suicidality was observed in 5.9 % of patients.

Most of the complications were transient, while long-term morbidity was reported in 16.5 % of cases, 6.2 % were surgical being related to surgery and/or hardware (HW) while 10.2 % were due to chronic stimulation. Permanent neurological complications (i.e., vertical gaze palsy, diplopia, and hand bradykinesia) were seen in 3 patients (Tables 1, 2, and 3) and reported to be secondary to ICH. ICH was reported in 6 patients (24–50 years old) operated for GTS (3 cases) or ODC (3 cases). One was asymptomatic and detected on postoperative images [49]. One bilateral frontal cortico-subcortical hemorrhage was revealed by persistent postoperative headaches in a 24-year-old GTS patient with blood homeostasis disturbances [38]. One ICH in the ventral capsule/ventral striatum (VC/VS) area induced apathy, resolving in 3 months [46•]. Two small deep brain hemorrhages occurred in the STN [21] and thalamus [33•] and induced permanent finger palsy and vertical gaze palsy, respectively. A small hematoma around the tip of the electrode was noted once [29]. The patient suffered permanent hand bradykinesia.

Other long-term complications related to surgery or HW were infections leading to HW replacement, poor scar healing, which required plastic surgery and hematoma in the internal pulse generator (IPG) area.

Chronic morbidity due to stimulation was higher in the OCD group (24.4 %, n=23/94 patients), than in the GTS group (6.0 %, n=5/82 patients). No long-term AE related to stimulation was observed in TRD patients. The long-term AE related to stimulation included alterations in sexual functioning, forgetfulness, weight gain, apathy, anxiety, agitation, and dysarthria (Tables 1, 2, 3, and 4).

Considering the total 272 patients, the most frequent AE were mood changes (16.2 % of the cases), infections (7.7 %), hardware-related complications (14.3 %), alterations in sexual function (4.8 %), apathy (4.8 %), intracranial hemorrhage (2.2 %), and psychosis (1.5 %).

Analysis of AE according to the disease (Table 4) showed that the highest rate of AE was observed in OCD patients (93 %). The most frequent AE in the OCD group was mood changes (38.3 %), especially frequent in ALIC-implanted patients (44.4 %, n=20/45) compared to NA (42.8 %, n=12/28) and STN (33.3 %, n=7/21) stimulated OCD patients.

In the GTS patients, apathy was the most frequent AE (15.9 %), observed exclusively in patients implanted in the thalamus.

In TRD patients, the most frequent AE were hardware-related (11.4 %) and suicidality (9.3 %). These AE were most frequently seen in subgenual cingulated gyrus (SCG) DBS.

As the analysis of AE per target excluded studies reporting on multiple targets, only 249 patients and 166 AE have been included in our analysis (Table 5). This analysis showed that the highest complication rate concerned the NA/ALIC/VC-VS area (84 %). The AE most frequently observed in patients

Table 5 Prevalence (in percentage) of complications per target

Targets	Patients	Indications	Death	Suicide	Suicidality	ICH	HWR	Infection	Anxiety	Mood changes	Psychosis	Apathy	Alteration sexual function	Total number of AE
NA	39	GTS, OCD, TRD	0	2.5 %	7.7 %	0	43.5 %	2.6 %	18 %	25.6 %	2.6 %	0	20.5 %	48
ALIC-NA	46	GTS, OCD	0	0	6.5 %	4.3 %	0	4.3 %	4.3 %	43.4 %	4.3 %	0	0	30
VC/VS	15	TRD	0	0	26.7 %	0	6.6 %	0	0	6.6 %	0	0	0	6
NA + ALIC + VC/VS	(100)	GTS, OCD, TRD	0	1 %	10 %	2 %	18 %	3 %	9 %	31 %	3 %	0	8 %	(84)
STN	21	OCD	0	0	9.5 %	9.5 %	0	9.5 %	23.8 %	33.3 %	0	0	0	17
GPi	19	GTS	0	0	0	5.2 %	15.8 %	15.8 %	26.3 %	5.3 %	0	0	0	13
TA	38	GTS	3	0	0	5.2 %	13.1 %	2.6 %	0	0	2.6 %	26.3 %	10.5 %	24
SCG	70	TRD	0	1.4 %	5.7 %	0	14.3 %	11.4 %	2.9 %	4.3 %	0	0	0	28
ITP	1	TRD	0	0	0	0	0	0	100 %	0	0	0	0	1
Total umber of AE	249	GTS, OCD, TRD	1	2	16	6	36	17	22	42	4	10	12	167

Studies reporting on multiple/combined targets excluded, as complication per target not specified

NSR not suicide related, *NA* nucleus accumbens, *ALIC* anterior limb of internal capsule, *STN* subthalamic nucleus, *GPi* globus pallidus internus, *TA* thalamus, *SCG* subgenual cingulate gyrus, *ICH* intracranial hemorrhage, *HWR* hardware related, *VC/VS* ventral capsule/ventral striatum, *ITP* inferior thalamic peduncle, *n°* number, *pts* patients

implanted in this group of targets was mood changes (31 %). Mood changes were also the most frequent AE in STN-implanted patients. The safest target appeared to be the SCG: only 28 AE were reported out of 70 patients, mainly HW-related complications or infections (18 cases); 1 patient committed suicide, reported to be unrelated to the DBS [61].

Discussion

Based on the available data the rates of serious complications of DBS for psychiatric diseases were low. The majority of reported complications for psychiatric diseases are best categorized as stimulation-related, transitory, or resolved promptly with modification of stimulation parameters. The overall mortality rate was low (1.1 %), and direct surgical mortality was zero. The most serious adverse events were suicide/suicidality and intracranial hemorrhage.

Not surprisingly, the highest rate of suicide/suicidality occurred in the TRD group (Table 3). Target specificity could not be established. None of the authors [21, 30•, 43•, 46•, 57, 60, 61, 62•, 65, 66] reported a definitive causal relationship between DBS and suicidality, and most of them thought that there was no relationship. In patients suffering from Parkinson's disease treated by DBS, the postoperative suicide rate is about 0.5 %, the risk factors for attempted or completed suicide being postoperative depression, unmarried status, younger age, previous history of impulse control disorders or compulsive medication use, and STN target [68]. Suicidality is multi-factorial and has a significant prevalence in the general population. The European Study on the Epidemiology of Mental Disorders (ESEMED) [69] reported for 21, 425 subjects a lifetime prevalence of suicidal ideation of 7.8 % and of suicidal attempts of 1.3 %. Major depressive episode was reported to be the most important risk factor for lifetime suicide attempt. Suicidality is increased in patients with psychiatric diseases, including TRD but also in OCD and GTS [70, 71]. The lifetime risk of suicide in untreated patients with depressive disorder is estimated to be 20 % [72]. Sokero et al. [73] reported that 58 % of patients with a MDD episode had suicidal ideation.

Several factors might explain the high rate of suicidality in the TRD patients treated by DBS [61, 74]. The TRD patients included in these DBS studies were particularly severe cases, refractory to any treatment, often with a past history of suicide attempt [43•, 46•, 57, 66] which is known to increase the risk of additional suicide attempt [74–76]. Moreover, these DBS studies focused on the early period after the DBS treatment onset, and it is known that severely depressed patients are at greater risk for committing suicide in the initial period of clinical improvement [4]. One should mind that about half of the TRD patients did not respond to DBS, and consequently these non-responders continue to experience major depression

and a high risk of suicide, as before surgery. Regrettably the authors did not specify in their articles if suicidality and suicide were linked with being responders or not responders. STN-DBS has been suspected to increase the risk of suicide in Parkinson's disease (PD) patients [77], but the results of a randomized controlled trial did not support an association between DBS surgery and an increased risk of suicide ideation or attempts [78]. In psychiatric indications, suicidality was observed in 10 % of the patients treated by STN-DBS, proposed only for OCD patients.

Consequently, these factors might play a role in the high percentage of suicidal behavior in the TRD group but no currently available data can determine if suicidal behavior was directly due to DBS or not. To clarify this issue, we need studies evaluating suicidality in this peculiar TRD population before surgery, or comparing prospectively DBS versus best medical treatment. However, a close perioperative monitoring of these patients is mandatory.

While the TRD group was characterized by the high percentage of suicidality, the OCD group (Table 2) was noted for its high complication rate of postoperative mood changes, probably related to the modulation of limbic neural circuits. These changes were particularly observed after acute stimulation during the parameters setting period. If the high percentage of mood changes was due to the variety of OCD-associated comorbidities remains speculative. Target specificity could be appreciated as 46 % of the patients experiencing mood changes were implanted in the ALIC-NA. Okun et al. [50] had noted that mood changes depend on the location of the site of stimulation within the ALIC-NA. Fear and panic appeared to be secondary to ventral stimulation. According to Flaherty [44], more ventral contacts within the ALIC induced apathy and depression, while stimulating through the more dorsal contacts resulted in hypomania. Hypomania was frequently observed in OCD patients treated by STN DBS. These patients were implanted in the anteromedial-limbic STN section [21, 58•], and it is known from patients treated with STN DBS for movement disorders that hypomania can be induced by stimulation of the limbic territory of the STN [79].

Somewhat surprising was that apathy was seen exclusively after thalamic DBS and not observed with other basal ganglia targets. Apathy is classically thought to be due to the alteration of the cortico-striatal-pallidal-thalamic-cortical pathways considering that apathy has been described after lesions of several basal ganglia structures, such as the medial-dorsal thalamic, internal pallidum, and caudate nuclei [80–82].

The surgical- and device-related complications were minor, except intracerebral hemorrhage (ICH). ICH was encountered in 2.2 % of subjects. The percentage of ICH in DBS for psychiatric diseases was somewhat similar to the rate of ICH in DBS for movement disorders, estimated to be between 0.8 and 3.3 % [83–86]. However, one might expect a lower rate of ICH in the psychiatric DBS population, giving that psychiatric patients are usually young and lack cardiovascular risk factors (an exclusion criteria in DBS studies). Idris [38] described a bilateral ICH in a young GTS patient with low factor XIIIA activity. This patient had previously been recruited for a study of factor XIIIA activity and cerebral hematoma. Despite the results of these additional tests would be available only after surgery, the intervention was not postponed. Low factor XIIIA activity is a risk factor for ICH and not detected on routine preoperative blood tests [87] and potentially related to low tryptophan levels. The fact that tryptophan blood level is decreased in GTS patients [88], might suggest that GTS patients have a higher risk of ICH, but this has to be demonstrated. Factor XIIIA and tryptophan status were not documented for the two additional GTS patients with ICH secondary to DBS. Interestingly, all six patients [21, 29, 33•, 38, 46•] with ICH had been operated using multi-tracts microelectrode recordings (MER), which has been advocated to potentially increase the risk of hemorrhagic complications [89]. Up to now, it has not been demonstrated that the use of MER was correlated to a better DBS outcome in psychiatric indications.

Hardware-related complications occurred in 14.3 % patients undergoing DBS for psychiatric diseases. This is consistent with the rates reported in DBS for movement disorders ranging between 6.8 and 32.9 % [90, 91]. Infection rate was higher in the GTS group, probably related to the compulsive touching of the surgical scares and/or due to a possible alteration of the immune system in GTS patients [31•].

Lesion procedures for psychiatric indications do not carry the risk of hardware complications but expose the patients to a similar risk of ICH, reported to be between 0 and 4.5 % across series [11, 92–97]. When reported, the suicide rate in lesion studies was 1–4.5 % [94–96, 98, 99]. Other complications depended on the lesion site. Complications of anterior cingulotomy were seizure (1–9 %), sphincter disturbances (7–22 %), transient mania (6 %), and memory deficit (3 %) [92, 94, 95, 97]. Complications of subcaudate tractotomy were infrequent, including seizure (0.7–2.2 %) and "undesirable personality traits" (6.7 %) [23•, 96] but patients did not display long-term adverse cognitive deficits [68]. Transient apathy (24 %), partial seizure (4.7 %), persistent lethargy (12 %), persistent incontinence (14.2 %), and short-term memory disorders were reported after limbic leucotomy, a procedure combining cingulotomy with subcaudate tractotomy [11, 100].

Complications of anterior capsulotomy were seizure, weight gain, excessive fatigue (32 %), urinary incontinence (4.5 %), and frequent but temporary disturbances of affects and cognition [92, 97, 98]. Despite evidence of efficacy and relative low risks, lesional psychosurgery is nowadays less popular than DBS, probably because the eventual mood and/or personality changes induced by the stimulation are reversible when the stimulation is stopped.

The findings of our review have to be considered within the context of several limitations. Our analysis was based mainly

on small non-randomized studies; the mean sample size of cohorts was only of six subjects. We had to exclude 33 studies from our analysis. As studies did not systematically specify the presence or absence of complications, it remained unclear in the excluded studies if complications were not reported because they did not occur or because authors did not disclose the related information. For a significant number of patients (approximately 150 patients) undergoing DBS for psychiatric diseases, no data on complications was available. Consequently, the exact prevalence of complications of DBS in psychiatric diseases could not be established. Although most of these studies were phase I studies, most of articles focused more on the efficacy outcome rather than safety data. All of these studies were prospective which aided the quality of the data. Further, given the high degree of heterogeneity in the data reporting and the lack of a generally accepted classification of complications, we had to select and regroup the most serious adverse effects in order to emphasize potential tendencies and to present the most important results in a coherent way. Unavoidably, a selection bias was introduced. These difficulties encountered in our methodology were echoed as well by Videnovic and Metman [101] in their study on DBS complications for movement disorders.

Conclusion

The reported adverse effects of DBS in OCD, GTS, or TRD appeared to be similar to the complications in DBS in movement disorders. The majority of reported AEs appeared to be transitory or resolved with stimulation settings changes. Mortality directly related to surgery was zero. Several deaths were reported, but more likely related to the severity of the patients included. Permanent morbidity was low. The risks related to the DBS approach has to be weighted against the severity of the patients, the morbidity risks related to the disease itself and its spontaneous evolution. Considering the overall risks and its reported efficacy in open studies, DBS in psychiatric diseases as TRD, OCD, and GTS seems to have a favorable risk/benefit ratio, although it has to be reiterated that definitive conclusions cannot be drawn based on currently available research evidence. In light of the high degree of suicidality, particularly observed in the TRD group, a close surveillance of patients undergoing DBS for psychiatric diseases is mandatory.

Class I evidence is lacking and is urgently needed. Negative outcome data should be rigorously compiled and published. Mood changes following intervention should be detailed to allow a more accurate evaluation of clinical outcome. DBS for psychiatric diseases is promising, but has still to be considered as an experimental treatment requiring additional evaluation [23•, 102].

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Compliance with Ethics Guidelines

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