

Deep brain stimulation in Tourette's syndrome: evidence to date

This article was published in the following Dove Medical Press journal:
Neuropsychiatric Disease and Treatment

Sara CB Casagrande¹
Rubens G Cury¹
Eduardo JL Alho²
Erich Talamoni Fonoff²

¹Department of Neurology, School of Medicine, Movement Disorders Center, University of São Paulo, São Paulo, Brazil; ²Department of Neurology, School of Medicine, University of São Paulo, São Paulo, Brazil

Abstract: Tourette's syndrome (TS) is a neurodevelopmental disorder that comprises vocal and motor tics associated with a high frequency of psychiatric comorbidities, which has an important impact on quality of life. The onset is mainly in childhood and the symptoms can either fade away or require pharmacological therapies associated with cognitive-behavior therapies. In rare cases, patients experience severe and disabling symptoms refractory to conventional treatments. In these cases, deep brain stimulation (DBS) can be considered as an interesting and effective option for symptomatic control. DBS has been studied in numerous trials as a therapy for movement disorders, and currently positive data supports that DBS is partially effective in reducing the motor and non-motor symptoms of TS. The average response, mostly from case series and prospective cohorts and only a few controlled studies, is around 40% improvement on tic severity scales. The ventromedial thalamus has been the preferred target, but more recently the globus pallidus internus has also gained some notoriety. The mechanism by which DBS is effective on tics and other symptoms in TS is not yet understood. As refractory TS is not common, even reference centers have difficulties in performing large controlled trials. However, studies that reproduce the current results in larger and multicenter randomized controlled trials to improve our knowledge so as to support the best target and stimulation settings are still lacking. This article will discuss the selection of the candidates, DBS targets and mechanisms on TS, and clinical evidence to date reviewing current literature about the use of DBS in the treatment of TS.

Keywords: deep brain stimulation, DBS, Tourette's syndrome, tics

Introduction

Tourette's syndrome (TS) is a neurobehavioral disease characterized by motor and phonic tics often associated with many behavioral comorbidities such as obsessive-compulsive disorder (OCD), attention-deficit hyperactivity syndrome, impulse control, and autism spectrum disorders.^{1,2} According to the last DSM-V criteria, TS is now classified as a movement disorder under neurodevelopmental disorders section and its diagnosis is based on the persistent occurrence of at least one vocal and two motor tics beginning before 18 years old and lasting longer than 1 year excluding other causes.³ Tics are defined as sudden, short, intermittent, "semi-involuntary" movements and vocalizations (can be suppressed temporarily) that are preceded by a premonitory urge or impulse.^{1,4} The family history of tics or behavior disorders is often positive.⁵ TS patients also present with other psychiatric comorbidities such as depression, anxiety and impulsivity, sleep disorders, learning disorders, and in some cases a self-injurious behavior.²

Typically, between 15 and 17 of age, the majority of TS patients experience a decrease in frequency and severity of tics. By early adulthood, about three-quarters

Correspondence: Erich Talamoni Fonoff
Department of Neurology, School of Medicine, University of São Paulo, Avenida Dr Arnaldo 455, São Paulo 01246-903, Brazil
Tel +55 112 661 7878
Email fonoffet@usp.br

of children with TS will have considerable improvement in symptoms and about 32% will be tic-free. While it does not affect cognition and the intellect itself, this condition can cause significant functional and social burden, sometimes affecting normal development in school and professional activities. Treatment includes mostly behavioral therapy and oral medications, alone or in association. At present, there are a variety of psychoactive medications that interact with dopamine (typical but mostly atypical antipsychotic agents) and non-dopamine systems (such as $\alpha 2$ agonists), associated or not with behavioral therapy, and psychoeducative interventions with responses ranging from 30% to 85%.⁶ Botulinum toxin injections can be effective in focal tics.⁷ However, there are patients who do not benefit from medication either due to poor response or due to unpleasant side effects that further limit their use. This subset of patients can evolve with the persistence of tics,^{2,8} thus becoming treatment-refractory and severely disabled.⁹ In this scenario, deep brain stimulation (DBS) can be considered as an additional therapeutic option for symptom control since the clinical benefits have been demonstrated and complications are at low rate.⁹

DBS has become an established treatment for movement disorders including Parkinson's disease, essential tremor, dystonia, and in some psychiatric disorders.¹⁰ The first stereotactic surgical treatment with thalamotomy on the centromedian-parafascicular complex for TS was introduced in 1970,^{11,12} and Vanderwalle et al reported the first case of severe DBS in 1999.¹³ Since then, many case series have been published,^{14–16} and also a few randomized clinical trials have been conducted in this area.^{17–19} While small and uncontrolled studies have demonstrated the positive effects of stimulation on motor symptoms in TS,^{20–24} its effects on Tourette psychiatric comorbidities remain uncertain and the published results are conflicting.^{25–27}

The precise pathophysiology of TS is unknown, but collective concepts include it among "brain circuits" disorders. A closer look at system dysfunctions suggests an overactivity in the basal ganglia thalamo-cortical (BGTCC) loops that may involve various networks, apparently involving a wide range of parallel loops, from ventral and mesolimbic structures to the sensory-motor dorsolateral segments of the circuit.^{28–30} Overall, DBS brain targets currently used for the treatment of TS mostly resemble the targets that are earlier used in focal ablative procedures such as the thalamus, pallidum, and ventral striatum/ventral capsule (VS/VC). Targets aim at the control of motor and psychiatric symptoms.³⁵

This article provides evidence on the applicability of DBS in the treatment of therapy-refractory TS, discussing

the best candidates for surgery and targets, and provides an overview of the mechanism behind the modulation of neural circuits in TS.

Indication criteria for DBS in TS (who?)

The current clinical indication criteria for DBS in a TS patient are based on clinical diagnosis, with high tic severity scores and the presence of symptoms, despite the use of at least three different pharmacological drugs: 1) an alpha-adrenergic agonist, 2) two dopamine antagonists, and 3) a drug from at least one additional class (eg, tetrabenazine or clonazepam).³¹ Although some recommendations use age as an exclusion criterion (impeding DBS to subjects below 18 or 25), this should not be an absolutely strict criterion (Table 1 and Figure 1).^{15,30} However, it is recommended to consult a local ethics committee when considering surgery for patients younger than 18 years of age.

The exclusion criteria comprise major unstable and non-treated psychiatric disorders, suicidal ideation or psychiatric hospitalization preceding 6 months of surgery, active dependence on alcohol or drugs, and pregnancy and severe cognitive impairments. Importantly, a multidisciplinary specialized DBS team including a neurologist, psychiatrist, neurosurgeon, neuropsychologist, speech therapist, and physiotherapist should make all of these assessments. Other exclusion factors include significant structural lesion or abnormalities on MRI.¹⁵ In addition, real expectations of motor outcome and social support are essential when referring patients for DBS.

Mechanisms of action of DBS in TS (how?)

The mechanism of action of DBS in movement disorders has not yet been fully elucidated. There are many theories that intended to explain how DBS interacts with specific brain structures modulating pathological oscillations on basal ganglia and related circuits. DBS is mostly based on focalized high-frequency stimulation (HF-DBS) in targets of basal ganglia and thalamus involved in the mechanism of movement disorders. The effect of HFS is classically described as focal "lesion-like" effect in most subcortical targets and stimulation of fibers, including the ones used for the treatment of TS. However, current concepts suggest that the effect of DBS may be more complex. In 2016, Florence et al published an article hypothesizing that the HF-DBS induces ionic changes focalized in the region surrounding

Table 1 Clinical criteria for the indication of DBS in Tourette's syndrome

	2006 guidelines	2015 MDS guidelines
Diagnosis	DSM-IV diagnosis of TS by expert clinician	DSM-V diagnosis of TS by expert clinician
Age	≥25 years old	Age is not a strict criteria *In patients ≤18 years old, a local ethics committee should be involved
Tic severity (measures)	A. Severe tic disorder with functional impairment B. Scales: YGTSS >35/50 C. Document with standardized video assessment	A. Severe tic disorder with functional impairment B. Scales: YGTSS >35/50 C. Document with standardized video assessment
Neuropsychiatric comorbidities	A. Tics as the most disable symptom B. Stable and treated comorbid conditions C. Scales: valid rating scales when available	A. Tics as the most disable symptom B. Stable and treated comorbid conditions C. Scales: valid rating scales when available
Refractoriness to conventional and optimal treatment	A. Failed treatment trials from three pharmacological classes: A.1: alpha-adrenergic agonist A.2: two dopamine antagonists (typical and atypical) A.3: benzodiazepine B. Evaluated for suitability of behavioral interventions for tics	A. Failed treatment trials from three pharmacological classes: A.1: alpha-adrenergic agonist A.2: two dopamine antagonists (typical and atypical) A.3: a drug from at least one additional class (eg, clonazepam, tetrabenazine) B. CBIT should be offered
Comorbid medical disorders	Stable for 6 months before DBS	Stable for 6 months before DBS
Psychosocial factors	A. Adequate social support without acute or subacute psychosocial stressors B. Active involvement with psychological interventions when necessary	A. Adequate social support without acute or subacute psychosocial stressors B. Active involvement with psychological interventions when necessary C. Caregiver available to accompany patient for frequent follow-up D. Psychogenic tics, embellishment, factitious symptoms, personality disorders, and malingering must be recognized and addressed
SI/HI	Not specifically addressed	Documentation of no active SI/HI for 6 months before surgery

Notes: *Guideline changes in clinical indication criteria for DBS in Tourette's Syndrome (modified from Schrock et al, 2015¹⁵).

Abbreviations: DBS, deep brain stimulation; SI/HI, suicidal/homicidal ideation; TS, Tourette's syndrome; YGTSS, Yale Global Tic Severity Scale; CBIT, comprehensive behavioral intervention for tics.

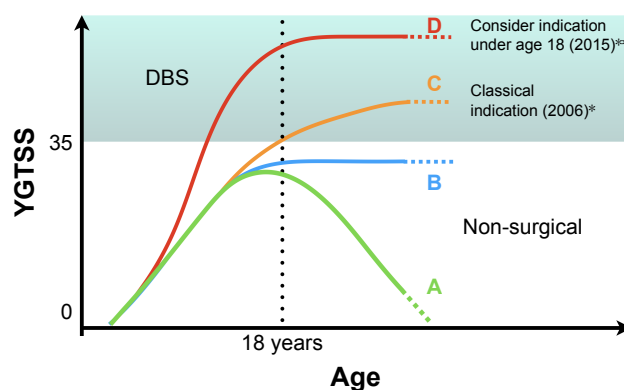


Figure 1 Diagram showing some of the possible clinical evolution that can be interpreted as natural history of TS or outcome from non-surgical therapeutic interventions based on YGTSS as a severity measure. This diagram intends to illustrate the current indications for DBS according to earlier and latest criteria. (A) Clinical resolution of TS symptoms. (B) Presence of tics that do not resolve spontaneously or are kept stable under non-surgical treatments. (C) Classical indication for DBS based on the severity of disease and age (18 years). (D) Latest proposed indication for DBS based on severity as a determinant factor even before 18 years of age.

Abbreviations: DBS, deep brain stimulation; TS, Tourette's syndrome; YGTSS, Yale Global Tic Severity Scale.

the active tip, reversibly increasing extracellular concentrations of potassium, which in turn affects the dynamics of both cell bodies and axons. This would contribute to the intermittent excitation and inhibition of these elements, reversibly interrupting local abnormal pathological activity and consequently correcting circuit irregularities.³²

Regarding TS, when HF-DBS is applied in the anteromedial globus pallidus internus (GPI), it reduces the amplitude of tic-associated phasic changes in the GPI. An animal study reported that the suppression of the brain activity related to tics was linked to a temporal locking of spiking activity with the stimulation pulse, which induces different patterns of inhibition and excitation in affected cells.³³ As previously mentioned, dysfunction in the pathways related to the cortico-basal ganglia integrative network has been associated with vocal and motor tics; based on this, several surgical targets have been proposed for the control of motor and

psychiatric symptoms.³⁴ Unilateral stimulation was found to be unsuccessful compared to bilateral stimulation in a double-blind study.¹⁷

In TS, although acute effects of high frequency stimulation (HFS) in deep structures are observed, the major response after DBS, as observed in idiopathic dystonia, is in general delayed and gradually built-in.³⁵ This suggests that the mechanism of DBS in TS may be mediated by neuroplastic changes in the circuit components. Conversely, although a carry-over effect has been observed, tics recur in most refractory cases after DBS has been turned off, suggesting that the plastic changes are of short or intermediate term. After the DBS, as also observed in dystonia, the improvements following TS DBS are delayed and are gradually progressive.³⁵

The role of dopaminergic modulation

Although different psychopharmacologic agents are used to treat TS, the D2/3 receptor antagonists are among the most effective. Therefore, this suggests that the least the dopamine released in striatal target neurons, the best the symptom control in TS. In order to investigate this hypothesis, Vernalaken et al reported an on/off stimulation experiment using [18F] fallypride-positron emission tomography scan during the steady phase of DBS treatment in a TS patient showing a dramatic increase of endogenous dopamine during off condition. So, bilateral thalamic stimulation somehow induces a decrease in dopamine in striatum.³⁶ Corroborating this hypothesis, a similar study involving three patients also showed that DBS acts by modulating dopamine transmission.³⁷ It is possible that the stimulation of the centromedian nucleus and substantia periventricularis suppresses excitatory feedback projections to motor and limbic circuits of the striatum, thereby decreasing tics and consequently improving behavioral disorders.¹³ Therefore, the chronic circuit abnormalities present in TS are probably related to the failure of cortical inhibition to the basal ganglia “filter”, which in turn will end-up in thalamic hyperactivity feeding the pathological loop, originating the Tics.

The role of pathological oscillations

The analysis of activity dynamics recorded from depth electrodes suggests that prominent oscillatory brain activity at low frequencies (2–7 Hz) and in alpha band (8–13 Hz), associated with decreased thalamic beta activity, may be an important component in the pathophysiology of TS.^{38–41} Comparisons of the effect of “on” and “off” stimulation in the dynamics of these frequencies suggested that HF-DBS is able to suppress the abnormal oscillatory activity within the motor cortico-basal ganglia network.^{38,39,41} Notable increases

in normalized gamma-band power activity (25–45 Hz) were also observed, which indicate clinical benefit. Correlation analysis showed that the power of the gamma oscillations was inversely associated with the degree of the TS symptoms, as measured by the Yale Global Tic Severity Scale (YGTSS).⁴² All of these information are fundamental to the development of advanced treatment strategies such as closed-loop deep brain stimulation, also called adaptive DBS (aDBS).⁴³

The functional brain (cortical) modulatory effects

The pathophysiology of TS is still under investigation, but some studies suggest overactivity in the BGTC.^{29,44} A functional study showed that TS patients have a decrease in the fractional anisotropy (FA) in many cortical areas, including the pars opercularis of the left inferior frontal gyrus, the medial frontal gyrus, and the right cingulate gyrus. There was a positive correlation between tic severity and FA scores in the corpus callosum, thalamus, temporal gyrus, and parahippocampal gyrus. Overall, the findings advocated that tics are mostly produced by alterations in prefrontal areas, thalamus, and putamen.³⁰

Regarding the effects of DBS in TS, few functional studies have explored the white matter pathways and the projections activated by stimulation in animal models and patients, and, in general, they support that good motor outcomes are related to the activation of several fiber pathways and brain cortical regions.^{39,45} The effect of DBS in TS, as in other conditions, seems to be related to local brain changes and also to the modulation of multiple cortical distance areas (through structural and functional connectivities).⁴⁰

The closed-loop stimulation

Adaptive stimulation from closed-loop devices (aDBS) depends on functional neural feedback through variables recorded by DBS electrodes (such as abnormal electrographic discharges or more recently on neurochemical feedback).^{40,43,46} The term “adaptive stimulation” was created with the concept that some implantable generators are not passive devices any more. Instead of only creating and delivering monotonous trains of electrical pulses, they perform recording and analysis of neural signals and can be programmed to deliver, stop, or change stimulation parameters when a certain neural pattern takes place. Although the studies that correlate recordings of deep brain activity and simultaneous occurrence of symptoms are still in the beginning stage, it seems that rather than rapid activity related to every behavioral event (tics), studies found changes in background activity that correlates with periods

of increased tics, which helps to predict when those events will arise. Therefore, detected changes in oscillatory activity can lead to automatic responses from the stimulator intended to suppress tic onset. When used in a more dynamic way, the aDBS can adjust stimulation parameters based on a feedback information, leading to a more individualized treatment.^{47,48}

The main targets (where?)

A variety of brain targets have been proposed as potential therapeutic targets for DBS in TS, along the BGTCC circuit. In recent years, the centers of DBS worldwide explored at least nine brain targets for the treatment of TS: centromedian-parafascicular-thalamic complex (CM-Pf), the intersection point between centromedian nucleus, periventricular substance, and inferior ventro-oral nucleus in the thalamus (CM-Spv-Voi), the posterior ventro-oral nucleus, the anterior ventro-oral, and Voi, the GPi anteromedial or posteroventral, the nucleus accumbens (NA), the anterior internal capsule (ALIC), subthalamic nucleus (STN), and globus pallidus externus (GPe) (Figure 2 and Tables 2 and 3).^{35,49–51} If TS is

considered a complex disease between movement and psychiatric disorders (with anxiety and compulsive symptoms), then both sensory-motor and associative/limbic areas may be used as targets. Therefore, of these options, regions of the medial thalamus and the GPi are the most frequently used targets probably because of historical reasons and their involvement in motor and limbic pathways. However, because of the close interconnection of basal ganglia structures, the effects of stimulation would block pathological signals in their local network as well as reduce aberrant signals in other connected structures associated with the mechanism of TS.^{52–55} Other authors have suggested that combining targets can provide additional benefits.⁵⁶

Thalamus

Several studies and clinical trials of thalamic DBS indicated that bilateral CM-Pf and Voi stimulation provide a beneficial therapeutic role in TS for both tic severity (motor via CM) and psychiatric symptoms (limbic via Pf).^{14,57,58} This target was introduced by the ablative surgery of Hassler and Dieckmann

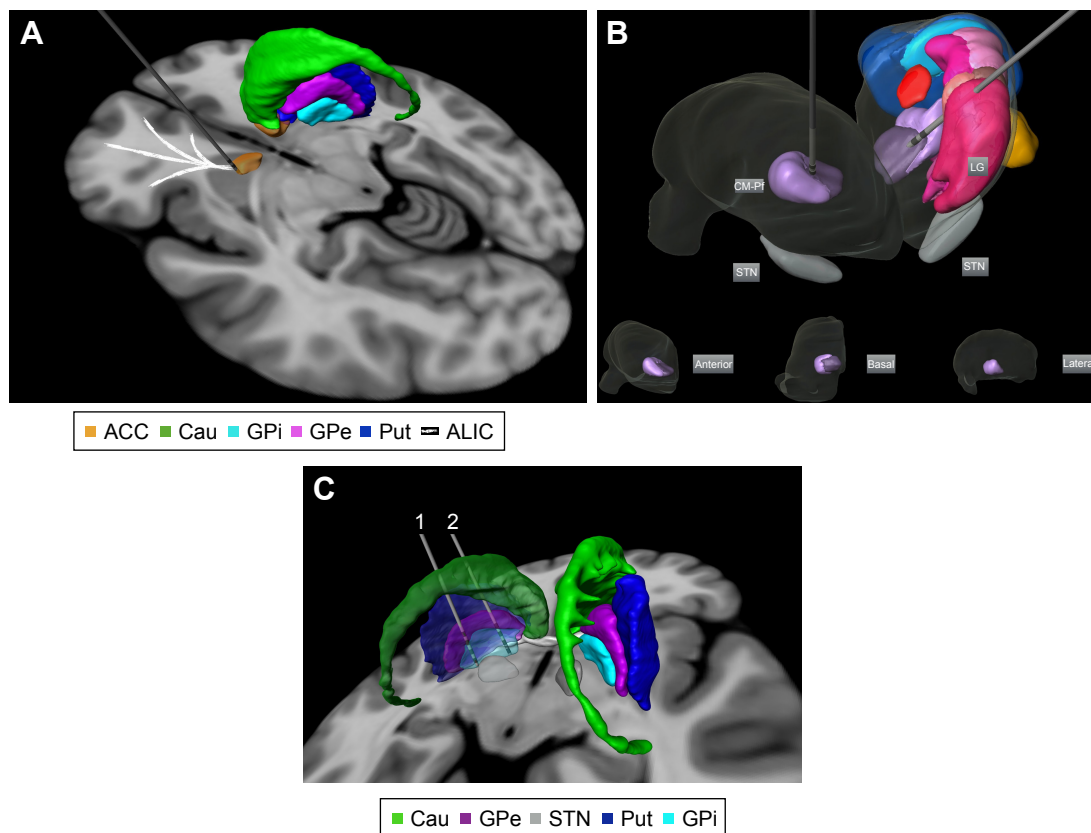


Figure 2 Targets proposed for DBS treatment in Tourette's syndrome: **(A)** anterior limb of internal capsule/accumbens; **(B)** bilateral centromedian-parafascicular complex targeted in an anterolateral thalamic view (basal, anterior, and lateral thalamic views of the right thalamus are displayed for localization within the thalamus); and **(C)** different parts of GPi. Electrode 1 is located in the posteroventrolateral GPi and electrode 2 is located in the anteromedial GPi. The 3D representations are histological postmortem reconstructions of the nuclei from the University of São Paulo – Würzburg Atlas of the Human Brain (Alho et al, 2018⁹⁶).

Abbreviations: ACC, accumbens; Cau, caudate nucleus; GPi, globus pallidus internus; GPe, globus pallidus externus; Put, putamen; ALIC, anterior limb of internal capsule; CM-Pf, centromedian-parafascicular-thalamic complex; LG, lateral thalamic group; STN, subthalamic group.

Table 2 Summary of the studies: level III evidence

Study	Patients (n)	Follow-up (months)	Target	Outcomes
Maciunas et al, 2007 ¹⁷	5	3	Centromedian-parafascicular and ventralis oralis complex of the thalamus	Three of five patients showed improvement: mean pre-op YGTSS – 37.2, 3-mo score – 28.2
Welter et al, 2008 ⁷⁷	3	20–60	Thalamus CM-Pf and GPi	30%–64% total YGTSS, 37%–41% tic severity subscale with CM-Pf; 65%–96%, 67%–90% with GPi; 43%–76%, 16%–70% with combined; recurrence of tics during sham but 32% improvement in 1 patient Crossover study of CM-Pf vs GPi vs combined vs sham (2 months per stimulation condition)
Porta et al, 2009 ⁶¹	15	24	Centromedian-parafascicular and ventralis oralis complex of the thalamus	5% improvement in tic scores. No deleterious effect on cognition, improvement in behavioral ratings
Kaido et al, 2011 ⁹⁷	3	12	Thalamus	YGTSS decreased from 42.7±2.7 (before DBS) to 26.0±1.7 (1 year after DBS)
Ackermans et al, 2011 ¹⁸	6	3, 6, 12	Thalamus	Improvement (37%) on the YGTSS scale (mean 41.1±5.4 vs 25.6±12.8, <i>P</i> =0.046) After 1 year: significant improvement (49%) on the YGTSS scale (mean 42.2±3.1 vs 21.5±11.1, <i>P</i> =0.028) when compared with preoperative assessments
Okun et al, 2013 ¹¹⁶	5	6	Centromedian-parafascicular and ventralis oralis complex of the thalamus	YGTSS decreased by 17.8 points (<i>P</i> =0.01), MRVRS decreased by 5.8 points (<i>P</i> =0.01)
Motlagh et al, 2013 ⁷²	8	6–107	Thalamus (5) and GPi (3) Two in the sensorimotor portion and one in limbic portion	YGTSS decreased by 0–72%
Dong et al, 2012 ⁷⁰	1	22 with DBS 26 without DBS	GPi	66.7% improvement
Schoenberg et al, 2015 ²⁵	5	5	Thalamus	24%
Huys et al, 2016 ⁶³	8	12	Ventral anterior and ventrolateral motor parts of the thalamus	YGTSS motor, impairment, and total scores decreased by 51, 60, and 58%, respectively, compared to baseline MRVRS score decreased by 58% Significant improvement in quality of life and global functioning measures were noted
Kefalopoulou et al, 2015 ¹⁹	15	6 months blinded and then 36 months unblinded	GPi (anteromedial location)	15.3%–40.1% YGTSS decreased by 12.4 between on and off states in the blinded phase (<i>P</i> =0.048), YGTSS decreased by 23.8–48.9 points (<i>P</i> <0.0001) between baseline and open-label phase
Servello et al, 2016 ⁹⁸	48	24	Thalamus – 42 aGPi – 2 NA – 4	78% of cases with >50% of improvement
Rossi et al, 2016 ⁵⁶	5	24	Thalamus CM-Pf	40%
Welter et al, 2017 ⁶	16	3	aGPi	No significant difference in YGTSS score

Note: Summary of the main published studies on DBS for the treatment of tics and Tourette's syndrome.

Abbreviations: YGTSS, Yale Global Tic Severity Scale; CM-Pf, centromedian-parafascicular-thalamic complex; GPi, globus pallidus internus; aGPi, anteromedial GPi; DBS, deep brain stimulation; NA, nucleus accumbens; MRTRSS, Modified Rush Tic Rating Scale Score total score.

in 1970.¹¹ Based on this, Vandewalle et al (1999)¹³ published the first report of thalamic DBS for a 42-year-old man with refractory TS. They applied high-frequency continuous bilateral stimulation (4 V, 130 Hz, 450 μ s). Preoperatively, he had 38 tics per minute; at 4 months, after 12 hours in the

off-stimulation condition, only eight tics per minute were counted; all tics subsided 5 minutes after the stimulation was switched on except for some excessive eye-blinking. After 1 year, stimulation of 1.5 V was sufficient to abolish his tics. In long term (5 years), the results of these patients

Table 3 Summary of studies: level IV evidence

Study	Patients (n)	Follow-up (months)	Target	Outcome
Vandewalle et al, 1999 ¹³	1	12	Thalamus	Total symptomatic improvement
Van der Linden et al, 2002	1	6	Medial thalamus and GPi	80% Improvement with thalamus at high intensities, 95% with GPi at lower intensities at 1 wk; GPi connected to implantable pulse generator (IPG), with similar results at 6 mo
Visser-Vandewalle et al, 2003 ⁶⁴	3	8–60	Thalamus	Improvement of motor and vocal severe tics
Houeto et al, 2005 ⁹⁹	1	3, 5, 7, 9, 10	CM-Pf and GPi	65% total improvement on YGTSS, 77% improvement on RVBTS after CM-Pf; 65% total impr on YGTSS, 67% impr on RVBTS after GPi. Return to the baseline with sham Stim; 70% total impr on YGTSS, 76% improvement on RVBTS after CM-Pf + GPi.
Flaherty et al, 2005 ⁸²	1	18	ALIC/NA	Symptomatic improvement
Diederich et al, 2005 ⁶⁵	1	14	pGPi	71.6% tic/min (on videotape) at 7 mo, 84.6% at 14 mo; 66.0% tic increase at 14 mo “off”; 47.0% total improvement on YGTSS (44.2% tic severity subscale); improved premonitory urges – recurrence at 7 mo “off”
Gallagher et al, 2006 ¹⁰⁰	1	Non-disclosed	GPi	Improvement
Ackermans et al, 2006 ⁷⁸	2	12	CM, Spv, Voi in patient 1 GPi in patient 2	85.0% (tics/min on videotape) in patient 1, 92.9% in patient 2; minor tics remained in both patients; acute increase and decrease of tics during “off” and “on,” respectively
Vilela Filho et al, 2007 ⁸⁵	2	23	GPe	Symptomatic improvement
Shahed et al, 2007 ²⁷	1	6	GPi posteroventral	76.0% motor, 68.0% phonic tics (84.4% total on YGTSS); 21.4% RVBTRS
Bajwa et al, 2007 ⁵⁹	1	1, 4, 6, 14, 20, 24	CM, Spv, Voi	66.2% YGTSS tic subscale; 98.0% reduced tic frequency via hand-held counter
Kuhn et al, 2007 ⁸¹	1	30	ALIC/NA	41.1% total on YGTSS, 50% RVBTRS at 30 mo
Zabek et al, 2008 ⁸⁰	1	Baseline, at 6 and 28	Right NA	26.7% at 1 wk, 74.2% at 6 mo, 79.7% at 28 mo (tics/15 min via videotape); 50% tics in “off”
Shields et al, 2008 ¹⁰¹	1	18	VS/VC, thalamus	45%
Khun et al, 2008 ¹⁰²	1	10	VS/VC	19.8% total on YGTSS at 1 mo, 51.9% at 10 mo; coprolalia nearly resolved
Dehning et al, 2008 ⁶⁶	1	12	GPi	66.3% total on YGTSS at 6 wk, 88.0% at 1 y (tics abolished)
Servello et al, 2008 ⁶⁰	18	3–18	Centromedian-parafascicular (CM-Pf) and ventralis oralis complex of the thalamus	YGTSS decreased from 33–48 to 7–22
Neuner et al, 2009 ⁸³	1	36	NA, ALIC	46.0% at 3 mo, 44.0% at 36 mo, 40% at 58 mo (total YGTSS), 60%, 58%, 57% (RVBTRS)
Servello et al, 2009 ⁸⁷	4	44/8–51	Internal capsule/NA in patients with centromedian-parafascicular and ventralis oralis complex of the thalamus (except one patient with only internal capsule/NA leads)	Two patients showed at best mild improvement in OCD and tic scores, two showed more clinically significant improvement in OCD scores and functionality, with limited effect on tics
Vernaleken et al, 2009 ³⁶	1	Non-disclosed	GPi, CM-Pf, DM	No clinical improvement with GPi; 35.9% total on YGTSS (22.2% motor and 40.0% vocal tics) with CM-Pf/DM

(Continued)

Table 3 (Continued)

Study	Patients (n)	Follow-up (months)	Target	Outcome
Kuhn et al, 2009 ¹⁰³	6	3–18	NA (n=2); GPi (n=2); thalamus (n=1); caudate (n=1)	50% improvement n=3; 50% in N=2; non response in n=1 during
Dueck et al, 2009 ¹⁰⁴	1	12	GPi	Improvement in YGTSS scores, but not substantial overall
Foltnie et al, 2009 ¹⁰⁵	1	Non-disclosed	GPi	88.7% motor and 90% vocal tics/5 min at 3 and 6 mo; reemergence of tics during “off” and of vocal tics when trying to speak; inner tension remained
Martinez-Torres et al, 2009 ⁷⁹	1	12	STN	89% at 6 mo, 97% at 1 y (tics/10 min)
Ackermans et al, 2010 ⁵⁸	2	120/60 12	Centromedian-parafascicular and ventralis oralis complex of the thalamus	YGTSS decreased from a mean of 42.3 prior to surgery to 21.5 on 1-y follow-up, $P=0.028$
Marceglia et al, 2010 ¹⁰⁶	7	24	CM-Pf, Vop	33% Improvement in YGTSS (6 mo-2 y follow-up) improvement in motor scale
Burdick et al, 2010 ⁸⁴	1	30	VS/VC	No improvement in tics, 120.0% (RVBTRS) and 115.2% (total YGTSS) at 6 mo
Lee et al, 2011 ¹⁰⁷	1	18	Thalamus (CM-Pf)	81% improvement in total tics count and 58% improvement on YGTSS
Martínez-Fernández et al, 2011 ⁷⁵	5	3–24	GPi (two patients with anteromedial location, two patients with posterolateral location, one patient initially with posterolateral switched after 18 mo to anteromedial location)	Mean YGTSS was 77.8 at baseline and 54.2 at last follow-up, mean MRVRS was 28.3 at baseline and 15.7 at last follow-up, Tourette Syndrome Quality of Life was 61.7 at baseline and 28.5 at last follow-up
Dehning et al, 2011 ⁷¹	4	5–48	GPi (posteroventrolateral location)	Two patients responded with >80% reduction in tics, two patients did not respond
Kuhn et al, 2011 ¹⁰⁸	2	12	Thalamus (CM-Pf)	↑100%/67%
Savica et al, 2012 ²³	3	12	Thalamus (CM-Pf)	↑70%
Dong et al, 2012 ⁷⁰	2	12	GPi D	↑58.5%/53.1%
Cannon et al, 2012 ⁷⁴	11	4–30	GPi (anteromedial location)	One patient did not respond; mean YGTSS was 84.45 before surgery and 42.55 at 3 mo, mean TSQOL was 39.09 before surgery and 79.09 at 3 mo
Maling et al, 2012 ⁴⁰	5	6	Centromedian-parafascicular and ventralis oralis complex of the thalamus	YGTSS decreased by 1%–41%; noted correlation between gamma-band activity change and YGTSS change after DBS
Hwynn et al, 2012 ¹⁰⁹	1	1, 3, 6, 9, 12, 24, 36	GPi	Improvement in tics and dystonia
Porta et al, 2012 ⁵²	18	60–72	Centromedian-parafascicular and ventralis oralis complex of the thalamus	Mean YGTSS was 80.83 prior to surgery and 22.11 at the extended follow-up ($P<0.001$) 72.6% Improvement.
Piedimonte et al, 2013 ⁸⁶	1	6	GPe	↑70.5%
Dehning et al, 2014 ⁶⁷	6	12–60	GPi (posteroventrolateral location)	Two patients were non-responders, mean YGTSS was 90.2 prior to surgery and 29.5 at last follow-up ($P=0.001$); TSQOL was 88.75 prior to surgery and 7.75 at last follow-up (one person did not fill TSQOL)
Huasen et al, 2014 ¹¹⁰	1	12	GPi anteromedial	55%
Zhang et al, 2014 ²⁴	13	13–80	GPi (posterolateral location)	Mean YGTSS decreased by 52.1% at last follow-up, mean TSQOL improved by 45.7% at last follow-up
Sachdev et al, 2014 ²²	17	48	GPi anteromedial	38%
Patel & Jimenez-Shahed, 2014 ¹¹¹	1	14	GPi	47%
Zekaj et al, 2015 ¹¹²	1	72	Thalamus	58.2% improvement during “off” condition

(Continued)

Table 3 (Continued)

Study	Patients (n)	Follow-up (months)	Target	Outcome
Testini et al, 2016 ¹¹³	12	Median 26	Thalamus (CM-Pf)	54% improvement
Smeets et al, 2016 ⁶⁸	5	1–12–38	Anterior internal globus pallidus	YGTSS was significantly lower than the preoperative score (42.2±4.8 vs 12.8±3.8, $P=0.043$). No significant difference in the secondary outcomes was found; however, there was an improvement at an individual level for obsessive–compulsive behavior
Cury et al, 2016 ²⁶	1	18	Thalamus (CM-Pf)	70.5%
Zhang et al, 2014 ²⁴	24	12	GPI	56%
Dwarakanath et al, 2017 ¹¹⁴	1	Non-disclosed	GPI anteromedial	72%
Hauseux et al, 2017 ⁸⁸	3	52	GPI posteroventral + GPe GPI posteroventral + GPI posteroventral + thalamus (CM-Pf) + NA	Symptoms improvement
Smeets et al, 2017 ¹¹⁵	7	12–78	Thalamus (CM-Pf)	Improvement from 9% to 88.1%

Note: Summary of the main published studies on DBS for the treatment of tics and Tourette's syndrome.

Abbreviations: mo, month; y, year; wk, week; YGTSS, Yale Global Tic Severity Scale; CM-Pf, centromedian-parafascicular-thalamic complex; GPI, globus pallidus internus; DBS, deep brain stimulation; STN, subthalamic nucleus; GPe, globus pallidus externus; NA, nucleus accumbens; ALIC, anterior internal capsule; VS/VC, ventral striatum/ventral capsule; pGPI, posteroventral GPI; OCD, obsessive–compulsive disorder.

were published in 2003, together with two more cases, and the results showed an average improvement of 72.2%–90% with no serious complications. Obsessive–compulsive and self-injurious behaviors completely disappeared in all patients.²¹ Ten years after surgery, patient 1 showed sustained improvement in tic frequency with no change in cognition.⁵⁹

The first blinded trial on thalamic stimulation for TS was conducted by Maciunas et al with five TS patients in 2007. Three of the five presented with 50% reduction in tics severity after open-label stimulation at 3 months. There was a marked improvement according to all primary (modified Rush Video-Based Rating Scale) and secondary outcome measures (OCD, depression, and anxiety scales).¹⁷ Also, this study showed that unilateral stimulation did not appear to be beneficial. Bajwa et al reported a patient who showed improved total tic score and Yale-Brown Obsessive-Compulsive Scale (YBOCS) by a mean of 66%, evaluated 24 months after the surgery.⁵⁹

In a larger series of study conducted by Servello et al, 15 of 18 patients showed YGTSS improvement between 24% and 79%, with improvement in comorbidities. Stimulation was performed with current between 1 and 5 mA, 100 Hz, and a pulse width of 60 μ s.⁶⁰ This same group of authors later published their long follow-up results of 36 TS patients with different DBS targets. Most of the patients had thalamic DBS, and significant improvements were documented. Servello et al also published their results of a cohort of 48 TS DBS patients. In 40 of them, the thalamus was the target chosen. The target was different than that chosen by Vandewalle et al (1999)¹¹⁷ because it is located 2 mm more anteriorly.

The authors stated that this can stimulate the limbic fibers and, consequently, act on the behavioral components of TS. The patients had a mean improvement of 47.5% in YGTSS after DBS and kept at 35% improvement at the final follow-up. After 2 years of thalamic DBS, Porta et al reported a clinical follow-up of 15 patients, whose YGTSS scores decreased from 76.5 to 36.6. The neuropsychiatric scales also improved.⁶¹ The same group of authors published a longer follow-up study (5–6 years) of the same cohort and showed a mean YGTSS improvement of 73% and YBOCS of 42%. However, compared with the results at 2 years, they demonstrated some long-term difficulties.⁶²

Similarly, in a 2-year follow-up study, Rossi et al showed that a 30% improvement in the total YGTSS scores (range 10%–58%) was observed in four CM-Pf DBS cases across the cohort.⁵⁶ In 2011, Ackermans et al studied six TS patients in a double-blind randomized trial in which chronic stimulation was delivered bilaterally in the CM-Spv-Voi complex (1–6 mA, 130 Hz, 60 μ s). The authors reported improvements in the YGTSS scores during the on- vs off-stimulation conditions. The YGTSS improved by 37% and remained after 1-year open-label follow-up, with a 49% improvement reported.¹⁸ In 2012, Savica et al described three patients with TS who underwent CM-Pf DBS with an excellent clinical outcome (mean reduction in the YGTSS of 70%) at 1-year follow-up.²³ Recently, two other prospective trials presented five and eight intractable TS patients.^{25,63} The first study indicated that bilateral CM-Pf DBS provided treatment for medically refractory TS with concomitant improvement

in depression and anxiety with no neuropsychological morbidity.²⁷ In the second study the patients were treated with DBS of the Voa-Vop, indicating a significant beneficial effect on psychiatric and motor symptoms of TS. In addition, the presence of compulsive behavior, anxiety, and emotional deregulation before surgery appeared to be significant predictors of good outcome after DBS.⁶³

Globus pallidus internus

Posteroventral GPi (pGPi)

The GPi stimulation affects both motor and limbic pathways; however, this specific target has been used for motor symptoms especially for Parkinson's disease and dystonia. Accordingly, pGPi as a target for DBS has been considered for the treatment of hyperkinetic movements as well as in TS. There are a number of case reports and trials using this target in TS. The first pallidal stimulation in TS was reported by Van der Linden et al.⁶⁴ The patient underwent both pGPi and thalamic DBS and showed 80% reduction in tics with thalamic stimulation and 95% with pallidal stimulation maintained for 6 months. In 2005, Diederich et al reported progressive improvements in tic frequency reaching 73% within 14-month follow-up after pGPi together with improvement in depressive and anxiety symptoms.⁶⁵ Dehning et al reported 87% improvement on YGTSS 1 year after bilateral pGPi electrodes in four patients with refractory TS with maintenance of the benefit for 4 years. The authors observed that the patients who improved after DBS had also shown prior response to electroconvulsive therapy.^{66,67} More recently, pGPi stimulation for the treatment of TS has been performed more frequently with substantial motor tics.^{24,25,68} The youngest TS patient ever treated by DBS received leads in the pGPi (Shahed et al's study), who showed 84% improvement on YGTSS after 6 months.²⁷ That patient was followed for 5 years and later reported, with other two patients (followed for 4 and 2 years), to show good results. Over the longitudinal evaluation, stimulation parameters were considered high (mean values 4.9 V, 198 ms, 168 Hz) and rechargeable batteries were eventually used. Transient reduction and gradual retitration of stimulation parameters were sometimes required after the battery exchange. Overall, clinical improvement was maintained over the treatment period. The authors demonstrated that the benefits over symptom could be maintained for up to 5 years.²⁷ There are also other series of cases reported in the literature with positive results.^{69–72}

Anteromedial GPi (aGPi)

The GPi is functionally divided into an anteromedial region that is part of the associative/limbic part of the BGCTCC

circuit.⁷³ There are studies that report good outcomes in stimulating the aGPi (the limbic subregion). This involves the limbic loops in tic expression.^{74,75} More recently, Akbarian-Tefaghi described 15 patients with aGPi DBS for severe TS and explored whether a specific anatomical location within the aGPi correlated with motor outcome for tics, obsessive-compulsive behavior (OCB), and mood. They demonstrated that the region within the ventral limbic GPi – specifically on the medial medullary lamina in the pallidum at the level of the anterior commissure-posterior commissure line (AC-PC Line) – was significantly associated with improved tics, but not mood or OCB outcome.⁴⁶ Another recent randomized clinical trial by Welter et al involved 19 patients and showed that aGPi DBS was insufficient to decrease tic severity after 3 months. Future research is warranted to explore the effectiveness of aGPi DBS over longer follow-up and optimal stimulation parameters as well as to study potential predictors of the therapeutic response.⁷⁶

Comparative studies

Gpi vs thalamus/Gpi and thalamus

In the search for an optimal surgical target, a few studies have compared the outcomes of stimulation in the limbic regions of the GPi and medial thalamus.^{77,78} A randomized blinded study evaluated the efficacy of stimulating the CM-Pf vs the ventromedial GPi in patients with TS refractory to medical treatment. Bilateral stimulation of the GPi reduced tic severity by 65%, 96%, and 74% in patients 1, 2, and 3, respectively, whereas CM-Pf DBS reduced tic severity by 64%, 30%, and 40%, respectively. The association of thalamic and pallidal stimulation showed no further reduction in tic severity. The tics returned during the sham condition.⁷⁷

aGpi vs pGpi/ aGpi vs pGpi

Martinez-Fernandez et al studied five TS DBS patients – three of them target-implanted in the pGPi and the other two in the aGPi. All patients experienced improvements in tic severity but to variable extents. The YGTSS scores reduced by 29% (before = 77.8, after = 54.2) and the YBOCS reduced by 34% (before = 16.3, after = 10.8) – this effect was sustained until the last follow-up. The authors stated that the anteromedial part of GPi appeared to be a more effective target.⁷⁵

Other targets

The STN, GPe, ALIC, and NA also referred as VS/VC can act as alternative targets for TS stimulation, and a few reports have been reported on this topic.

- STN: A case report was published in 2009 of a patient who had Parkinson's disease (PD) and TS and who received

STN DBS; the patient showed a 97% improvement in both tics and parkinsonian symptoms after stimulation.⁷⁹

- VS/VC: Stimulation of VS/VC has been used as a main target in treatment-resistant OCD; it has also been proposed as a treatment for disorders that are highly associated with psychiatric comorbidities, such as TS. Based on this, a few studies have reported that stimulation of VS/VC target moderately improved motor severity and significantly improved OCD.^{80–82} However, clinical evidences from these targets rely on case reports and small series since there are no controlled studies yet.

In 2005, a study showed that a TS subject who was treated with ALIC DBS presented with only 23% improvement on the YGTSS.⁸² For this reason and also due to device problems, the authors opted to change the target to thalamus, which resulted in more satisfactory outcomes with a 46% decrease in the symptoms. In 2007, Kuhn et al described another case of TS/OCD which also improved YGTSS scores.⁸¹ Two years later, Neuner et al reported a follow-up of 36 months after VS/VC DBS and documented close to 50% improvement in YGSTS and significant reduction in the YBOCS.⁸³ Burdick et al also shared their experience about an OCD/TS patient who was implanted in the VS/VC target; their study revealed no objective assessment improvement, despite the positive opinion of the patient.⁸⁴

- GPe: Only case reports are available for GPe stimulation in TS, and all of them have shown good outcomes. In 2007, Vilela Filho et al reported GPe DBS for TS with a double-blind assessment design. The authors reported 81% reduction in tic scores and 84% reduction in OCD scores, 23 months after the procedure.⁸⁵ Later, Piedmonte et al also described a case of GPe stimulation for TS and showed a 70.5% improvement on average in anxiety and motor symptoms.⁸⁶

Non-motor symptoms effects

Although most studies focus on the effects of motor tic, some also have reported neuropsychological correlates of DBS in TS.^{26,87–89} Besides the most used targets (GPi and thalamus), DBS in the VS/VC, STN, and GPe have also recorded beneficial effects in OCD components and other psychiatric comorbidities.

In a recent study of 15 severe TS patients with long-term aGPi DBS, Akbarian-Tefaghi et al investigated whether a specific anatomical site within the aGPi correlated with optimal clinical outcome for the measures of tics, OCB, and mood changes. The authors observed that a region within the ventral limbic GPi, specifically on the medial medullary lamina in the pallidum at the level of the AC-PC, was significantly

associated with improved tics, but changes in the mood and OCB were less significant.⁴⁶ Cury et al reported that a 23-year-old TS patient treated with CM-Pf DBS showed very severe scores and high anxiety rate with 70.5% improvement on YGTSS and also a significant improvement in the anxiety scores (53%), with clinical global impression “much improved” (from 1 to 6) after 18 months of follow-up.²⁶

Adverse effects and complications

DBS for TS is overall considered a safe procedure; however, some facts must be pointed out. A recent publication from the prospective International Deep Brain Stimulation Database and Registry presented 185 patients with refractory TS who underwent DBS implantation from January 2012 to December 2016, at 31 institutions in 10 countries worldwide. Thirty-five percent reported a total of 160 adverse events during the first year of follow-up, including dysarthria that was reported 17 times in 10 of 158 patients (6.3%), and paresthesia that was reported 15 times in 13 of 158 patients (8.2%). All of these events were stimulation-induced and transitory without major complications, and no deaths were reported. The infection rate was reported to be 2.5% (4/158), the hemorrhage rate was 1.3% (2/158), and total explant rate at 1 year was 0.6% (1 of 158).³¹

Hemorrhage was described as a serious surgical complication only in a few cases.^{90,91} Servello et al in 2011 showed a higher rate of postoperative infections of extracranial cables and generator pockets in TS patients compared with other movement-disorder patients (18% vs 3.7%).⁹²

Other side effects probably stimulation-related effects such as fatigue, apathy, lethargy, and also maniac symptoms have been reported occasionally with several targets.^{20,21,66,72,83,93} Sedative effects have been reported mainly at high-amplitude stimulation. There are also reports of stimulation-induced changes in sexual behavior.^{72,94} Duits et al have hypothesized that the surgical procedure or stimulation may have caused an imbalance in the limbic and associative cortico-basal ganglia-thalamocortical loops, thus leading to psychiatric symptoms.⁹³ Recently, in a long-term follow-up of seven TS patients who underwent bilateral DBS (CM-Pf-Voi), the authors showed that a possible imbalance between beneficial and adverse effects at long term can lead to either switching the stimulator off or a proposal for an implant in a different target.⁹⁵

Conclusion

TS is a relatively rare neurodevelopmental disorder that probably originates due to dysfunction in motor-limbic brain circuitry linking exacerbated anxiety to the triggering of

recurring behaviors and tics; however, the precise mechanisms are still largely unknown. Mostly, TS starts in teenagers, improves with conventional treatment, and tends to disappear toward adulthood. Only severe cases, which are uncommon, really need additional treatment. Although DBS is not an approved therapy for TS in most countries, positive evidence from several case and series reports and some comparative studies together suggest that DBS is partially effective in alleviating symptoms in severe and medication-resistant cases of TS. Generally, clinical evidence has been produced by applying chronic bilateral DBS more frequently in the CM-Pf complex but also in the pGPI (motor GPI) or aGPI (limbic GPI) and less frequently in VS/VC and STN targets. This multiplicity of targets in the literature reflects the fact that there is no consensus on which target is the most effective. Also, there are no defined predictors of outcome; however, high scores in tic severity scales may be indirectly related to better response after the DBS.

Future research involving the clinical phenomenology, structural and functional neuroimaging together with data from intraoperative multi unit neuronal and multi target local field potential recordings in TS patients will probably allow better understanding the pathophysiology if this complex disease, guiding interventions such as conventional or adaptive DBS, leading to an individualized treatment. Severe and refractory TS is, in fact, a rare disease. In these circumstances, it is unlikely that large controlled trials will be performed in order to determine the efficacy of each DBS target. It is more likely that data from registry cohorts will provide less-qualified evidence that will lead to a more forgiving and humanitarian approval as it has occurred with OCD in most countries.

Many questions are still left with no specific answers: Is there a best DBS target for TS? Are there specific clinical subsets of TS that would preferentially improve with this or that target? If so, who are the best candidates for each target? Is adaptive DBS better than continuous stimulation?

Disclosure

Rubens G Cury has received honoraria from Medtronic, TEVA, UCB, and Roche for lecturing and scientific board services. Erich Talamoni Fonoff has received honoraria for lecturing and technical assistance, grants, personal fees, and non-financial support from Boston Scientific. The other authors report no conflicts of interest in this work.

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