

Surgical Treatment of Movement Disorders

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The surgical treatment of movement disorders has evolved considerably over the last decade in terms of the scope of the indications for surgery, and in terms of technique. Deep Brain Stimulation (DBS) has an established role in the treatment of Parkinson's disease and essential tremor. As a surgical procedure, it offers inherent advantages over ablative therapies, as the therapeutic and side effects of stimulation can be modulated by adjustment of multiple stimulation parameters. DBS is finding increasing application for the treatment of dystonias, and for tremor disorders other than essential tremor. These conditions, many of which are notoriously difficult to treat medically, are reviewed in this article. The objective is to focus on the conditions for which surgical treatments may be beneficial, the indications and contraindications to these procedures, and on the surgical techniques and outcomes.



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Overview of Surgical Procedures.

Surgical techniques can be roughly divided into ablative procedures, neurostimulation procedures, and procedures aimed at the enhancement of drug delivery. Added to this scheme more recently are the trials of augmentative and restorative therapies, such as transplantation of fetal mesencephalic tissue into the striatum of patients with Parkinson's disease. The different surgical strategies are summarized in *Table I*. Currently, Deep Brain Stimulation (DBS) represents the most commonly employed procedure, with an extensive literature that supports efficacy for the treatment of Parkinson's disease and essential tremor. It possesses an inherent advantage over ablative procedures, because of the ability to modulate both therapeutic and adverse effects of stimulation—effects are typically fixed following lesioning. Several restorative therapies have been subjected to controlled studies to date; none have demonstrated efficacy similar to that seen with DBS.

Targets of surgical treatments consist largely of the structures of the basal ganglia and thalamus, specifically the internal

segment of the Globus Pallidus (GPi), the subthalamic nucleus (STN), and the Ventralis intermedius nucleus of the thalamus (Vim). The modern targets for surgical treatment of movement disorders were discovered somewhat serendipitously, with the observation over 50 years ago that an iatrogenic infarct in the basal ganglia produced effective tremor control in a Parkinsonian patient. Further exploration of the effects of lesions in multiple sites within the basal ganglia gave rise to the stereotactic thalamotomy and pallidotomy. Lesions of the subthalamic region were complicated by hemiballismus, and bilateral lesions of the thalamus or pallidum were frequently accompanied by fixed corticobulbar or corticospinal deficits. The ability to modulate the majority of therapeutic and side effects with adjustable stimulation has overcome these serious limitations of lesion surgery. Deep Brain Stimulation has generally supplanted ablative techniques, because DBS makes possible bilateral surgery, and surgery employing the subthalamic nucleus as a target. While the risks specific to the creation of a lesion (ie,

Table 1. Summary of Neurosurgical Procedures Used for the Treatment of Movement Disorders

<u>PROCEDURE</u>	<u>CURRENT STATUS</u>
<i>Lesioning and Ablative Procedures</i>	
Thalamotomy	Proven benefit for tremor only, not recommended for use on both sides of the brain.
Pallidotomy	Proven benefit up to 5 years for tremor, rigidity, bradykinesia, and levodopa induced dyskinesias. Not recommended for use on both sides of the brain.
<i>Denervation Procedures</i>	
	Examples include partial denervation of the accessory nerve for cervical dystonia, selective dorsal rhizotomy for spasticity. As with lesioning procedures, denervation does not afford the opportunity to modulate either the therapeutic or adverse effects.
<i>Deep Brain Stimulation</i>	
Chronic thalamic stimulation (Vim DBS)	Reduces tremor but not the other signs of PD; approved by U.S. Food and Drug Administration in 1997 for unilateral use in the treatment of tremor. Commonly used off-label for the treatment of bilateral essential tremor. Growing literature on the use of thalamic stimulation for the treatment of non essential tremor, such as tremor from MS, and Holmes' tremor.
Chronic pallidal stimulation (GPi DBS)	Reduces tremor, rigidity, bradykinesia, and gait disorder; approved by FDA in 2002 for use in Parkinson's disease. FDA granted Humanitarian Device Exemption in 2003 for use in the treatment of dystonia.
Chronic stimulation of subthalamic nucleus (STN DBS)	Reduces tremor, rigidity, bradykinesia, and gait disorder; approved by FDA in 2002 for use in Parkinson's disease. FDA granted Humanitarian Device Exemption in 2003 for use in the treatment of dystonia.
<i>"Restorative" Therapies & Drug Delivery Strategies</i>	
Human fetal cell transplantation	Experimental; human trials have not shown overall efficacy. One recent trial showed only modest benefit in a subgroup of younger patients, and production of uncontrollable dyskinesias was an adverse effect in some patients.
Stem cell transplantation	Studied in laboratory animals only; not yet applicable in humans
Intracerebral injection of growth factors	Experimental; Most recent trial of intracerebral administration of Glial cell. Derived Neurotrophic Factor (GDNF) halted by manufacturer due to safety concerns.
Gene therapy by intracerebral injection of genetically modified viral vectors	Studied in laboratory animals, initial human studies (Phase I) are being conducted.

dysarthria, ataxia) are clearly lower with DBS, there remains with this surgery a risk of hemorrhagic complications, and of hardware-related complications, including infection. The risk of intracranial hemorrhage with DBS surgery is typically cited at around 3 percent in large series, though in

general, less than half of these are symptomatic.¹

Essential Tremor. Thalamic DBS for the treatment of medically refractory essential tremor (ET) is extremely effective in the treatment of upper extremity tremor,

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14. Goto S, Yamada K. Combination of thalamic Vim stimulation and GPi pallidotomy synergistically abolishes Holmes' tremor. *J Neurol Neurosurg Psychiatry.* 2004;75(8):1203-1204.

often with secondary improvement in head tremor, and sometimes in voice tremor. Surgical treatment is reasonable to consider in patients with a clear diagnosis of ET, who have substantial disability and impairment in quality of life despite therapy with beta-blockers and primidone. Additional medical therapy including topiramate, baclofen, or clonazepam may be attempted prior to considering surgery, though some estimates have as many as 50 percent of patients with persistence of disabling symptoms despite maximal medical therapy.² While the FDA has approved the device for unilateral implantation for the treatment of disabling tremor, it is not unusual that patients with bilateral symptoms require bilateral stimulator placement for effective treatment. The risks of irreversible dysarthria and gait disorder, which proved to be serious limitation to bilateral thalamotomy are much less serious with bilateral DBS surgery, as such side effects are largely subject to modulation with changes in stimulation parameters.³

Parkinson's Disease. Parkinson's disease is characterized by the cardinal symptoms of tremor, rigidity, bradykinesia, and postural instability. For patients with early Parkinson's disease, levodopa and other antiparkinsonian medications are usually effective for maintaining a good quality of life. As the disorder progresses, however, most patients develop a fluctuating response to levodopa, often vacillating between "on" and "off" states many times a day. Additionally, levodopa-induced dyskinesias, consisting of involuntary, often choreo-athetotic movements, can occur with the peak dose or with the onset and wearing-off of the dose (diphasic dyskinesias). Dosing changes, sustained-release preparations of

levodopa, dopaminergic agonists, and other medications can often address these motor fluctuations and complications of levodopa therapy for a period of time. Continued difficulties with fluctuations in motor symptoms and/or levodopa-induced dyskinesias are the primary indications for surgical treatment. *Table 2*, adapted from the University of California, San Francisco, summarizes the selection criteria employed for DBS surgery at the University of Colorado, along with the rationale for each criterion.

The selection criteria are largely derived from the observed benefits of DBS surgery. Stimulation of both the Subthalamic nucleus (STN) and the internal segment of the Globus Pallidus (GPi) produce significant improvement in the off-medication severity of all of the cardinal symptoms of Parkinson's disease (widely accepted criteria for selecting between the GPi and STN targets do not exist as yet). The degree of benefit is rarely greater than that afforded by medication, but the same level of benefit achieved by medications can often be achieved surgically. Thus, benefits of stimulation can be maintained with a substantial reduction or even elimination of medications, which in turn contributes to a reduction of levodopa-induced dyskinesias. As well, the benefit achieved with surgery is typically sustained over the course of the day, and thus addresses the problems related to frequent "on-off" fluctuations in motor symptoms experienced by most patients as the course of their disease progresses.⁴

Other selection criteria are also derived from outcomes data. The few reports of DBS as a treatment for "atypical" parkinsonism, such as multiple systems atrophy, suggest little or no benefit of surgery for these patients.⁵⁻⁷ Thus, the certainty of the diag-

nosis of idiopathic Parkinson's disease is important. Observations of the potential for negative neuropsychological sequelae of surgery have highlighted the importance of identifying cognitive impairment in surgical candidates, and counseling those with significant impairment against the procedure.

Dystonia. Dystonia is a heterogeneous disorder, classified roughly according to etiology, insofar as this is known. It consists of primary dystonias, secondary dystonias, heredodegenerative dystonias, and "dystonia-plus" syndromes. It can also be described as focal, segmental, or generalized. As a symptom, it consists of simultaneous, sustained contraction of agonist and antagonist muscles, resulting in a fixed, abnormal, and often painful postures. Surgical experience with DBS for many different forms of dystonia has grown significantly over the last 5 years, and the Food and Drug Administration (FDA) granted DBS therapy a "Humanitarian Device Exemption" status in 2003 for implantation of the Globus Pallidus Interna or Subthalamic Nucleus for the whole spectrum of disorders characterized as dystonia. This designation has led to improvement in third party payer reimbursement for the procedure, making it an increasingly accessible option for patients. As this surgical experience grows, recommendations are likely to evolve regarding patient selection criteria, ideal surgical target, and efficacy.

As with all other surgical therapies, medical therapies and alternatives should be thoroughly explored before undertaking the potentially irreversible risks of surgery. For dystonia, the anticholinergic drug trihexyphenidyl and oral or intrathecal baclofen are typically employed prior to consideration of surgery. Medical therapy may be deemed ineffective due to lack of efficacy, or due to

side effects. If the most disabling dystonic symptoms are quite focal, then intramuscular injections of botulinum toxin can be an effective treatment. Care should be taken when labeling symptoms refractory to botulinum toxin, as reasons for lack of efficacy can include technical factors, and the procedure is ideally performed with electromyographic recording. Another reason for lack of efficacy may be the development of neutralizing antibodies to specific serotypes of the toxin, and the use of alternative serotypes can sometimes restore benefit.

Consideration of surgery should be offered to patients with disabling dystonic symptoms that are not effectively treated with the above measures. DBS of the GPi target has been employed for a variety of dystonias, and this has shown dramatic results in the treatment of primary generalized dystonias, especially when the patient harbors the DYT-1 genetic mutation.⁸ The results of GPi DBS in the case of secondary dystonias, including adult-onset cervical dystonias, are more mixed, though some patients do make impressive gains with this surgery.⁹ Selective denervation or rhizotomy of the spinal accessory nerve is another procedure sometimes employed in the treatment of cervical dystonias. The irreversible nature of any resultant weakness, the tendency of symptoms to progress through this treatment, and the frequency of bilateral involvement of the disorder make denervation a less attractive option than DBS in many cases.

Surgery for Non-Essential Tremor.

Increasingly, DBS is being applied to the treatment of tremor disorders other than Parkinson's disease and ET. The tremor associated with multiple sclerosis (MS) can produce severe disability, and can be difficult

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Table 2. Selection Criteria for Deep Brain Stimulation (DBS) surgery at the University of Colorado

<u>CRITERION</u>	<u>RATIONALE</u>
Clear diagnosis of Idiopathic Parkinson's disease	Patients with atypical parkinsonism or "parkinson's plus" syndromes do not respond to DBS. If there are features in the history and physical that are suggestive of atypical parkinsonism (such as very rapid progression of symptoms, autonomic failure or postural instability as early features of the disease, signs of cerebellar or pyramidal dysfunction) or an MRI suggesting an atypical syndrome, surgery is contraindicated.
Clear evidence of motor improvement with levodopa (Sinemet), with good motor function in the best on-medication state	A good screening test is the Unified Parkinson's disease Rating Scale (UPDRS) part III, performed in 12 hours off of medication and repeated following a supratherapeutic sinemet dose. An improvement of 30% or more in this score with sinemet is desirable. The patient should be ambulatory in the best on state without much assistance. In general surgery makes the "off" states more like the "on" states but rarely does better than the best "on" state, so a patient with poor function in best "on" state (for example, nonambulatory in best "on") is a poor surgical candidate. Patients who fluctuate between good motor function while "on" and poor motor function while "off" are usually good surgical candidates.
Degree of disability	DBS is a poor procedure to rescue someone with end stage PD, although these can be the most desperate patients. It is also not appropriate for early PD when the symptoms are very well controlled on medical therapy. Patients should have an off-medication UPDRS-III score of > 25. The best time to intervene surgically is when the patient is just beginning to lose the ability to perform activities meaningful to him/her, in spite of optimal medical therapy. In a patient who is still working, the time to intervene is before the patient is forced to retire on disability.
Lack of comorbidity	Serious cardiac disease, uncontrolled hypertension, or any major other chronic systemic illness increases the risk and decreases the benefit of surgery.
Realistic expectations	People who expect a sudden miracle are disappointed with the results, and become frustrated with the complexity of the therapy.
Screening MRI of the brain	This should be free of severe vascular disease, atrophy that is out of proportion to age, or signs of atypical parkinsonism.
Intact cognitive function	A good screening test is the mini-mental status test. A score of >26 is ideal, < 24 an absolute contraindication. Patients with cognitive dysfunction have difficulty tolerating awake surgery, may have permanent worsening of cognitive function postoperatively, deal poorly with the intrinsic complexity of DBS therapy, and realize little overall functional gain even if motor performance is improved. Formal neuropsychological testing is often obtained as part of the preoperative evaluation process.
Patient Age	The benefits of DBS for PD decline with advancing age, and the risks go up. Patients over 75 are informed that their benefits are likely to be modest, though "physiological age," and disease status described above are perhaps more significant considerations.
Ability to remain calm and cooperative	The patient remains awake during neurosurgery lasting about 2-3 hours per side of brain. Patient cooperation and feedback during surgery contributes to technical success. A helpful "screening test" for this is how well the patient tolerates an MRI scan.

to treat medically. A reasonable set of criteria for considering surgery are the presence of a severely disabling tremor, clinically stable or worsening for at least 6 months despite optimal medical treatment, with lack of significant weakness, sensory impairment, dysarthria, swallowing difficulties, severe cognitive impairment, or significant cerebral atrophy on MRI. A review of 75 previously published cases of DBS for the treatment of MS tremor revealed that surgery resulted in tremor reduction and improvement in some measure of daily functioning respectively in 87.7 percent and 76.0 percent of patients.¹⁰ As with many studies of tremor, standardized, qualitative outcomes measures were not used in most of these reports, and few reports involved follow-up beyond 1 year. The majority of these patients were treated with stimulators implanted in the Vim nucleus of the thalamus, as for essential tremor, and it appears that distal limb tremor is more easily treated than either proximal limb tremors or axial tremors.

A disabling tremor can result from lesions of the dentato-rubro-thalamic pathway (so-called “cerebellar outflow tremor”), particularly in the vicinity of the red nucleus. The term “rubral tremor”, also called Holmes’ tremor, refers to a 2 Hz to 5 Hz rest, postural, and kinetic tremor, usually of an upper extremity in the presence of such a lesion. In a handful of reported cases, unilateral Vim thalamotomy or Vim DBS has provided effective control of tremor.¹¹⁻¹³ Two case reports detail the efficacy of Vim DBS in controlling the distal component of the postural and kinetic tremor, with control of the axial and proximal appendicular components achieved with the addition of a lesion in the GPi in one case,¹⁴ and control of the resting component of the tremor with a stimulator implanted into the STN contrala-

teral to the tremulous extremity in another.⁵

Conclusion. The surgical treatment of movement disorders has advanced significantly over the last decade. Many patients whose symptoms have not been well controlled medically now have surgical options, as in the cases of several non-essential tremor conditions and dystonias. With increasing collective experience, it is becoming clearer which subsets of these patients are likely to derive benefit from surgery and which are not. When dealing with relatively rare conditions, or with diagnostic categories that encompass a heterogeneous group of patients, it is less likely that data from large, prospective, randomized trials will be available or that reasonable inferences can be made in applying such results to individual patients. In some instances, anecdotal and case reports constitute the only available support for the application of DBS to treat a patient whose disabling symptoms do not respond to medical therapy. Third party payers may draw their own conclusions in regard to the level at which efficacy must be demonstrated in order to justify treatment, potentially limiting patients’ access to this therapy. Careful study and reporting of the results of treatments of these unusual conditions, as well as regular reviews of the state of the art are therefore critical to the development of surgical selection criteria and the rational application of these techniques as treatments.

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