# Treatment of Dystonia with Deep Brain Stimulation

Jill L. Ostrem*† and Philip A. Starr†‡

*Department of Neurology, University of California, San Francisco, California 94143; †Parkinson's Disease Research, Education and Clinical Center (PADRECC), San Francisco, California 94121; and ‡Department of Neurological Surgery, University of California, San Francisco, California 94143

**Summary:** Pallidal deep brain stimulation (DBS) is an established treatment option for medically refractive dystonia. The mechanism by which globus pallidus pars interna (GPi) DBS improves dystonia is still unclear. Primary generalized dystonia usually responds well to this therapy, as recently confirmed in two well-designed, double-blind, controlled trials; however, predictors of outcome within this population are not well known. The role of GPi DBS in idiopathic cervical dystonia resistant to treatment with botulinum toxin, in tardive dystonia, and in some types of secondary dystonia are emerging as populations of patients who may also benefit, but outcomes are not well documented. Serious complications from this therapy are rare. Future research will likely continue to address the most appropriate programming settings for various populations of dystonia, the mechanism by which DBS affects dystonia, and the possibility of alternative brain targets that might have less associated side effects or greater efficacy than the GPi. **Key Words:** Dystonia, deep brain stimulation, surgical outcomes, implantable device, neuromodulation, globus pallidus.

## INTRODUCTION

Dystonia is a syndrome of sustained muscle contractions producing twisting and repetitive movements or abnormal postures often resulting in simultaneous contraction of both agonist and antagonist muscles.[1] During voluntary movement, there is often activation of additional muscles not necessary for the intended movement.

Dystonia is classified as primary or idiopathic dystonia when it occurs without other neurologic signs and without brain abnormalities evidenced with magnetic resonance imaging (MRI). Dystonia is classified as secondary when it occurs in association with a lesion in the CNS, which can be caused by stroke, cerebral palsy, encephalitis, other environmental insults, or neurodegenerative diseases. In secondary dystonias, there is usually abnormality in cranial MRI or a known history of major CNS insult. Tardive dystonia is a special case of secondary dystonia that occurs following exposure to dopamine antagonist medications.

Dystonia is also commonly classified by anatomical distribution of the dystonia (focal, segmental, or generalized) or by age of symptom onset (juvenile or adult onset). Primary dystonias (especially generalized) are often hereditary and may be subdivided by genotype. There are several single-gene loci that have been associated with dystonia, the best known of which is the *TOR1A* locus (previously *DYT1*). A three-base pair deletion at the *TOR1A* locus is responsible for approximately 30% of juvenile-onset, primary generalized dystonias.[2] In addition, involuntary dystonic movements can be described as mobile or phasic, in which there are rapid movements, or as fixed, in which longer lasting abnormal postures occur.

The pathophysiology of dystonia is not well understood. Several lines of evidence suggest that the basal ganglia play in important role in dystonia. Secondary dystonias are frequently associated with lesions of the putamen or globus pallidus.[3] In functional imaging of primary dystonia, the putamen is a consistent site of metabolic abnormalities.[4,5] Finally, single-neuron electrophysiologic recording in the globus pallidus pars interna (GPi) of dystonic humans shows abnormal discharge patterns and abnormal oscillatory activity, compared with control data from normal nonhuman primates.[6–11] Some evidence from rodent models and from human functional imaging also suggests cerebellar involvement.[12]

Address correspondence and reprint requests to: Jill L. Ostrem, M.D., Assistant Professor of Neurology, University of California, San Francisco, 400 Parnassus Ave., Box 0348, San Francisco, CA 94143; E-mail: jill.ostrem@ucsf.edu.

Dystonia may respond to anticholinergic medications, especially in childhood-onset primary dystonia, but anticholinergics are generally less effective and poorly tolerated in adults.[13–15] A levodopa trial should be performed (especially in childhood-onset generalized dystonia) to rule out the possible diagnosis of dopa-responsive dystonia (Segawa's dystonia). Tetrabenazine, antiepileptic, and benzodiazepine medications have been reported to improve dystonia in a small number of case reports. Oral baclofen is also often tried in patients with secondary dystonia. For focal or segmental dystonias, EMG-guided chemodenervation with botulinum toxin can be very effective and has been recommended by the National Institutes of Health in a consensus statement.[16] For idiopathic cervical dystonia, botulinum toxin injection is considered the first-line therapy.[17] Although less common with newer refined botulinum toxin products, some patients develop antibodies with prolonged use, reducing the effectiveness of this treatment.[18] Despite these options, many generalized and some focal dystonia patients experience inadequate relief from medical therapy, at which time neurosurgical treatment options may be considered.

Neurosurgical intervention in dystonia has a rich history and includes a variety of procedures: peripheral denervation (typically in cervical dystonia),[19] intrathecal baclofen pump implantation (typically in generalized dystonia with associated spasticity),[20–22] and permanent lesioning of the basal ganglia (pallidotomy) or thalamus (thalamotomy).[23,24] Currently, deep brain stimulation (DBS) is the most promising procedure performed for the treatment of dystonia and will be the focus of this review article.

## DEEP BRAIN STIMULATION

The best-studied applications for DBS in movement disorders are thalamic stimulation for essential tremor and GPi or subthalamic nucleus (STN) stimulation for Parkinson's disease (PD). In 2003, the Medtronic Activa DBS device was granted limited Food and Drug Administration (FDA) approval in the United States for primary generalized and segmental dystonia, in patients ages 7 years or greater, under a humanitarian device exemption (HDE). Both GPi and STN targets were included in the HDE labeling. Most of the published work on DBS in dystonia focuses on GPi stimulation, although a small literature on thalamic and STN stimulation exists.

Deep brain stimulation alters neuronal discharge or axonal propagation (or both) in the target structure that is stimulated, although the exact mechanism by which this effect occurs is still unclear. The Medtronic Activa DBS system consists of an implantable pulse generator (IPG), an extension wire, and a four-contact brain lead which is placed into the desired target. Stimulation parameters are programmed noninvasively by the physician and can be adjusted as necessary for the patient's specific symptoms. In general, DBS has several advantages over ablative procedures, in that it is nondestructive, reversible, and adjustable. DBS also can be used safely bilaterally, without producing permanent speech, swallowing, or cognitive adverse effects, as have been seen with bilateral lesioning procedures.[23]

### Surgical indications and patient evaluation

**Surgical indication.** At most major surgical centers, patients are considered for surgical treatment if they meet the following criteria: 1) unequivocal diagnosis of primary or secondary dystonia, made by a movement disorders neurologist; 2) failure to manage dystonia with anticholinergic, antiepileptic, benzodiazepine medications, baclofen, or, in patients with focal or segmental dystonia, treatment failure after injection of botulinum toxin with appropriate muscle selection and dosing; 3) significant disability, despite optimal medical management (disability may be due to impaired movement, pain, social isolation, or a combination of these). Patients who are surgical candidates should undergo surgery prior to the onset of fixed orthopedic deformities, because these may limit functional improvement even when dystonia symptoms are ameliorated.[25]

Typically patients have a screening MRI scan of the brain (and, if indicated, the cervical spine), undergo neuropsychological and psychiatric assessments, and participate in a detailed videotaped clinical evaluation, including standardized dystonia rating scales, before surgery.

**Rating scales for dystonia.** A major difficulty in understanding the literature on surgical treatment of dystonia is the paucity of studies documenting the outcome of surgery in a reliable manner, using validated measures. For future studies, it will be critical that all patients be carefully studied with the use of standardized rating scales preferably performed by a movement disorders neurologist.

The most commonly used rating scale for generalized dystonia is the Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS).[26,27] This scale is composed of a movement scale (based on an objective motor exam) and a disability scale (based on a patient interview). The BFMDRS motor score is a 120-point scale that rates the severity of dystonia in nine body regions, taking into account both the severity and frequency of the dystonic movements. This scale has shown excellent interrater reliability and is the preferred rating scale for generalized dystonia.[26,27] The most commonly used rating scale for cervical dystonia is the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS),[28] an 85-point scale with subscores for dystonia severity, functional disability, and pain.

For both scales, a higher score indicates more severe dystonia. Although these rating scales result in objective outcome measures, they are limited in measuring fixed *versus* mobile dystonia and complex movements. Hence, there is always a need to perform videotaped exams to provide clear documentation of surgical outcome.

**Stereotactic targeting and microelectrode recording**

The optimal technique for accurate placement of DBS electrodes for dystonia has not been defined. Nearly all groups used MRI-based stereotactic localization. Some surgeons use stereotaxy as the sole localization technique and perform the implantation with the patient under general anesthesia,[29] whereas others supplement stereotactic localization with microelectrode recording and intraoperative test stimulation in awake patients.[25]

At our center, adults with dystonia usually have lead implantation under monitored local anesthesia, but children are operated upon under general anesthesia. After stereotactic headframe placement and after MR imaging has been obtained, targeting is performed using surgical planning software. For GPi DBS, the target point for the tip of the DBS lead is typically at the base of the posterior globus pallidus, immediately superior to the dorsal border of the optic tract in a coronal plane 2 mm anterior to the mid-commissural point. The spatial coordinates of the GPi show great interindividual variability, with the lateral coordinate for the lead tip ranging from 16 to 23 mm from midline. An example of typical lead location is shown in Figure 1.

Single-unit microelectrode recording is useful to help confirm correct placement of the DBS lead, although most multicenter trials of DBS for dystonia have not used this technique. GPi neurons in dystonia discharge at lower frequencies than in PD, and the distinction between neuronal firing rate in the external *versus* internal pallidal segments is not as pronounced as in parkinsonian patients.[6–11,25] To confirm electrode location and test for possible unacceptable stimulation-induced side effects, intraoperative test stimulation is also performed after the lead has been placed, to check thresholds for stimulation-induced activation of the corticobulbar, corticospinal, and optic tracts.

There are a few published case series in which the location of the electrically active contacts associated with good clinical outcome have been well documented.[25,30–32] The active contact location associated with major clinical improvement appears to be in the posterior GPi, 3 mm to 4 mm from the pallidocapsular border, and 2 mm to 5 mm dorsal to the optic tract (FIG. 1). In this region, an effect of stimulation on the external pallidum as well as the internal pallidum cannot be ruled out.

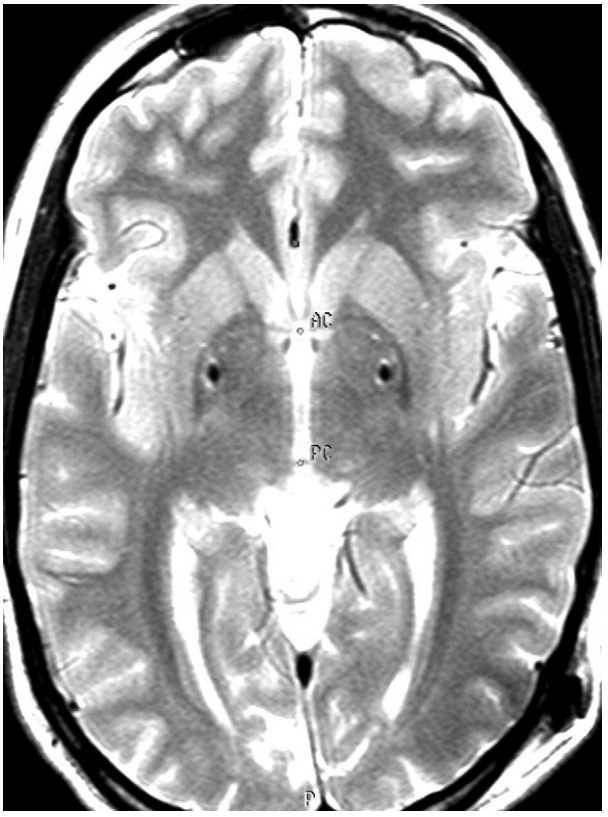


**FIG. 1.** Postoperative axial T2-weighted MRI demonstrating typical bilateral GPi positioning of deep brain stimulation leads in a 24-year-old patient, positive for the *TOR1A* mutation (previously *DYT1*), with generalized dystonia who experienced a 60% improvement in BFMDRS movement score 6 months after surgery.

**Programming**

Postoperative programming of the DBS system is more challenging than in patients with PD or essential tremor, because improvement may take months to occur. Some groups have reported early improvement (days to weeks) after programming, usually in conditions involving mobile dystonia or pain,[32–34] but most patients experience a slower improvement after programming (months). Given this delay in the effect of programming, the decision of when to make changes in contact choice or other parameters is often difficult and subjective.

In general, stimulation currents for GPi DBS in dystonia are somewhat higher than for GPi DBS in PD, and consistently higher than for STN DBS in PD. In many series, pulse widths are $>180$ $\mu$s, whereas those typically used in PD are 60 $\mu$s to 90 $\mu$s. Some groups, however, are reporting excellent outcomes in dystonia with the use of smaller pulse widths,[35,36] and a recent article comparing various pulse widths in primary generalized dystonia failed to show any difference in outcome when using short, medium, and long pulse-width durations.[37] High-frequency stimulation (130–185 Hz) has also been used historically, with effective outcomes. Recently, low-frequency stimulation has been shown to

be effective in primary generalized dystonia (60 Hz),[38] and in cervical dystonia (50–60 Hz).[39] We have preliminary evidence to suggest that lower frequency stimulation (60 Hz) may not be as effective in patients with cranial–cervical dystonia (personal observation). The optimal frequency setting may depend on the type of dystonia, a question that deserves additional study. Overall, the high pulse widths and voltages needed in many dystonia patients can result in frequent battery changes (as often as 1 to 2 years when using the Medtronic Kinetra dual channel pulse generator).

### Clinical outcome

Clinical outcomes after GPi DBS are described in the following sections, according to the type of dystonia.

## DBS IN PRIMARY DYSTONIA

### Primary generalized dystonia

Patients with medically refractory primary generalized dystonia, both with and without the *TOR1A* mutation (here referred to as $DYT1^+$ and $DYT1^-$), are the largest group to be studied with GPi DBS. We have found 249 cases reported in the literature to date, with the outcomes of surgery summarized in Table 1.[25,30,32,35,38,40–56] Almost all studies have reported some improvement with DBS; however, the degree of improvement varies widely across studies, ranging from 21% to 95%[46,57] in the BFMDRS movement score, with most studies showing 60% to 70% improvement. Most of these cases were reported in small, open-label, nonblinded studies.

Recently, two important prospective, randomized multicenter double-blind European trials of GPi DBS were published. Vidailhet et al.[32] studied 22 patients with primary generalized dystonia who were evaluated preoperatively, and at 3, 6, and 12 months postoperatively. A mean improvement of 54% in the BFMDRS movement score and 44% in the BFMDRS disability score were seen at 12 months with chronic stimulation, relative to baseline.[32] At 3 months, patients underwent videotaped double-blind evaluations in the presence and absence of neurostimulation (up to 10 hours, if tolerated) on alternate days. When stimulated, patients showed a statistically significant mean improvement of 29% in the BFMDRS movement score, compared with the unstimulated condition.[32]

Subsequently, Kupsch et al.[41] reported a series of 40 patients with primary segmental and primary generalized dystonia treated with bilateral GPi DBS with randomization to either neurostimulation or sham stimulation for 3 months. At 3 months, patients receiving neurostimulation had a mean improvement of 39.9% in BFMDRS movement scores and 38% in BFMDRS disability scores, compared with 4.9% and 11% in the sham group. After chronic stimulation for 6 months, patients showed a mean improvement of 45% in BFMDRS movement scores and 41% in BFMDRS disability scores. These two trials[32,41] provided the first class I evidence for the use of bilateral pallidal DBS in dystonia.

The largest series of cases of GPi-DBS in primary generalized dystonia with greater than 1 year follow-up was provided by Coubes et al.,[49] who found a 79% mean improvement in the BFMDRS movement score in 31 patients 2 years after surgery. A recent long-term follow-up study by Vidailhet et al.[40] also showed continued mean improvement in BFMDRS movement scores and disability scores (58% and 46%, respectively) in their previously reported 22 patients.

Most series describe continued improvement in dystonia symptoms over the first year.[32] Loss of benefit of GPi DBS after 1 year has only rarely been reported[53]; however, some reports describe subsets of patients with only modest improvement or less commonly no meaningful improvement.[32] Possible reasons for failure include suboptimal DBS lead location, suboptimal DBS programming, or incorrect diagnosis at time of surgery (e.g., patients with unrecognized secondary dystonia, heredodegenerative syndromes, or dystonia-plus syndromes).

Currently, the ability to predict outcomes preoperatively is limited. Initial reports described patients with the *TOR1A* mutation as having better outcomes than patients without the mutation,[53,57] but more recent reports indicate that both groups have a similar benefit from GPi DBS.[32,41,49] Age of onset of dystonia has also not been found consistently to be predictive of outcome. Patients with longer disease duration may be at increased risk of developing secondary fixed contractures and may not have as great a functional outcome after surgery.[38] Also, some studies have shown more improvement in appendicular dystonia (limb) than axial dystonia (speech and swallowing) symptoms.

For now, pallidal DBS remains an extremely powerful and important therapy, with dramatic improvements seen in most patients. Specific predictors of outcome will remain elusive, however, until larger series of patients are studied in blinded, well-designed clinical trials, clearly documenting lead location, programming parameters, and detailed patient characterization.

### Primary cervical dystonia

Patients with medically intractable primary cervical dystonia who have failed botulinum toxin therapy may also benefit from pallidal DBS. There is one report of unilateral GPi DBS successfully treating cervical dystonia,[58] but most published cases have involved bilateral stimulation, including the first reported series of three patients by Krauss et al.[59] in 1999. To date, approximately 53 cases of patients with GPi DBS for cervical dystonia have been published in the literature,

**TABLE 1.** *Published Results of GPi DBS for Primary Dystonia in Series with >5 Patients*

| Type of Dystonia | *N* | Scale (Subscale) | Baseline Score | FU Time (mo) | FU Score | Percent Improvement |
|---|---|---|---|---|---|---|
| Vercueil et al.[48] (2001)[a] | | | | | | |
| Primary generalized* | 1 | BFMDRS (m/d) | NA | 12 | NA | 67/81 |
| Primary generalized* | 1 | BFMDRS (m/d) | NA | 6 | NA | 70/50 |
| Primary DYT1$^+$ | 1 | BFMDRS (m/d) | NA | 12 | NA | 86/86 |
| Primary DYT1$^-$ | 1 | BFMDRS (m/d) | NA | 24 | NA | 41/43 |
| Cranial–cervical | 1 | BFMDRS (m/d) | NA | 6 | NA | 66/66 |
| Krauss et al.[61] (2002) | | | | | | |
| Cervical | 5 | TWSTRS (s/d/p) | 20.5/40.5/6 | 20 | 7.5/12.7/3 | 62/69/50 |
| Bereznai et al.[30] (2002) | | | | | | |
| Segmental | 3 | BFMDRS (m) | NA | 3–12 | NA | 72.5[†] |
| Primary DYT1$^+$ | 1 | Tsui scale | NA | 3–12 | NA | 45 |
| Cervical (1 MS) | 2 | NA | NA | 3–12 | NA | |
| Yianni, Bain, Gregory et al.[45] (2003).[b] | | | | | | |
| Primary DYT1$^+$ | 2 | BFMDRS (m) | NA | 12 | NA | 85[‡] |
| Primary DYT1$^-$ | 11 | BFMDRS (m) | NA | | NA | 46[‡] |
| Cervical | 7 | TWSTRS (s/d/p) | 21.3/21.7/15.1 | | 10/14/8.3 | 50/38/43 |
| Yianni, Bain, Giladi et al.[51] (2003). | | | | | | |
| Generalized | 12 | BFMDRS (m) | 79.7 | 4–184 | 45.3 | 46 |
| Cervical | 7 | TWSTRS (t) | 57.8 | 12–2 | 23.0 | 59 |
| Cif et al.[44] (2003) | | | | | | |
| Primary DYT1$^+$ | 15 | BFMDRS (m/d) | 60.8/16.7 | 24–36> | 14.2/5.7 | 71/63 |
| Primary DYT1– | 17 | BFMDRS (m/d) | 56.5/16.4 | 24–36 | 15.1/9.5 | 74/49 |
| Krauss et al.[52] (2003) | | | | | | |
| Primary DYT1– | 2 | BFMDRS (m) | 81 | 24 | 21.5 | 73 |
| Kupsch et al.[96] (2003) | | | | | | |
| Primary DYT1$^+$ | 1 | BFMDRS (m) | 34.5 | 3–12 | 27 | 22 |
| Primary DYT1$^-$ | 3 | | 40 | | 20 | 50 |
| Segmental | 1 | | 32 | | 19 | 41 |
| Katayama et al.[54] (2003)[c] | | | | | | |
| Primary | 5 | BFMDRS (m) | 18–62 | 6 | 4–23 | 51–92 |
| Coubes et al.[49] (2004)[d] | | | | | | |
| Primary DTY1+ | 17 | BFMDRS (m) | 62.6 | 24 | 12.4 | 83 |
| Primary DYT1$^-$ | 14 | FMDRS (m) | 56.3 | 24 | 13.4 | 75 |
| Vayssière et al.[31] (2004) | | | | | | |
| Primary generalized* | 19 | BFMDRS | NA | NA | NA | >80 |
| Eltahawy et al.[57] (2004)[e] | | | | | | |
| Primary DYT1$^+$ | 1 | BFMDRS (m) | 88 | 6 | 66 | 25 |
| Primary DYT1$^-$ | 1 | BFMDRS (m) | 48 | | 16 | 21 |
| Cervical | 3 | TWSTRS (t) | 37.7 | | 16 | 57 |
| Krause et al.[53] (2004) | | | | | | |
| Primary DYT1$^+$ | 4 | BFMDRS (m) | 72 | 12–66 | 34 | 53 |
| Primary DYT1$^-$ | 6 | BFMDRS (m) | 73.9 | | 50 | 32 |
| Cervical | 1 | BFMDRS (m) | 6 | | 6 | 0 |
| **Vidailhet et al.[32] (2005)** | | | | | | |
| **Primary DYT1$^+$** | **75** | **BFMDRS (m/d)** | **55.1/14.72** | **12** | **26.1/85** | **53/45.6** |
| **Primary DYT1$^-$** | **1** | **BFMDRS (m/d)** | **41.96/10.2** | | **18.7/5.5** | **55.4/45** |
| Bittar et al.[43] (2005)[f] | | | | | | |
| Primary DYT1$^+$ | 2 | BMFDRS (t) | 103.8 | 24 | 55.8 | 46[§] |
| Primary DYT1$^-$ | 4 | TWSTRS (t) | 57.8 | 24 | 23.7 | 59 |
| Cervical | 6 | | | | | |
| Zorzi et al.[55] (2005) | | | | | | |
| Primary DYT1$^+$ | 1 | BFMDRS (m/d) | 47/11 | 4 | 14/6 | 70/45 |
| Primary DYT1$^-$ | 8 | BFMDRS (m/d) | 68.9/17.9 | 19.1 | 46.5/12.6 | 32/37 |

**TABLE 1.** *Continued*

| Type of Dystonia | *N* | Scale (Subscale) | Baseline Score | FU Time (mo) | FU Score | Percent Improvement |
|---|---|---|---|---|---|---|
| Diamond et al.[42] (2006)[g] | | | | | | |
| Primary DYT1$^+$ | 5 | UDRS | 44.6 | 27.5 | 4.8 | 15.3 |
| Primary DYT1$^-$ | 5 | | | | | |
| **Kupsch et al.[41] (2006)[h]** | | | | | | |
| **Primary DYT1$^+$** | **6** | **BFMDRS (m/d)** | **36.4/10.0** | **6** | **20.2/5.9** | **45/41** |
| **Primary DYT1$^-$** | **27** | | | | | |
| **Primary*** | **7** | | | | | |
| Starr et al.[25] (2006) | | | | | | |
| Primary DYT1$^+$ | 6 | BFMDRS (m) | 59.6 | 13.2 | 24.2 | 59 |
| Primary DYT1$^-$ | 1 | BFMDRS (m) | 94 | NA | NA | NA |
| Segmental | 3 | BFMDRS (m) | 22.6 | 21.7 | 12 | 47 |
| Cranial–cervical (MS) | 1 | BFMDRS (m) | 30.0 | 9 | 3 | 90 |
| Generalized* | 2 | BFMDRS (m) | 83 | 10.5 | 72.8 | 12 |
| Hung et al.[36] (2007) | | | | | | |
| Cervical | 10 | TWSTRS (s/d/p) | 21.9/18/11.7 | 12–67 | 9.9/7.4/5.8 | 54.8/52.1/50.5 |
| Alterman et al.[38] (2007) | | | | | | |
| Primary DYT1$^+$ | 12 | BFMDRS (m/d) | 35/8 | 12 | 4/2 | 89/75[§] |
| Primary DYT1$^-$ | 3 | | | | | |
| Tisch et al.[35] (2007) | | | | | | |
| Primary DYT1$^+$ | 7 | BFMDRS (m/d) | 38.9/9.0 | 6 | 11.9/4.1 | 69.5/58[§] |
| Primary DYT1$^-$ | 8 | | | | | |
| Ostrem et al.[33] (2007) | | | | | | |
| Cranial–cervical | 6 | BFMDRS (m/d) | 22/6 | 6 | 6.1/3.7 | 72/38 |
| | | TWSTRS (t) | 39 | | 17 | 54 |
| **Kiss et al.[34] (2007)** | | | | | | |
| **Cervical** | **10** | **TWSTRS (s/d/p)** | **14.7/14.9/26.6** | 12 | **8.4/5.4/9.2** | **43/64/65** |
| Grips et al.[97] (2007)[i] | | | | | | |
| Segmental | 8 | UDRS | 36.9 | NA | 16.1 | 55.7 |
| | | BFMDRS | 35.6 | | 13.1 | 60.6 |
| | | GDS | 29.3 | | 10.3 | 66.5 |
| Vidailhet et al.[40] (2007)[j] | | | | | | |
| Primary DTY1$^+$ | 7 | BFMDRS (m/d) | 46.3/11.6 | 36 | 19.3/6.3 | 58/46[§] |
| Primary DYT1$^-$ | 15 | | | | | |

Series with Class 1 evidence are highlighted in bold type.
BFMDRS = Burke–Fahn–Marsden Dystonia Rating Scale; DYT1$^+$ = negative for mutation in *TOR1A* (previously *DYT1*); DYT1$^-$ = negative for *TOR1A* mutation; FU = follow-up; GDS = Global Dystonia Scale; MS = Meige syndrome; NA = not available; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale; UDRS = Unified Dystonia Rating Scale. *Subscales and scoring:* d = disability; m = movement; p = pain; s = severity; t = total score.
*Unknown subtype. [†]Primary and segmental groups analyzed together. [‡]Estimated. [§]DYT1$^+$ and DYT1$^-$ groups analyzed together. [a]Series also included 12 patients treated with thalamic DBS alone and 3 with thalamic DBS then GPi DBS; 2 patients had no follow-up. [b]Same patients as Yianni et al.[51] [c]One patient bilateral thalamotomy, one patient unilateral pallidotomy. [d]Longer term follow-up from Cif et al.[44] (2003). [e]Study also includes pallidotomy patients. [f]Both primary groups analyzed together; 12-month follow-up data gathered. [g]Two patients with pallidotomy; outcome for all patients analyzed together. [h]All groups analyzed together. [i]All patients previously reported. [j]Same patients as Vidailhet et al.[32] (2005).

most described as individual case reports or small series.[30,34,36,39,43,51,57,58,60–62]

Outcome data again are variable, ranging from 43% to 76% improvement in TWSTRS scores (Table 1). Recently, a well-designed, blinded-rater study reported outcomes in 10 patients at 12 months after surgery, showing a 44%, 64%, and 65% mean improvement in TWSTRS severity, disability, and pain subscores, respectively.[34] Hung et al.[36] reported long-term sustained benefit in a series of 10 cervical dystonia patients up to 3 years postoperatively. Although most reports suggest overall improvement, there are several reports suggesting only minor improvement in head and neck position, but significant improvement in associated neck pain.

There is one report of a patient with cervical dystonia who showed improvement after 5 years of chronic bilateral GPi DBS, with sustained improvement for at least 6 months after stimulation was discontinued.[63] A similar case of cranial dystonia has also been described.[64] Such sustained benefit raises the possibility that GPi DBS in

focal dystonia may permanently correct abnormal motor circuits. In most cases, however, patients remain stimulator dependent. Although DBS is clearly promising, considerably more data are needed to better define the role of DBS in cervical dystonia, including patient selection, optimal programming settings, and long-term outcomes.

### Primary cranial–cervical dystonia (Meige syndrome)

There are now several reports of GPi DBS in patients with medication-refractory, idiopathic cranial–cervical dystonia (Meige syndrome). In the 13 cases reported, outcomes range from 45% to 80% improvement in BFMDRS at short follow-up times (typically <6 months).[30,33,48,65–68] In a series of six patients, we reported a mean improvement of 71% in BFMDRS movement score in an open-label trial 6 months postoperatively.[33] Some patients, however, developed reversible stimulation-induced bradykinesia in previously nondystonic limbs after prolonged GPi DBS.[33] Whether adjustments in programming can optimize dystonia control without the development of subtle bradykinesia, or if stimulation in other brain targets (e.g., STN) minimizes this adverse effect, remains to be evaluated.

## DBS IN SECONDARY DYSTONIAS

### Heredodegenerative syndromes

Limited data suggest that patients with symptoms of dystonia associated with some of the heredodegenerative syndromes may improve substantially in the short term with GPi DBS. Castelnau et al.[69] published a series of six patients with pantothenate kinase-associated neurodegeneration (PKAN), demonstrating a 75% mean improvement in BFMDRS movement scores, with follow-up from 6 to 42 months. Three other PKAN cases in the literature also reflect similar short-term improvement in dystonia symptoms.[53,70,71]

### Tardive dystonia

Thus far, there have been limited results with patients undergoing GPi DBS for tardive dystonia. Since 2001, there have only been 25 cases reported, all showing some improvement in BFMDRS movement scores (range, 35%–73%) at various postoperative time points.[25,51,53,57,72] A recently published, multicenter double-blind trial of GPi DBS in 10 patients with medically refractory tardive dyskinesia showed a 50% significant mean improvement in the extrapyramidal symptoms rating scale score[73] using blinded assessments after 6 months of stimulation.[74] Most reports also comment on the quick improvement in symptoms (within days) after the DBS is activated.

### Dystonia-plus syndromes

Studies of GPi DBS in myoclonic dystonia have shown improvement in both dystonic and myoclonic features of this disorder.[51,75,76] Also, a case of X-linked dystonia of parkinsonism has also been reported to respond,[77] whereas a case of rapid-onset dystonia-parkinsonism was reported to not respond.[78]

### Other secondary dystonia

Summarizing the outcomes of GPi DBS in other forms of secondary dystonia is difficult, because of the inherent heterogeneity of this population of patients, small numbers of cases reported, and variability in outcome measures used. In general, secondary dystonia does not respond as consistently or as markedly as primary dystonia. Cases treated with GPi DBS include posttraumatic,[25,48,51,53,79,80] postanoxic or cerebral palsy associated,[25,48,52,53,55] postencephalitic,[55,57] and poststroke cases. There are also a few case reports of DBS for dystonia associated with multiple sclerosis,[51] Huntington's disease,[57] and basal ganglia calcification.[55]

Clearly, the outcome assessment in secondary dystonia is complicated by the heterogeneity of this population, with mixed etiologies and often with coexisting neurological deficits. Our early experience suggests that phasic movements may improve but fixed dystonic postures do not. In this population, although dystonia improvement may be minimal, the patient and family might still find the improvement meaningful.

## MECHANISM OF DBS ON DYSTONIA

The mechanism of action of GPi DBS in dystonia is not well understood. The GPi is the major output nucleus of the basal ganglia, influencing supplementary motor cortex via the ventrolateral thalamus, and the brain stem–spinal cord via the pedunculopontine nucleus. The rationale for GPi DBS in dystonia has been empiric rather than theoretical, growing from earlier work on pallidotomy for dystonia, as well as the positive results from pallidotomy and pallidal DBS for dystonic symptoms in patients with Parkinson's disease. There is evidence that globus pallidus neuronal activity in dystonia is abnormal.[6–11] GPi DBS is presumed to override the existing abnormality, although it clearly does not restore normal function. Functional imaging indicates that GPi DBS corrects abnormal hypermetabolism in supplementary motor areas,[81] presumably by ameliorating the abnormal influence of GPi on thalamocortical pathways.

## COMPLICATIONS AND ALTERNATIVE TARGETS

Deep brain stimulation is relatively safe in the hands of neurosurgeons experienced in performing this proce-

**TABLE 2.** *Cases in the Literature of Subthalamic Nucleus Deep Brain Stimulation for Dystonia*

| Type of Dystonia | *N* | Scale | Baseline Score | FU Time (mo) | FU Score | Percent Improvement |
|---|---|---|---|---|---|---|
| Pastor-Gómez et al.[92] (2003) | | | | | | |
| Generalized | 1 | NA | NA | NA | NA | NA |
| Detante et al.[93] (2004) | | | | | | |
| Primary generalized | 13 | NA | NA | 3 | NA | No improvement |
| PKAN | 3 | | | 3 | | |
| Chou et al.[91] (2005) | | | | | | |
| Cervical dystonia and ET | 1 | TWSTRS (s/d) | 14/20 | 6 | 3/0 | 79/100 |
| Zhang et al.[98] (2006)[a] | | | | | | |
| Tardive dystonia | 1 | BFMDRS (m) | 98.8 | 3 | 8 | 91.9 |
| Antiemetics | 1 | BFMDRS (m) | 26.5 | 3 | 2 | 90.6 |
| Neonatal anoxia | 2 | BFMDRS (m) | 76 | 6 | 7 | Did poorly |
| Lesion in lentiform nuclei | 1 | | | | | 90.8 |
| Neonatal jaundice | 1 | | | | | Did poorly |
| Posttraumatic thal infarct | 1 | | | | | Did poorly |
| NA and jaundice | 1 | | | | | Did poorly |
| No cause | 1 | | | | | Did poorly |
| Kleiner-Flisman et al.[90] (2007)[b] | | | | | | |
| Segmental–major cervical | 1 | BFMDRS (m/d) | 36.5/5 | 12 | 29/10 | 21/50 |
| | | TWSTRS (s/d/p) | 31/27/14 | | 23/20/5.5 | 26/26/61 |
| Segmental–major cervical | 1 | BFMDRS (m/d) | NA/NA | | NA/NA | NA/NA |
| | | TWSTRS (s/d/p) | 21/16/17 | | 12/5/14.25 | 43/69/16 |
| Segmental–major cervical | 1 | BFMDRS (m/d) | 53/14 | | 59/17 | −11/−21 |
| | | TWSTRS (s/d/p) | 26/27/15.25 | | 28/24/18.25 | −8/11/−20 |
| Primary generalized | 1 | BFMDRS (m/d) | 43/5 | | 12/3 | 72/40 |
| | | TWSTRS (s/d/p) | 19/8/3.5 | | 14/1/0 | 26/88/100 |
| Sun et al.[94] (2007)[c] | | | | | | |
| Primary generalized | 12 | BFMDRS | NA | 6–42 | NA | 76–100 |
| Tardive dystonia | 2 | | | | | |
| Novek et al.[95] (2007)[d] | | | | | | |
| Primary generalized | 1 | BFMDRS (m/d) | NA | 29 | NA | 23/42 |

BFMDRS = Burke–Fahn–Marsden Dystonia Rating Scale; ET = essential tremor; FU = follow-up; NA = not available; PKAN = pantothenate kinase-associated neurodegeneration; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale. *Subscales and scoring:* d = disability; m = movement; p = pain; s = severity; t = total score; thal=thalamic.
[a]Bilateral STN, 6 cases; unilateral STN, 2 cases; left STN and right GPi, 1 case. [b]Also performed 3 months follow-up and used blinded raters. [c]Groups reported together. [d]Patient with previous left pallidotomy.

dure. The most common serious complications with DBS include stroke, infection, and lead fracture. Most of the rates quoted for these complications come from mixed populations of patients having DBS, not specifically for dystonia. For all patients considering DBS surgery, we typically quote a 1% risk of hemorrhagic stroke per brain hemisphere, a 5% risk of device-related infection severe enough to require further surgery for hardware removal, and a 1% per year risk of lead fracture.

Combining the experience from the two recent, blinded trials of GPi DBS for primary generalized and segmental dystonia[40,41] and the largest published series by Coubes et al.[49] allows an evaluation of adverse effects in a total of 93 patients followed for 6 to 36 months. In this cohort of patients, there were no reports of stroke. In our series, currently at 70 patients, one patient suffered a symptomatic venous hemorrhage, and two have had small asymptomatic hemorrhages.[25] Typically, dystonia patients are younger than patients undergoing DBS for essential tremor and PD, which may reduce the surgical risk for hemorrhagic stroke.

In the three trials just mentioned,[40,41,49] there were a total of six cases of infection (6 of 93, or 6%), with four of them requiring partial or complete hardware removal. In our series, 2 of the 70 patients have had infections requiring device removal (3%), both of them children under 10 years of age with severe generalized dystonia.[82]

Yianni et al.[83] found a disproportionate risk of lead fractures and lead migration (singly or in combination) in their dystonia patients (18.4%), compared with all patients implanted with DBS systems (5.3%). This high rate of hardware complications may be explained by severe phasic neck movements resulting in increased stress on the hardware in dystonia. In the combined cohort of 93 patients mentioned above,[40,41,49] 4 patients experienced this problem (4%). We had 2 of 70 dystonia

patients (3%) develop lead fractures; with a mean follow-up of approximately 3 years, but the incidence will undoubtedly increase with longer follow-up times.

Many other questions remain for the application of DBS for dystonia. The best brain target is not yet clear. The results of thalamic stimulation in dystonia, reported for approximately 20 cases, have been disappointing.[48,72,84–87] One exception is that occupational dystonias, such as writer's cramp, appears to be uniquely sensitive to thalamic surgery, which suggests a different pathophysiology from primary dystonias.[88,89] Although GPi is currently the most popular brain target, the STN as a target for dystonia has not been fully explored[90–95] (Table 2), and the theoretical basis for selecting any one target over another is poor.

## SUMMARY

GPi DBS is an important treatment option for medically refractory dystonia. The mechanism by which GPi DBS improves dystonia is still unclear. Accurate placement of DBS leads into the posterioventral GPi is important for optimal outcomes. Primary generalized dystonia can respond dramatically; however, predictors of outcome within this population are not well-known. The positive role of GPi DBS in idiopathic cervical dystonia, tardive dystonia, and some cases of secondary dystonia is also emerging, but outcomes are not well documented, and additional studies are needed. For neurosurgeons experienced in performing this procedure, serious complications from DBS therapy are rare. Future research will need to continue to address the most appropriate programming settings, the mechanism by which DBS affects dystonia, and the possibility of alternative brain targets (e.g., STN) that might have lesser associated side effects or greater efficacy than GPi DBS for dystonia.

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