Surgical treatments for Parkinson's disease

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abstract

OBJECTIVE This article reviews surgical treatments for Parkinson's disease, emphasizing aspects pertinent to family physicians: rationale for and description of surgeries, patient selection issues, and outcome expectations.

QUALITY OF EVIDENCE No published series describes long-term follow up of a randomized controlled study of any surgery for Parkinson's disease. Some reports, however, describe thorough but brief follow up of functioning in small numbers of patients following surgery. MEDLINE articles were identified using Parkinson's disease, surgery, pallidotomy, thalamotomy, stimulation, grafting, and transplantation as search words. Articles chosen for this paper described patients with systematic follow up using accepted validated rating scales.

MAIN MESSAGE Reported series show impressive improvements in patients undergoing lesioning, stimulation, and grafting surgery for Parkinson's disease. These patients are typically severely disabled but highly selected, and follow up is brief. Stereotactic lesioning (pallidotomy and thalamotomy), deep brain stimulation (thalamic, and elsewhere) and grafting (striatal) can be performed safely, but results vary greatly among centres.

CONCLUSIONS Certain Parkinson's disease patients might benefit from surgery. Ideal candidates for pallidotomy experience motor fluctuations with disabling levodopa-induced dyskinesias. Tremors resistant to antiparkinsonian medications sometimes respond to thalamotomy or thalamic stimulation. Other parkinsonian syndromes, dementias, and difficulties with gait and balance respond poorly to unilateral pallidotomy. Bilateral deep brain stimulation procedures could benefit "midline" dysfunction.

résumé

OBJECTIF Cet article passe en revue les thérapies chirurgicales pour la maladie de Parkinson, mettant en évidence les éléments pertinents aux médecins de famille: la justification et la description des interventions chirurgicales, les questions entourant la sélection des patients et les attentes quant à l'issue du traitement.

QUALITÉ DES DONNÉES Aucune série publiée ne décrit le suivi à long terme d'une étude aléatoire contrôlée des interventions chirurgicales pour la maladie de Parkinson. Par contre, certains rapports décrivent un suivi approfondi mais bref du fonctionnement chez un petit nombre de patients après la chirurgie. Les articles de MEDLINE ont été recensés à l'aide des mots «maladie de Parkinson», «chirurgie», «pallidotomie», «thalamotomie», «stimulation», «greffe» et «transplantation». Les articles sélectionnés pour la présente étude décrivaient le suivi systématique à l'aide de barèmes de cotes validés acceptables.

PRINCIPAL MESSAGE Les séries rapportées signalaient des améliorations impressionnantes chez les patients ayant subi des interventions chirurgicales ablatives, des stimulations et des greffes pour la maladie de Parkinson. Typiquement, ces patients sont gravement handicapés mais sélectionnés avec rigueur et la durée du suivi est brève. La création stéréotaxique d'une lésion (pallidotomie et thalamotomie), la stimulation profonde du cerveau (au niveau du thalamus et ailleurs) et les greffes (striatales) peuvent être exécutées en toute sécurité, mais les résultats varient grandement selon les centres.

CONCLUSIONS Certains patients souffrant de la maladie de Parkinson pourraient bénéficier d'une intervention chirurgicale. Les candidats idéaux pour la pallidotomie éprouvent des fluctuations motrices accompagnées de dyskinésie invalidante causée par la lévodopa. Les tremblements résistants aux médications contre le Parkinson réagissent parfois à la stimulation thalamique ou à la thalamotomie. D'autres syndromes du Parkinson, les démences et les problèmes de démarche et d'équilibre réagissent faiblement à la pallidotomie unilatérale. Les interventions de stimulation bilatérale profonde du cerveau pourraient être bénéfiques pour les dysfonctions «médianes».

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Lay literature and mass media descriptions of surgery for Parkinson's disease often give patients and their families the impression that today's surgeries offer miraculous results to all patients undergoing procedures. Few presentations address the more mundane issues of patient selection for, risks associated with, and reasonable outcome expectations from surgery.

Understandably, family physicians will often be faced with patients and families who have seen television programs or other media presentations and who wish to learn more about surgery (or be "booked for surgery" later in the week). This article reviews surgery for Parkinson's disease with an emphasis on aspects pertinent for family physicians: rationale for and description of surgeries, patient selection issues, and outcome expectations.

Quality of evidence

No published articles report randomized controlled trials of any surgery for Parkinson's disease. Because Parkinson's disease is a progressive disorder, serial evaluations of outcomes over an extended period would be crucial in determining the relative utility of treatments. No reported studies, however, document outcome in surgically versus non-surgically treated Parkinson's disease or systematic follow up of a large series for more than 3 years. Consequently, evidence is mainly based on thorough, but relatively brief, follow up of small numbers of patients undergoing surgery. Yet the magnitude of improvement in certain patients, who had usually been quite seriously disabled, is of such degree that there seems little doubt that surgery can be beneficial for selected individuals. The longevity of benefit remains to be established.

Articles were identified through a MEDLINE search using Parkinson's disease, surgery, pallidotomy, thalamotomy, stimulation, grafting, and transplantation as search words. Articles chosen for this paper reported on patients who had systematic follow up using accepted validated rating scales.

Rationale for surgery

Basal ganglia neuroanatomic connections have been studied extensively in non-human primates, and various animal models of parkinsonism have been developed. These models have consistently led to findings of neurophysiologic overactivity and underactivity, relative to neuronal electrical activity, within certain basal ganglia nuclear regions interacting with motor circuits from frontal lobe and thalamic structures. For example, neuronal activity within the medial portion of the globus pallidus (also known as the internal segment of the globus pallidum, or Gpi) and the subthalamic nucleus (STN) has been shown to be neurophysiologically higher than normal. In contrast, regions of the thalamus (ventral anterior and lateral nuclei) receiving inhibitory output from the Gpi are excessively inhibited and therefore become relatively hypoactive. Consequently, thalamic excitatory output to motor nuclei in the cerebral cortex is relatively meagre and results in a predominantly akinetic-rigid or parkinsonian state.

While such models do not explain all aspects of parkinsonism, the same electrophysiologic findings have been found in humans with Parkinson's disease (by microelectrode recordings from these nuclear sites obtained during brain surgery). By reducing levels of hyperactivity in certain basal ganglia nuclei, the balance in the striato-thalamocortical pathways seems to be at least partially restored, as judged by improvement in motor functioning in animals and humans with Parkinson's disease.

Other means of influencing these circuits include attempts to rejuvenate or create anew the brain regions ravaged by neurodegeneration in Parkinson's disease (eg, the ventrolateral tier of the substantia nigral dopaminergic neurons that normally project to the caudate nucleus or putamen, collectively known as the striatum).[1]

Types of surgery

There are essentially three types of surgery currently available for Parkinson's disease: lesioning (irreversible destruction of hyperactive neurons), stimulation (reversible "stunning" of hyperactive neurons), and grafting (transplantation of neurons, cells, or trophic factors). Two forms of treatment, lesioning and stimulation, reduce function within specific target regions of the brain.

The rationale for these surgeries is that some regions of the extrapyramidal pathways become disinhibited as a result of neurodegeneration elsewhere in the brain. Consequently, such areas as the Gpi and STN demonstrate excessive neuronal activity in Parkinson's disease. By minimizing this overactivity, through permanent destruction (with lesioning) or temporarily disabling neurons with electrical "jamming" (by stimulation), control of movement through these extrapyramidal pathways improves. Stimulation with small amounts of electrical current can be carried out for many years without apparent damage to neurons.

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Grafting seeks to supplement function by providing a source of neurotransmitters and the neural scaffolding to deliver the neurotransmitters. Transplantation can be performed with tissue blocks or with cell suspensions. "Transplantation" of neurotrophic factors is also under study.

At the moment, surgery for Parkinson's disease focuses on several brain targets (**Table 1**). These targets are selected on the basis of patients' symptoms.

Each of the surgeries employs stereotactic technology. To begin the procedure, a frame is attached to the patient's head while the patient is under local anesthetic. The patient is then studied with magnetic resonance imaging or computed tomography allowing imaging of the brain target in conjunction with the stereotactic headframe. Embedded within the frame are fiducial markings that can be seen during imaging and serve as points of reference. Computerized software uses these markings to plot the trajectory of the surgical track with reference to the headframe. Some institutions are able to simulate the surgery with computerized software, showing the anatomic track to be certain that safety is maximized. After the surgery has been planned, the patient is placed on the operating table and the headframe attached to the table. Local anesthetic is used before a 5-cm incision is made for placement of a burr hole through the skull.

Some institutions employ electrophysiologic equipment to confirm radiologic targeting; some neurosurgeons create lesions or place stimulation leads merely on the basis of radiologic targeting. Stereotactic equipment allows for a microelectrode to be lowered through the burr hole and along the planned track. When the tip of the electrode has reached the anatomic target (thalamus, pallidum, or STN), characteristic electrophysiologic recordings can be made through the microelectrode using amplification equipment.

Once electrophysiologic recordings are completed and the appropriate target delineated, a lesioning electrode (in the case of pallidotomy or thalamotomy) is placed at the target. By heating the tip of the radiofrequency lesioning electrode to approximately 70°C for 1 minute, a small lesion (of several millimetres' diameter) is produced. Further lesions can be placed on the basis of immediate clinical response (ie, tremor resolution, reduction in rigidity). In the case of stimulation operations, a deep brain stimulation lead tip is brought to the target and a hand-held stimulator is connected to the other end of the lead. Electrical stimulation can then be carried out; the lead location is further adjusted according to the clinical results obtained.

Table 1. Brain targets for surgery in Parkinson's disease

ANATOMIC TARGET	TYPE OF PROCEDURE	COMMENTS
Thalamus (ventral intermediate nucleus)	Lesioning, stimulation	Improves tremor on contralateral side of body; lesioning is relatively contraindicated bilaterally; paresthesias can occur with stimulation
Medial pallidum (internal globus pallidus)	Lesioning, stimulation	Improves tremor, rigidity, bradykinesia, and levodopa-induced dyskinesia; offers little benefit for instability
Subthalamic nucleus	Stimulation	Can improve all cardinal features of parkinsonism; reduces levodopa requirement
Striatum (caudate and putamen)	Grafting or transplantation	Can improve rigidity, bradykinesia, and tremor; different grafts under study: fetal (human, porcine), adrenal medulla, and peripheral nerve

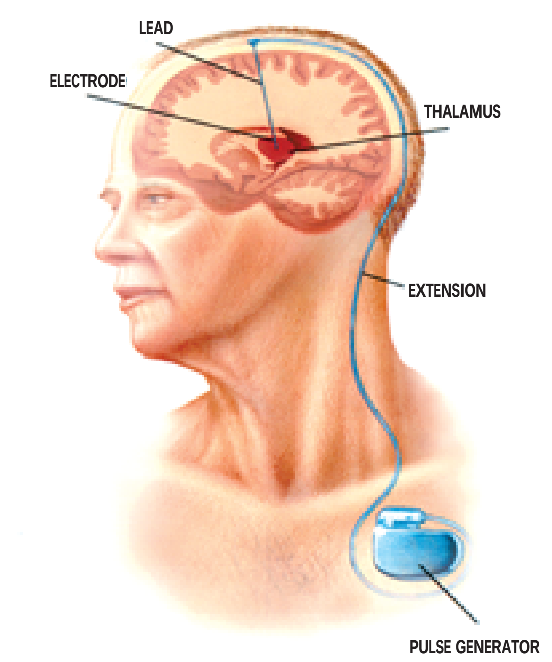
With lesioning operations, surgery concludes when the final lesion is placed and the burr hole is sutured over. With deep brain stimulation procedures, the deep brain stimulation lead is secured in place by attaching a "button" over the burr hole. The end of the brain lead is connected to an extension lead. The patient is placed under general anesthesia for subcutaneous tunneling of the extension lead along the scalp and neck and out to the subclavian site (**Figure 1**). The pulse generator is placed in the subclavian site (as with a cardiac pacemaker) and the extension lead connected.

Most patients spend the night in hospital and are dismissed the day after surgery. Patients with deep brain stimulators will require follow up for programming the device (typically at 1 day, 1 week, and 1 month after surgery).

Patient selection

Pharmacologic therapy for Parkinson's disease has advanced greatly over the past three decades. Within the past 10 years, surgical treatment for Parkinson's disease has become available. Surgery offers potential benefits for selected patients experiencing disability despite optimal medical management. Several centres in Canada have reported their experience with such surgery, including university centres in Vancouver, BC, and Toronto, Ont. The number of

Figure 1. Deep brain stimulation: *Thalamic deep brain stimulation apparatus*



patients who could benefit from this surgery over the course of illness is considerable, and the possible 5000 to 10 000 surgical candidates in Canada would quickly overwhelm existing resources.

Once it is established that a patient has received optimal medical therapy but continues to have severe disability, he or she should be considered for surgery.

Determining factors for considering surgery for Parkinson's disease are few but complicated. The initial determination is whether patients have actually received and failed to benefit from optimal medical management. Because of the inherent risk of brain surgery, patients need to have exhausted optimal medical therapy. For Parkinson's disease patients in typical family practices this includes treatment with levodopa (or carbidopa and levodopa) and use of at least one dopamine agonist.

Unfortunately, many patients on surgical evaluation waiting lists have never had adequate trials with dopamine agonists in conjunction with appropriate levodopa regimens. These medications need to be optimally regulated (which is outside the scope of this article) to assure that surgery is required. Patients who fail to respond beneficially in some way to levodopa could actually not have Parkinson's disease but some other parkinsonian syndrome. Patients with parkinsonian syndromes other than Parkinson's disease are unlikely to benefit from and can worsen with surgery. **Table 2** reviews criteria for considering surgery for Parkinson's disease patients.[2-6]

Surgery selection

The ideal surgery for Parkinson's disease patients who are experiencing disability does not always exist. Patients with dementia and severe instability typically do not benefit from any surgical procedure, and surgery could even be counterproductive. The best surgery can be determined by considering a patient's primary problem. **Table 3** outlines common parkinsonian problems and the appropriate procedure. This arena is dynamic, and recommendations might change, depending upon future technologic advances and publication of outcome studies.

Outcome expectations

Many patients and their families have seen short television segments portraying fantastic results following surgery for Parkinson's disease. They understandably approach their physicians with unreasonably high expectations regarding surgical outcome. It is important to remind patients that these well publicized cases typically represent those very few instances in which the patient is highly selected and the surgery highly successful. Patients should consider whether they would accept more modest benefit, given the potential for side effects, before committing to any surgical procedure.

Benefit

Nearly all (90%) patients with thalamotomy or thalamic stimulation for unilateral limb tremor can expect improvement (complete or near resolution of tremor).[7] Resting and postural tremor is most likely to be ablated; kinetic action tremor is somewhat less likely. Midline tremor involving the head and neck and voice might improve with a unilateral procedure, but is typically most influenced by bilateral surgeries. Tremor reduction maintained 3 months after surgery is usually sustained over years (>10 years). Follow up with thalamic stimulation has shown ongoing benefit for as long as 8 years.

The cardinal signs of bradykinesia and rigidity predictably improve following pallidotomy (approximately 90%) but are not affected by thalamotomy or thalamic stimulation. The magnitude of benefit on average is about a 30% reduction in the severity of bradykinesia and rigidity, as judged by standard clinical rating scales. Most new antiparkinsonian medications would not afford this degree of change (usually about 15% to 20%). Levodopa therapy produces about a 30% reduction in the severity of parkinsonism in

Table 2. Patient selection for surgical treatment for Parkinson's disease[2-6]

INCLUSION CRITERIA
Disabled: despite optimization with levodopa (or carbidopa and levodopa) and a dopamine agonist (bromocriptine, pergolide, pramipexole, or ropiniprole)
Levodopa-responsive
EXCLUSION CRITERIA
Parkinsonism but *not* Parkinson's disease (eg, progressive supranuclear palsy, multiple system atrophy)
Substantial dementia
RELATIVE CONTRAINDICATION
Patient requires anticoagulation

Table 3. Surgery selection by primary problem

PRIMARY PROBLEM	TYPE OF SURGERY
Severe tremor: unilateral	Thalamotomy Thalamic stimulation
Severe tremor: bilateral	Bilateral thalamic stimulation Thalamotomy and thalamic stimulation Bilateral subthalamic stimulation
Severe bradykinesia, rigidity: unilateral	Pallidotomy
Levodopa-induced dyskinesia	Pallidotomy
Prominent motor fluctuations	Pallidotomy
Severe bradykinesia, rigidity: bilateral	Bilateral subthalamic stimulation Bilateral pallidal stimulation Bilateral pallidotomy
Younger patients with severe bradykinesia, rigidity: bilateral	Bilateral transplantation
Falling, postural instability, unintelligible speech	?None

patients undergoing surgery. The benefit from levodopa following surgery continues to be on the same order of magnitude, ie, levodopa is no less effective following surgery (and often no longer causes dyskinesia, a common side effect before surgery).

As a general rule, about one third of patients experience excellent or phenomenal improvement, one third moderate, and one third modest benefit following pallidotomy. If patients are carefully selected, a higher percentage will experience excellent outcome. Patients who are falling before pallidotomy will likely continue to fall afterward, as the surgery does little to change postural instability.

Benefit following pallidotomy appears to last for at least 3 years. Advancing signs of parkinsonism continue on the non-operated side of the brain, however, and patients' overall improvement, therefore, is not always maintained. Longer follow-up studies have not been reported.

Adverse events

Severe adverse events (hemorrhage causing stroke and death) typically occur at the time of surgery or immediately afterward. Patients with pallidotomy occasionally have small hemorrhages in the internal capsule months after surgery. Most series report a risk of approximately 2% for serious adverse events with these stereotactic procedures. The risk is far higher (up to 30%), however, in some reported series. Consequently, it is important to inquire about an institution's track record. Bilateral thalamotomy or pallidotomy produces dysarthria or dysphonia in up to 20% of patients.

Postoperative confusion, drowsiness, and headaches are relatively common but typically short-lived. Patients occasionally experience a visual field cut (usually a quadrantic hemianopsia) following pallidotomy, but this is rare with microelectrode-guided procedures. Rarely, patients will have postoperative seizures. These are usually isolated and typically do not require long-term use of anticonvulsants. Mild cognitive dysfunction is sometimes more apparent following surgery, but most centres have documented only trivial changes with neuropsychologic testing. Changes in neuropsychologic functioning are most common in patients older than 65 years at the time of surgery who have an operation involving the language-dominant hemisphere. Changes typically include declines in expressive vocabulary, letter and semantic fluency, and novel problem solving. For the most part, these changes do not affect patients seriously in their everyday activities.

Time course and follow up

Lesioning and stimulation procedures typically produce clinical benefit immediately. Grafting procedures usually require a year or more before improvements are clinically measurable. Patients undergoing stimulation procedures could observe "otomy" effects. For example, patients with thalamic stimulation can experience a "mini-thalamotomy" effect with resolution of tremor even when the pulse generator providing stimulation is "off." Such "otomy" effects are typically short-lived; therefore, ongoing adjustment of stimulation parameters is required.

Most institutions adjust pulse generators in stimulation patients within the first week, first month, and after 3 months. Further adjustments are often needed but are far less frequently made. For this reason, all patients undergoing stimulation procedures need to commit to regular follow up, particularly in the first year following the procedure. Adjustments are performed with a computer-assisted device, which requires an in-person clinic visit. Pulse generators cannot be tested or adjusted over the telephone (in contrast to some pacemaker pulse generators).

Patients with lesioning and transplantation procedures could require adjustments in their antiparkinsonian medication regimens, but these are usually relatively easily made. It is not unusual for patients to reduce or discontinue medications only to recognize that they still require them. Some patients undergoing pallidotomy take higher doses of levodopa postoperatively, as they are no longer limited by levodopa-induced dyskinesia. Patients with bilateral subthalamic stimulation typically require a reduction in their antiparkinsonian medications, as these can still produce dyskinesia following the procedure.

Conclusion

Surgery for Parkinson's disease can be effective in reducing disability. Proper selection of patients and targeted surgery increases the likelihood of significant benefit. Current neurosurgical techniques have increased the chances of success to approximately 90%, although the degree of benefit can vary. Most institutions with experienced stereotactic neurosurgeons report low morbidity and mortality, making surgical treatment feasible for many Parkinson's disease patients.

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Key points

- Surgery for Parkinson's disease is a new treatment that has shown considerable efficacy in certain patients.
- Three techniques are used: lesioning (permanent destruction) or stimulating (electrical "jamming") neurons that show excessive activity, and grafting, which transplants new sources of neurotransmitters.
- Operations are performed using stereotactic techniques, which locate the area to be treated precisely using computed tomography, magnetic resonance imaging, and sometimes computer software.
- Eligible patients are those who have failed to benefit from advanced medical management. In Canada access to surgery is quite limited.
- Patients typically experience modest to excellent benefit in reduction of tremor, bradykinesia, and rigidity, and effects have lasted as long as 10 years.

Points de repère

- Les interventions chirurgicales pour la maladie de Parkinson sont un nouveau traitement qui s'est révélé d'une efficacité considérable chez certains patients.
- On a recours à trois techniques: la chirurgie ablative (destruction permanente) ou la stimulation (blocage électrique) des neurones qui manifestent une activité excessive et les greffes visant à transplanter de nouvelles sources de neurotransmetteurs.
- Les interventions sont exécutées à l'aide de techniques stéréotaxiques, qui localisent avec précision les zones à traiter au moyen de la tomographie assistée par ordinateur, de l'imagerie par résonance magnétique et parfois de logiciels informatiques.
- Les patients admissibles sont ceux chez qui la prise en charge médicale avancée ne s'est pas révélée bénéfique. Au Canada, l'accès à ces interventions chirurgicales est plutôt limité.
- Typiquement, les patients bénéficient d'améliorations allant de modestes à excellentes dans la réduction des tremblements, de la bradykinésie et de la rigidité et les effets ont duré jusqu'à dix ans.

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