

## ● REVIEW

# Current surgical treatments for Parkinson's disease and potential therapeutic targets

Darrin J. Lee\*, Robert F. Dallapiazza, Philippe De Vloo, Andres M. Lozano

Division of Neurosurgery, Toronto Western Hospital, Department of Surgery, University of Toronto, Toronto, Canada

## Abstract

Currently, the most common surgical treatment for Parkinson's disease is deep brain stimulation (DBS). This treatment strategy is typically reserved for bradykinesia, rigidity and tremor in patients who no longer respond to medication in a predictable manner or who suffer medication-induced dyskinesias. In addition to DBS, ablative procedures like radiofrequency, radiosurgery and focused ultrasound are also utilized for select tremor symptoms. In this review, we discuss evolving surgical techniques, targets, and emerging technology. In addition, we evaluate potential paradigm shifts in treatment, including gene therapy, immunotherapy and cell transplantation. While these new techniques and treatment options are still in their infancy, advances in Parkinson's disease treatment are rapidly expanding.

**Key Words:** Parkinson's disease; deep brain stimulation; pallidotomy; thalamotomy; focused ultrasound; gene therapy; immunotherapy; cell transplantation

## \*Correspondence to:

Darrin J. Lee, M.D., Ph.D.,  
darrin.lee@uhnresearch.ca.

## orcid:

0000-0002-0798-8731  
(Darrin J. Lee)

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## Introduction

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder that affects the motor system and has variable non-motor components including cognitive and autonomic changes in the later stages of the disease. PD is characterized by altered activity within the basal ganglia and is typified by profound degeneration of dopaminergic neurons within the substantia nigra pars compacta. Medications to replace or prevent degradation of dopamine (*i.e.*, levodopa, catechol-O-methyl transferase inhibitors, dopamine agonists, monoamine oxidase inhibitors) have had a dramatic impact on the lives of PD patients. Surgical treatments involving lesioning the basal ganglia also have a long history. Despite the initial decline in surgery following the discovery and clinical introduction of levodopa in 1961, surgery has become a standard adjunct to medical treatment. Since the late 1940's, there have been over 12,000 articles published on the surgical management of Parkinson's disease (Lozano et al., 2018).

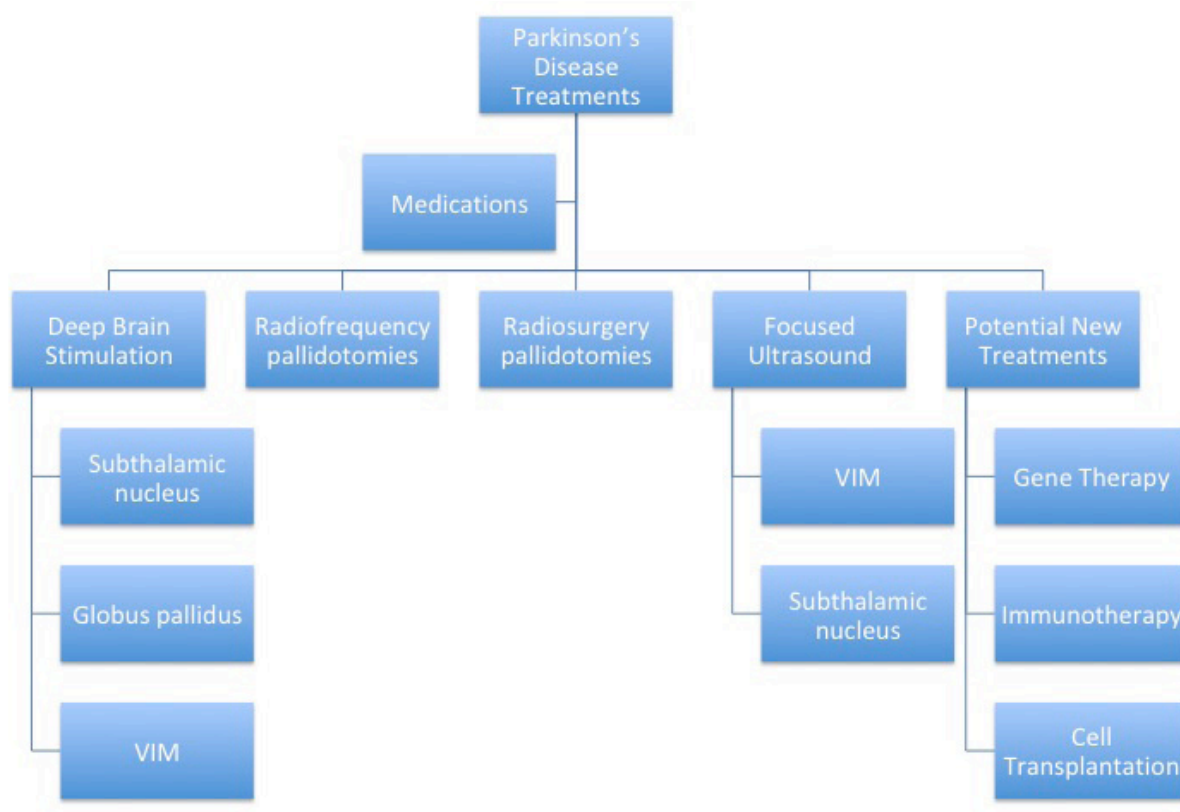
The first published surgical treatments for PD occurred in the early 1950s, and involved lesioning regions of the basal ganglia (pallidotomy and thalamotomy) (Narabayashi and Okuma, 1953; Hassler and Riechert, 1954; Cooper, 1955). However, it was not until 1980 that Brice and McLellan utilized chronic electrical stimulation of the midbrain and basal ganglia to suppress intention tremor (Brice and McLellan, 1980). Since deep brain stimulation (DBS) is reversible, adjustable, and has a more favorable safety profile it

has become the predominant surgical procedure for PD over pallidotomies and thalamotomies. While current treatments are effective at treating disabling motor symptoms, there currently are no treatments that alter the underlying disease pathophysiology. Here, we discuss the current management and recent surgical advances as well as potential paradigm shifts in treatment.

## Current Surgical Treatments

DBS is the most common surgical procedure to ameliorate motor symptoms of PD. Moreover, it reduces the occurrence of "off" episodes that usually occur throughout the day in more advanced stages of medically treated PD. However, DBS has variable effects on other motor symptoms, such as postural and gait disturbances or non-motor symptoms (cognitive decline, sleep, swallowing, speech or micturition disturbances). The two most common targets for DBS are the subthalamic nucleus (STN) and the globus pallidus pars interna (GPi). Large, randomized, controlled studies have demonstrated similar motor benefits between these two targets; however, after STN DBS, dopamine replacement medications can generally be reduced, while GPi DBS results in fewer cognitive and mood side effects (Follett et al., 2010). There is some evidence that targeting the pedunculo-pontine nucleus may improve gait instability and freezing (Stefani et al., 2007; Thevathasan et al., 2011).

Radiofrequency and radiosurgery pallidotomies were initially used to treat tremor symptoms alone.



**Figure 1** Current and potential surgical treatments for Parkinson's disease. VIM: Nucleus ventero-intermedius.

These types of lesional procedures have been used to some extent in PD patients who decline or are poor candidates for DBS. More recently, there has been increased interest in the use of focused ultrasound (FUS) thalamotomies for tremor as it does not require a craniotomy and physical brain penetration. Successful FUS thalamotomy for essential tremor has led investigators to treat highly selected tremor-dominant PD patients with FUS thalamotomy when the tremor is disabling (Bond et al., 2017) and FUS subthalamotomy when there is an asymmetric disease presentation (Martínez-Fernández et al., 2018). While being a therapy that does not require an implanted device and successive operations for battery changes, lesional procedures are not reversible and thus are primarily performed unilaterally, limiting its effectiveness in a bilateral disease process.

### Recent Advances

Since the first DBS surgeries, there have been many advances in technology used for surgical PD management. The internal pulse generators (IPGs) used to

charge the stimulation have become more efficient, and now have the potential to be recharged transcutaneously, limiting the number of surgeries the patient has to undergo for IPG changes. Newer versions of the DBS components are MRI compatible, which gives the patients and their physicians more flexibility in diagnosing and treating PD as well as other conditions. The electrode leads have also become more complex, allowing for directional current compared to radial current spread. Furthermore, multiple different stimulation paradigms can be programmed simultaneously, allowing for more flexibility, complexity and specificity of stimulation. These advances in lead and IPG technology allow for more complex and patient-specific programming.

DBS for PD utilizes continuous high frequency stimulation to the basal ganglia. While the mechanism of DBS is not entirely understood, it is clear that DBS interferes with both pathological and physiological neural circuitry. Newer IPGs can record and store local field potential data while simultaneously multiple targets, which can enable physicians and

researchers to better understand the pathophysiology of the disease and the mechanism by which DBS ameliorates symptoms (Swann et al., 2018). Current DBS utilizes an “open-loop” (continuous stimulation) paradigm; however, its benefits can often be limited by side effects and/or partial efficacy. Moreover, patients do not suffer from the same exact motor symptoms continuously throughout the day. These potential limitations may result from the fact that DBS disrupts not only pathologic neural oscillations and connectivity, but also disrupts normal physiology. One conceivable treatment option could be to identify aberrant local field potential biomarkers in real-time and utilize an adaptive or “closed loop” form of stimulation to disrupt or modify that specific electrophysiology (Rosin et al., 2011).

Imaging the specific DBS targets and basal ganglia circuitry has also become more sophisticated. Magnetic resonance imaging continues to increase in resolution, which improves targeting of specific regions of the intended structure (STN, GPi). With advances in tractography, it is also possible to be able to target output and input circuitry as opposed to only the nodes within the basal ganglia. Studies suggest that not only is diffusion tensor imaging feasible for surgical planning of movement disorders, psychiatric disorders and pain DBS, but it may also improve surgical outcome (See and King, 2017). Furthermore, advances in imaging techniques, such as functional MRI and magnetoencephalography, provide tools to better understand connectivity between various regions of the brain as well as brain activity associated with electrical stimulation. This information potentially could help in determining better functional and anatomic targets for DBS.

One of the principle concerns with DBS is its invasive nature. A recent study by Grossman et al suggested that non-invasive DBS might be possible by offsetting non-physiologic high frequency stimulation (*i.e.*, 2.00 kHz and 2.01 kHz) to produce low frequency stimulation at a subcortical location (Grossman et al., 2017). In this rodent study, they were able to steer and target oscillatory activity within the hippocampus, but did not affect the pathway from the source of stimulation to the target, similar to the concept of using multiple sources to lesioning a specific target in radiosurgery. This approach could reduce the morbidity associated with open surgery (*i.e.*, infections, intracranial hemorrhage, lead migra-

tion/fracture, *etc.*), as well as decrease the need for permanent internalized batteries. Furthermore, this type of technology could theoretically enable noninvasive test stimulation mapping for lesional experiments and potentially be a permanent adaptable and noninvasive treatment option.

### Potential Future Treatments

Current treatments and recent advancements primarily treat the motor symptoms of PD; however, future disease-modifying treatments are necessary to alter the course of the disease and treat the neurodegenerative and cognitive aspects of the disease. As with any disease process, it is necessary to understand the underlying pathophysiology. In that vein, there have been a number of PD gene therapy clinical trials that focus on improving motor symptoms *via* altering local neurotransmitters or neurotrophic factors in the basal ganglia. While these trials have demonstrated that gene therapy can be safely delivered to the brain and induce specific neuronal protein expression, the clinical results have been less encouraging (Bartus et al., 2014).

There has also been interest in immunotherapy as a potential treatment approach. Animal studies and clinical trials have largely targeted using antibodies against misfolded  $\alpha$ -synuclein, the main constituent of Lewy bodies (George and Brundin, 2015). However, like the gene therapy trials, the studies merely demonstrate safety, but not necessarily efficacy. Consequently, there remain a number of hurdles to translate the promising animal studies into successful clinical trials (*i.e.*, significant placebo response, limited validated biomarkers, differences in rodent versus human biology).

Cell transplantation also offers a hypothetically intriguing treatment option. Ever since it had been shown in 1979 that fetal rat dopamine-containing neurons could be transplanted into a PD rodent model with improved motor function, there has been significant interest in cell transplantation for PD. To date, there have been cell transplantation clinical trials using autologous and nonautologous cells, including the use of human embryonic stem cells and induced pluripotent stem cells. The additional hurdle for cell transplant is the potential ethical considerations that need to be addressed when using stem cells. Unfortunately, like the gene therapy and immunotherapy trials, the results have been equivocal

(Yasuhara et al., 2017).

While there are currently very effective medical and surgical treatments for the motor symptoms of PD, patients continue to suffer from this progressive debilitating disease. Future research is necessary to understand the underlying disease process in order to better treat the disorder as a whole, rather than reducing very specific motor symptoms. While newer techniques, imaging, and medications have been able to suppress certain aspects of this motor disorder; disease-modifying or disease-reversing treatments still remain the ultimate goal (**Figure 1**).

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## References

- Bartus RT, Weinberg MS, Samulski RJ (2014) Parkinson's disease gene therapy: success by design meets failure by efficacy. *Mol Ther* 22:487-497.
- Bond AE, Shah BB, Huss DS, Dallapiazza RF, Warren A, Harrison MB, Sperling SA, Wang XQ, Gwinn R, Witt J, Ro S, Elias WJ (2017) Safety and efficacy of focused ultrasound thalamotomy for patients with medication-refractory, tremor-dominant parkinson disease: a randomized clinical trial. *JAMA Neurol* 74:1412-1418.
- Brice J, McLellan L (1980) Suppression of intention tremor by contingent deep-brain stimulation. *Lancet* 1:1221-1222.
- Cooper IS (1955) Chemopallidectomy: an investigative technique in geriatric parkinsonians. *Science* 121:217-218.
- Follett KA, Weaver FM, Stern M, Hur K, Harris CL, Luo P, Marks WJ Jr, Rothlind J, Sagher O, Moy C, Pahwa R, Burchiel K, Hogarth P, Lai EC, Duda JE, Holloway K, Samii A, Horn S, Bronstein JM, Stoner G, et al. (2010) Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. *N Engl J Med* 362:2077-2091.
- George S, Brundin P (2015) Immunotherapy in Parkinson's disease: micromanaging alpha-synuclein aggregation. *J Parkinsons Dis* 5:413-424.
- Grossman N, Bono D, Dedic N, Kodandaramaiah SB, Rudenko A, Suk HJ, Cassara AM, Neufeld E, Kuster N, Tsai LH, Pascual-Leone A, Boyden ES (2017) Noninvasive deep brain stimulation via temporally interfering electric fields. *Cell* 169:1029-1041.e16.
- Hassler R, Riechert T (1954) Indications and localization of stereotactic brain operations. *Nervenarzt* 25:441-447.
- Lozano CS, Tam J, Lozano AM (2018) The changing landscape of surgery for Parkinson's Disease. *Mov Disord* 33:36-47.
- Martínez-Fernández R, Rodríguez-Rojas R, Del Álamo M, Hernández-Fernández F, Pineda-Pardo JA, Dileone M, Alonso-Frech F, Foffani G, Obeso I, Gasca-Salas C, de Luis-Pastor E, Vela L, Obeso JA (2018) Focused ultrasound subthalamotomy in patients with asymmetric Parkinson's disease: a pilot study. *Lancet Neurol* 17:54-63.
- Narabayashi H, Okuma T (1953) Procaine-oil blocking of the globus pallidus for the treatment of rigidity and tremor of parkinsonism. *Proc Jpn Acad* 29:134-137.
- Rosin B, Slovik M, Mitelman R, Rivlin-Etzion M, Haber SN, Israel Z, Vaadia E, Bergman H (2011) Closed-loop deep brain stimulation is superior in ameliorating parkinsonism. *Neuron* 72:370-384.
- See AAQ, King NKK (2017) Improving surgical outcome using diffusion tensor imaging techniques in deep brain stimulation. *Front Surg* 4:54.
- Stefani A, Lozano AM, Peppe A, Stanzione P, Galati S, Tropepi D, Pierantozzi M, Brusa L, Scarnati E, Mazzone P (2007) Bilateral deep brain stimulation of the pedunculopontine and subthalamic nuclei in severe Parkinson's disease. *Brain* 130:1596-1607.
- Swann NC, de Hemptinne C, Miocinovic S, Qasim S, Ostrem JL, Galifianakis NB, Luciano MS, Wang SS, Ziman N, Taylor R, Starr PA (2018) Chronic multisite brain recordings from a totally implantable bidirectional neural interface: experience in 5 patients with Parkinson's disease. *J Neurosurg* 128:605-616.
- Thevathasan W, Coyne TJ, Hyam JA, Kerr G, Jenkinson N, Aziz TZ, Silburn PA (2011) Pedunculopontine nucleus stimulation improves gait freezing in Parkinson disease. *Neurosurgery* 69:1248-1253; discussion 1254.
- Yasuhara T, Kameda M, Sasaki T, Tajiri N, Date I (2017) Cell therapy for Parkinson's disease. *Cell Transplant* 26:1551-1559.