REVIEW

# What's New in Surgical Treatment for Dystonia?

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**ABSTRACT:** It is now established that pallidal deep brain stimulation (DBS) is effective in the treatment of generalized and segmental primary dystonia, although there is still insufficient evidence to support its benefit in focal and secondary dystonia. Because several studies have demonstrated that pallidal DBS improves quality of life (QoL), reduced QoL and disability that are nonresponsive to medical treatment are probably the main factors guiding the decision to consider surgery. Some studies have indicated that young patients with primary dystonia who have shorter disease duration and less severe dystonia are likely to have the best outcome from DBS. Therefore, surgery should not be delayed when disability and QoL are impaired to the extent that justifies the surgical risk. A case-by-case approach is recommended in patients who have secondary dystonia. The globus pallidus internus is considered the best target for dystonia. There are still not enough data about the effectiveness of thalamic, subthalamic nucleus, and premotor cortex stimulation. Targeting with multiple electrodes and intra-individual comparisons of outcomes may help determine which target would be more beneficial. With regard to the role of lesions, pallidotomy for dystonia is still performed in several countries and can play a role in selected patients. New technologies are already available to improve the stimulation programming for DBS patients and to increase battery longevity. In the near future, it is possible that we will be able to shape stimulation settings according to disease type and symptoms. © 2013 *Movement* Disorder Society

**Key Words:** deep brain stimulation; dystonia; pallidotomy; surgery

New advances in functional stereotactic neurosurgery that have occurred within the last 20 to 30 years have revolutionized the treatment not only of Parkinson's disease (PD) but also of dystonia. A comprehensive review about the history of functional surgical treatment of dystonia recently was published.[1]

After some benefit observed with thalamotomy and pallidotomy in both primary and secondary, generalized/segmental and focal dystonias,[2–4] the interest of physicians quickly moved to deep brain stimulation (DBS) surgery because of the clinical success obtained in patients with PD[5] and the striking benefit obtained with the first clinical trials in patients with dystonia.[4,6,7] It is interesting to note that, although there is now level A evidence that pallidal DBS is effective in treating patients with primary generalized/segmental dystonia, the use of this treatment has only been approved in the form of humanitarian device exemption by the US Food and Drug Administration. This high level of evidence was reached in 1 class I study[8] and 1 class II study.[9] The former was a German multicenter, randomized, sham-controlled study that demonstrated a significant improvement in the severity of dystonia in 20 patients who had generalized/segmental primary dystonia at 3-month follow-up after bilateral globus pallidus internus (GPi) DBS[8]; and the latter was a French multicenter, prospective, controlled study that involved 22 patients with primary generalized dystonia who had a significant improvement in dystonia severity with pallidal stimulation in a double-blind evaluation with and without stimulation at 3 months of follow-up.[9]

However, when considering the effectiveness of DBS in primary focal, secondary, and neurodegenerative

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dystonias, more data are needed to support the evidence of benefit. In this regard, there have been 4 class III studies[10–13] of cervical dystonia, 1 class III study of tardive dystonia,[14] and 1 class III study of secondary dystonia with different etiology.[11] Those studies demonstrated the effectiveness of bilateral GPi DBS both in cervical dystonia and in tardive dystonia. Concerning the whole body of literature on several types of secondary and neurodegenerative dystonias, only a class III study in patients with cerebral palsy is available to date.[15] Notably, it has been observed that secondary/neurodegenerative dystonias respond less well than primary dystonia to pallidal DBS,[4] with the exception of tardive dystonia.[14]

Nevertheless, long-term data on outcomes in primary and secondary dystonia are starting to emerge; and, overall, those data seem to confirm a long-lasting benefit from pallidal DBS.[13,16–20] With the spreading success of DBS therapy, other targets have been considered for surgery. Recently, the subthalamic nucleus (STN) has been tested as a target potentially as effective as the pallidum in treating dystonia. Published data have mainly concerned primary cervical dystonia,[21] primary generalized dystonia, and tardive dystonia.[22] To date, there is no available randomized clinical study that has compared the 2 targets. As such, the advantages and limits of GPi DBS and STN DBS in dystonia remain unclear.

Because of the less striking benefit of DBS in secondary dystonia and the smaller volume of literature on focal dystonia, some interest has been focused on other surgical techniques and targets, such as gamma knife thalamotomy[23] and premotor cortical stimulation.[24] However, currently, there is not enough evidence to support the use of these surgeries for secondary dystonia.

The new trends in surgery for dystonia currently concern more research on the criteria of inclusion for secondary dystonia, the predictive factors of DBS benefit or failure, the mechanisms of action of DBS in dystonia, and the use of new technical devices. In this article, we have focused our attention particularly on criteria for the selection of patients with dystonia for surgery, brain targets for surgery, and types of surgeries. Finally, we have taken a look into the future, considering what may be available and useful to address the current issues with DBS in dystonia.

## When Is Medical Therapy Not Enough?

Although some types of dystonia require specific treatment (such as levodopa for dopa-responsive dystonia or decoppering therapy for Wilson's disease), unfortunately, the overall medical management of dystonia is not as well defined and as evidence-based as for other movement disorders like PD. Indeed, the level of supportive evidence is lacking for most of the drugs commonly used, with the exception of high doses of trihexyphenidyl in generalized/segmental dystonia and botulinum toxin type A injections in some focal dystonias, such as cranial dystonia (excluding oromandibular), cervical dystonia, and writer's cramp.[25,26] As such, the number of patients who fail medical treatment is higher among those with generalized/segmental dystonia. Reasons for failure are not only the lack of benefit but also poor tolerability, especially when using high doses of anticholinergic drugs in adults.

Patients with dystonia are usually young or relatively young (thus, with a disease onset while they are still working or building a family). Health-related QoL (HRQoL) is significantly impaired in patients with dystonia, especially in domains related to physical and social functioning.[27,28] Disability, disfigurement, body concept, depression, extent of dystonia, and employment status were strongly correlated with HRQoL in 276 patients with different types of dystonia.[28] In addition, negative body concept, low self-esteem, and perceived disfigurement were associated with depression.[29] Reduced QoL and disability that is nonresponsive to medical treatment should be the main factors guiding patients and physicians regarding when and whether to consider surgery. Several studies have demonstrated that pallidal DBS improves QoL.[9–11,30–32] However, the actual number of patients with primary dystonia who require surgery because of drug failure and severe disability probably is not very high.

Strict guidelines about which steps are necessary before considering patients with dystonia for surgery do not exist. These points have been addressed in part by the National Institute for Clinical Excellence in 2006,[33] by the European Federation of Neurological Societies (EFNS),[26] and by the Movement Disorders Society (MDS) Task Force on DBS for Dystonia.[34] In general, there is common agreement about the following points:

1. Surgery is considered a good option after failure of anticholinergic drugs, benzodiazepines, and levodopa in generalized/segmental dystonia and after failure of botulinum toxin injection in cranial and cervical dystonia. In this regard, however, there is no consensus about which type of medication, which dose, and how many trials are needed before surgery. This is mostly because treatment is usually individualized to each dystonia patient. As such, it is not mandatory to try all available medications.
2. Symptoms should be disabling enough to justify the surgical risk. In this regard, there is no agreement about which scales to use to assess symptoms or which cut-off scores for disability, dystonia, and pain severity are needed for surgery. In any case, because HRQoL is often the main reason for surgery, appropriate QoL scales should be considered.[35]

3. For cervical dystonia, peripheral denervation has been considered second-line treatment in relatively simple cases (botulinum toxin-resistant).[26] For patients who are not ideal candidates for this type of surgery because of the complexity of dystonic movements, pallidal DBS has been suggested. However, because of the accumulating experience of DBS benefit[10–13] and the lack of new evidence coming from the other surgical procedures,[36] DBS surgery can be directly suggested as second-line treatment for cervical dystonia.[26] To support this practice, there are some reports of patients who failed peripheral surgery but underwent successful DBS surgery afterward.[37]

## How Do You Select the Best Patients for the Best Outcome?

The small number of patients with dystonia who have undergone DBS surgery and the complexity of the syndrome are largely responsible for the great difficulty in identifying predictive measures of benefit or failure after DBS.[34] Indeed, results coming from the literature are quite heterogeneous. Concerning primary dystonia, some studies have identified no predictive factors of outcome,[8,9] whereas others have focused on the importance of duration of dystonia at the time of surgery, showing a negative correlation.[38] Some studies have pointed out the importance of age at the time of surgery[32,38–40] and also the severity of dystonia at the time of surgery.[16] DYT-1 was correlated with better motor improvement but not with function,[32] whereas the postoperative pallidotomy-like effect did not predict benefit.[16] A recent meta-regression analysis of individual patient outcomes also reported a positive correlation with shorter duration of dystonia, lower severity scores, and positive DYT-1 status.[40] Mobile versus fixed dystonic movements and the presence of contractures did not predict outcome. Concerning secondary dystonia, greater variability of the results and smaller samples still prevented the identification of any prognosticator. Some key points can be summarized as follows:

1. Patients with primary dystonia are likely to have the best outcome from DBS surgery, especially those who are younger, DYT-1–positive, those with shorter disease duration, and those with less severe dystonia.
2. DBS surgery for patients with tardive dystonia can be considered a good option, especially because the magnitude of the surgical benefit is similar to that observed in patients with primary dystonia.[14]
3. DBS surgery for patients with secondary dystonia should be carefully considered, because it is generally less effective. However, because the literature is rather controversial in this regard, a case-by-case approach is recommended.
4. No special imaging requirement is recommended before surgery (once the etiology of dystonia has been clarified).[34,35] However, in patients with severe cervical dystonia, a cervical spine magnetic resonance imaging study may be useful to better quantify the role of spinal degeneration in cervical pain,[41] to clarify patient's expectations, and to rule out the need for spinal surgery before or after DBS.[42] In addition, especially in children, skeletal imaging might be useful to quantify and qualify deformities.[34]
5. Neuropsychology/psychiatric assessments have not been considered mandatory for surgery.[26] Cognitive deterioration has not been reported after GPi DBS.[43] However, there is high psychiatric comorbidity in the dystonia population, and a few suicides have been reported after GPi DBS.[44] As such, a preoperative and postoperative psychiatric assessment in selected patients with psychiatric history is highly recommended.
6. A specialized surgical team is required.

## Is the Internal Segment of the Globus Pallidus the Best Target?

The GPi is the main output nucleus of the basal ganglia network projecting through the thalamus to the cortex. Neuromodulation of its posteroventral lateral portion, which contains the motor circuits, has an impact on both striatopallidal pathways: the direct pathway, and the indirect pathway, which processes information through the globus pallidus externus (GPe) and the STN. The concept that both pathways are dysfunctional in dystonia supports use of the GPi as a target for neuromodulation, because it is located strategically at the site where both pathways converge.[45]

The effects of DBS in dystonia are difficult to explain according to the rate model of neuronal activity. However, recording of oscillatory activity in local field potentials through implanted electrodes has provided further support for the suitability of the GPi as a target for DBS. In patients with different phenotypes of dystonia, high theta power has been detected in the GPi compared with that in the GPe.[46] Furthermore, the peak theta oscillatory activity clearly differed from the activity observed in other movement disorders. It also was demonstrated that oscillatory activity in the GPi was coherent with phasic dystonic muscle contractions.[47] Only recently, a peak in theta power also was observed in a single patient who underwent implantation of DBS electrodes in the STN.[48]

The clinical benefit of pallidal DBS in patients with primary dystonia has been demonstrated in numerous studies, as outlined above in more detail, whereas overall serious side effects have been rare. Although

the GPi territory also has been regarded as relatively safe with regard to negative effects on mood and cognition, it was discovered only recently that pallidal stimulation may induce bradykinetic symptoms or parkinsonism in patients who receive effective stimulation for dystonia.[49–52] Such symptoms may include freezing, postural instability, and micrographia. Schrader et al.[51] reported the occurrence of hypokinetic gait and freezing in 8.5% of patients with various phenotypes of dystonia upon chronic pallidal DBS. When stimulation was stopped, both hypokinetic gait and freezing disappeared within 24 hours. Blahak et al.[52] reported significant reduction of both character height and width when comparing preoperative versus postoperative handwriting samples from patients who underwent successful pallidal DBS for treatment of segmental dystonia. Most patients were unaware of the changes in handwriting.

In contrast to findings in PD, in which stimulation through electrode contacts in the dorsal GPi or in the GPe had an anti-akinetic effect (and sometimes a prodyskinetic effect),[53] in patients with dystonia, stimulation through electrode contacts that are placed perfectly in the GPi and yield good clinical improvement may induce bradykinetic symptoms (similar to the effects of ventral GPi stimulation).[49–52] It is unclear how the bradykinetic effect of chronic pallidal DBS may depend on the frequency of stimulation. Anecdotal findings suggest that stimulation with frequencies below 100 Hz may be less likely to result in bradykinesia,[50] but this strategy also was associated with less clinical benefit after a period of several months of stimulation.[54] The occurrence of bradykinetic symptoms in patients with dystonia upon chronic stimulation seems difficult to explain. Most likely, the functional status of the basal ganglia in a certain disorder is responsible for that effect. In line with the fact that chorea or ballism after a structural lesion in the STN is less likely to occur in a patient with PD,[55] increased bradykinesia would not be observed in a patient with PD after pallidotomy or pallidal DBS, although it may occur in normal individuals or in patients with dystonia. This is also in accordance with the well known observation that bradykinesia can be the consequence of pallidal lesions after manganese or disulfiram intoxication.[56,57]

Usually, a compromise can be achieved in the majority of patients between improvement of dystonia and the occurrence of bradykinetic symptoms by reprogramming stimulation settings and by lowering the total energy delivered to the target through the electrodes. Nevertheless, the observation that pallidal DBS may induce bradykinesia has stimulated a discussion about reconsidering alternative targets for chronic DBS in dystonia. Also, the limited efficacy of pallidal DBS in patients with secondary dystonia has sparked interest in alternatives. In this context, it should be noted that the major target for radiofrequency lesioning over many decades before the introduction of modern DBS was not the pallidum but the thalamus. Moreover, data from nonhuman primate animal models of dystonia indicate that stimulation of the supplementary motor area might be an interesting therapeutic approach for secondary dystonia.[58]

To date, there has been little contemporary experience with other targets for DBS in dystonia. The STN reportedly can provide benefit in single instances with limited follow-up data.[22] Recently, a group in San Francisco started to explore the option of STN stimulation more systematically.[21] The authors reported significant improvements in dystonia and QoL among 9 patients with cervical dystonia at 1 year follow-up after surgery. No patient developed bradykinetic symptoms, but all patients had transient dyskinesias, and several patients reported depression and weight gain. There are scant comparative data on the efficacy of STN versus pallidal DBS in patients with dystonia. A patient with sporadic dystonia-parkinsonism achieved improvement of dystonia with either GPi or STN stimulation but fared better on the long run with GPi DBS.[59]

Because many patients with dystonia also present with tremor (and sometimes dystonic tremor may dominate the clinical picture), thalamic targets might be considered an alternative in certain patients. Since Mundinger used thalamic DBS to treat cervical dystonia as early as the middle 1970s, relatively little has been published on this subject.[60] Thalamic DBS has been shown to be an effective treatment for dystonic tremor of the upper extremities[61] and of the head and the trunk.[62] Myoclonic dystonia and writer's cramp are other dystonic movement disorders for which beneficial outcome was reported with thalamic DBS.[63,64] It is unclear which thalamic target is most favorable for chronic stimulation. Although the tremulous components in some dystonia patients may favor the ventralis intermedius nucleus (Vim) (ie, the region of the thalamus that receives cerebellar input), in patients who have more phasic or tonic components, more anterior regions in the ventral thalamus also would be of interest, ie, the region previously called the ventralis oralis posterior nucleus (Vop) (in Hassler's nomenclature), which is now classified as the interface between the ventralis lateralis anterior nucleus (VLa) and the ventralis lateralis posterior nucleus (VLp) (according to the nomenclature of Jones). Another option would be to target the ventralis oralis anterior nucleus (Voa) (in Hassler's nomenclature), which corresponds to the anterior VLa, because it is the area that receives pallidal input.

Until additional data become available, the GPi is still considered the best target for dystonia. Targeting with multiple electrodes and intra-individual comparisons of outcomes after the stimulation of different

targets might be a way to determine which target would be more beneficial in a given context.[65] Finally, it will be important to establish individualized surgical treatment concepts that take into consideration the specific constellation of dystonic symptoms.

## Is There Any Role for Pallidotomy?

Based on a literature review that comprised only class IV data, in 2006, a joint task force (EFNS/MDS-ES) discouraged bilateral pallidotomies, usually performed by radiofrequency thermocoagulation, because of the relatively high risk of side effects compared with DBS.[66,67] This conclusion has not changed in the new EFNS guidelines due to lack of class I and II studies.[26] Fittingly, in a recent comprehensive review of surgical treatment for dystonia, the word "pallidotomy" appeared only twice.[1] However, old therapies often experience new life, and thermal ablation—having already experienced a renaissance in the 1990s—is no exception.

New therapies are propelled by (1) limitations of the old therapy, (2) new technology, and (3) market forces. In the 1960s, suboptimal therapies (limited by inconsistent targeting technology and incomplete knowledge of the appropriate targets) were replaced by new medical treatments. In the 1990s, the limits of those medical therapies, in conjunction with "new" technology (including computed tomography imaging, better understanding of basal ganglia anatomy and physiology, microelectrode recording techniques, and clinical trial techniques), spurred the resurgence of pallidotomy and thalamotomy. In turn, complications from bilateral surgery and fear of potential adverse effects of lesioning the STN, in conjunction with new DBS technology, again led to the demise of lesion therapy. With time, however, has come an appreciation of the limitations of DBS, which include: (1) *hardware complications*, including the need for a large number of pacemaker replacements in this usually younger population, hardware breakage, and erosions/infections; and (2) *expense* of the initial procedure, of the aforementioned complications, and of the clinician hours required for proper maintenance. The latter incorporates the interplay of market forces, which, associated with expensive technologies like DBS in the context of skyrocketing global healthcare expenses, are playing an increasingly large role in the 21st century. These factors alone, in fact, have been associated with the continued use of pallidotomy (see below) and, indeed, subthalamotomy[68] in developing regions, but market pressures that threaten to disfavor DBS are increasing in more developed countries as well. If "new technology" surrounding ablative surgery is compounded to the limitations of DBS and market forces, then the prospects of "old" ablative therapy replacing "new" DBS becomes fathomable.

## Continued Use of Radiofrequency Ablation of the Pallidum, Thalamus, and Subthalamic Nuclei

A thorough review of the modern use of pallidotomy (beginning in 1996[69,70] through 2008) was published in 2008.[71] Since then, only 4 reports on pallidotomy have been published in the English literature,[72–75] reflecting the demurring interest in pallidotomy. Overall, including the patients who were included in the previous review,[71] in a few overlooked reports,[2,76–80] and in the new reports, 57 patients reportedly have undergone bilateral pallidotomies, and 18 have undergone unilateral pallidotomies, reflecting the greater incidence of generalized dystonia requiring bilateral surgery even among secondary cases. In addition, Murat et al.[81] described a complex series of 58 patients, mostly with secondary dystonias, who underwent a combination of thalamotomies and pallidotomies that is difficult to tease apart; and Szolna et al.[82] reported on 30 patients in the Polish literature who underwent 28 pallidotomies and 22 thalamotomies. Not including the latter 2 reports, there were 32 patients with primary dystonias and 43 patients with secondary dystonias who underwent surgery, reflecting the greater incidence of the latter but likely tempered by diminished expectations of improvement.

These series are heterogeneous with respect to quantified versus qualitative outcome measures. Using reported global outcome scores (GOS) (in which 4 indicates marked improvement, and 0 indicates no improvement) or assigning GOS scores based on clinical reports when they were not included (in a manner similar to that described by Yoshor et al.[2]) yields the following information: Primary dystonia treated mostly bilaterally produced a mean GOS ($\pm$ standard deviation) of $3.48 \pm 0.93$ (moderate improvement; similar to the 3.25 derived by Yoshor et al.[2] based on 17 patients). Patients with secondary dystonia after mostly bilateral pallidotomies had a mean GOS of 1.29. However, that number is strongly weighted by the poor results reported by Lin et al.,[83] whose 18 patients with secondary generalized dystonias improved by a meager 13% (GOS = 0) on the Burke-Fahn-Marsden dystonia rating scale after bilateral pallidotomy. Excluding these data yields a mean GOS of $2.25 \pm 1.75$ in 18 patients, precisely identical to that calculated by Yoshor et al.[2] in only 7 patients. It should be noted, however, that there is greater variance (reflected in the standard deviations) in the response among those with secondary dystonia versus primary dystonia: although several patients had no response, others manifested marked responses.[72,74,79,84,85] In particular, patients with tardive dystonia[74,78,80,86] and status dystonicus[72,77,79] appeared to respond well to unilateral and bilateral pallidotomies (as with DBS[14,87,88]).

The recent literature on pallidotomy for dystonia is sparse, but it probably under-represents the actual

incidence of its use. Cautionary words regarding the adverse effects of bilateral pallidotomies,[66,89] particularly in patients with speech disturbance, belie their incidence in the literature. Permanent speech disturbance (ranging from mild dysphonia to anarthria) was noted in only 4 patients[2,4,17] (7% of 57 bilateral patients), although the underestimation of adverse effects in retrospective literature must be considered.[90] Other complications that were reported more than once included transient lethargy/somnolence/stupor in 8 bilateral patients[2,83,91,92] (14%) and transient hemiparesis in 3 patients[83,92] (5%) who underwent bilateral surgery. Thus, it is possible that the balance between factors (such as market forces) that may drive the relative use of lesion over-stimulation and those that weigh against their use (such as permanent deficits) still may lean toward the former in some circumstances. In this regard, it is notable that 8 of the 9 most recent publications on pallidotomy and thalamotomy for dystonia have originated from outside the United States, including: Hungary,[75] Japan,[74] Argentina,[26] Poland,[82] Saudi Arabia,[83] Turkey,[81,93] Brasil,[79] and Holland.[78] These include the 2 largest series of 58 patients from Turkey[81] (albeit operated between 1991 and 1999) and 30 patients from Poland,[82] at a minimum testifying to the delayed penetration of DBS in those markets.

However, there remains a role for pallidotomy for dystonia in more developed markets as well, in the following circumstances. *First*, there are some patients in whom the balance of risks and benefits favors lesion over-stimulation. This occurs in the following settings: (1) advanced dystonia, in which body habitus and extreme dystonic contractions predispose to hardware-related complications, and life-threatening status dystonicus or "dystonic storm," in which the time necessary for repeated programming sessions is disadvantageous[72,74,77,79,94]; (2) early childhood dystonia, in which, again, body-related issues preclude a neurostimulator system[94]; and/or (3) pre-existing neurological deficits caused by dystonia, including speech disturbances (such as advanced dysphonia and dysarthria and/or dysphagia with feeding tube), which make the risk of such effects from bilateral pallidotomies less of a concern.[72] *Second*, some patients may not wish to have an implanted neurostimulator system because of hardware considerations,[75] or it is not feasible to implant 1 due to decreased access to a programming center. Unilateral pallidotomy is reasonable in these situations, but careful deliberation is necessary before contralateral pallidotomy given the risk (albeit small but still not well quantified) of speech and swallowing complications. In some circumstances, DBS on 1 side and contralateral pallidotomy may be the appropriate choice. *Third*, after complications develop from an implanted DBS system, such as erosion/infection, consideration may be given to replacing at least 1 system with a lesion. In fact, it is feasible to perform the pallidotomy through a previously documented, well positioned DBS lead.[73]

## Looking Into the Future

New exciting developments are likely to happen and to make a considerable impact on our clinical practice in the near future. DBS technology is quickly evolving, allowing both patients and physicians to adapt stimulation settings according to both disease type and symptoms. Indeed, the most recent DBS batteries are providing more flexibility in stimulation programming and increased battery duration. These new features will considerably reduce the relevant number of surgeries for battery changes that dystonic patients usually require and potentially may avoid a dramatic recurrence of dystonic symptoms when the battery suddenly expires. More possibilities for managing the electrical parameters also will allow for customizing the stimulation for each side of the body, visualizing the diffusion of current, and shaping the current to improve benefit and avoid side effects.

More clinical and neurophysiological data will allow a better understanding of how to predict DBS benefit and improve criteria for the selection and timing of surgery. New data also will clarify the use of DBS in secondary dystonia. Accordingly, the future will shed more light into the pathogenesis of dystonia and, conversely, will help to target new, potentially relevant areas.

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