

Review

The Choice Between Advanced Therapies for Parkinson's Disease Patients: Why, What, and When?

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Abstract. When oral dopaminergic medication falls short in the treatment of Parkinson's disease, patients are left with motor response fluctuations and dyskinesias that may have a large impact on functioning in daily life. They may benefit from one of the currently available advanced treatments, namely deep brain stimulation, continuous levodopa-carbidopa intestinal gel, and continuous subcutaneous apomorphine infusion. The indication, choice between the separate advanced treatments and the timing can be challenging and will be discussed against the background of the progressive nature of the disease, the heterogeneity of disease manifestation and variable patient characteristics.

Keywords: Parkinson's disease, deep brain stimulation, external infusion pumps, parenteral infusions, carbidopa, levodopa drug combination, apomorphine, review literature

INTRODUCTION

The characteristic motor symptoms of Parkinson's disease (PD) are bradykinesia, rigidity, and tremor. These symptoms are due to nigrostriatal degeneration and improve with levodopa and other dopamine replacement therapies (DRT), such as dopamine agonists and selective monoamine-oxidase-B inhibitors (iMAO-B) [1]. Additionally, various non-motor symptoms (NMS) may occur even in the early stages

of the disease, which include daytime sleepiness, pain, urinary dysfunction and psychiatric symptoms such as anxiety [2].

After a few years, the duration of the beneficial motor response to each levodopa dose shortens and patients may notice reemergence of their motor symptoms ("wearing-off") alternating with dyskinesia [3]. These fluctuations arise from the progressive decline in the buffering capacity of dopamine producing neurons, gastroparesis [4], microbiome-related effects [5], and postsynaptic changes [6], among other factors. Strategies to lessen the fluctuations include shortening the intervals between levodopa doses, introducing a long acting dopamine agonist, or adding a medication that

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Table 1
Treatment characteristics of the available advanced therapies

	Deep Brain Stimulation (DBS)	Continuous apomorphine infusion (CAI)	Levodopa-carbidopa intestinal gel (LCIG)
	Administration of electrical pulses into a target area of the brain	Administration of medication through a subcutaneously placed needle	Administration of medication to the duodenum through a PEG tube
Mono- or combination therapy	DBS is combined with oral medication	Apomorphine generally used with oral medications, sometimes as monotherapy	LCIG can be used as monotherapy or with oral medications
Possible side-effects and risks	Infections due to surgery	Subcutaneous nodules and erythema at the insertion site are common; severe local reactions are uncommon	Obstruction, pump malfunction
	Speech problems	Nausea	Nausea
	Delirium	Hypotension	Inflammation around the PEG tube entry site
	Cognitive problems	Ankle edema	Leakage around the opening in the abdominal wall
	Behavioral changes	Somnolence Hallucinations	Displacement of the tube Weight loss Biphasic dyskinesia Constipation
	Technical problems or empty battery leading to re-operation	Dopamine dysregulation syndrome and impulse control disorders	
	Balance and gait problems		
	Brain hemorrhage	Drug-induced hemolytic anemia	Peritonitis
Possible disadvantages	Risks inherent to a neurosurgical procedure	Patient must carry the pump during the day	Patient must carry the pump during the day
	No possibility for test treatment	Every day, placing the subcutaneous needle and connecting the pump, care for the skin at the insertion site	Every day, connecting and disconnecting the pump, cleaning the tube, and care for the skin at the insertion site
	Some systems are not MRI-compatible		An operation is needed for placement of the tube
	Can be problematic for passing of a metal detector	Possible problems/malfunctions of the pump	Possible problems/malfunctions of the pump
	Battery needs to be replaced every 5–9 years in case of a non-rechargeable battery	Loss of efficacy may occur, partly due to skin changes interfering with drug absorption	
Possible advantages	In comparison with CAI and CLI, there are no daily limitations, not having to carry an external pump	No surgery is required Many patients are eligible Possibility of testing the treatment, easily reversible	Many patients are eligible Possibility of testing treatment

reduces levodopa metabolism, such as an iMAO-B or catechol-O-methyltransferase inhibitor [7].

When standard DRT treatment falls short, advanced therapies should be considered. Currently available advanced therapies are deep brain stimulation (DBS), continuous levodopa-carbidopa intestinal gel (LCIG), and continuous subcutaneous apomorphine infusion (CAI) (Table 1). In the following paragraphs, the indications, timing and decision-making process for advanced treatment in PD will be further outlined.

WHY: INDICATIONS FOR ADVANCED THERAPIES

Advanced therapies for PD can reduce the motor fluctuations by either smoothing dopaminergic stimulation through continuous delivery of levodopa (LCIG) [8] or apomorphine (CAI) instead of pulsatile stimulations of receptors, or by improvement of OFF symptoms by influencing the neural networks (DBS) [9]. The advanced treatments are considered when either bothersome motor fluctuations become refrac-

Table 2
Current perspectives on potential symptom improvement and contra-indications for the available advanced therapies

	Deep Brain Stimulation (DBS)		Continuous apomorphine infusion (CAI)		Levodopa-carbidopa intestinal gel (LCIG)	
	Potential symptom improvement	Contra-indication	Potential symptom improvement	Contra-indication	Potential symptom improvement	Contra-indication
Patient characteristic						
Lack of caregiver/nurse support	NA	–	NA	+	NA	+
Older age (>70)	NA	+	NA	–	NA	–
Symptom						
Motor fluctuations	++	–	++	–	++	–
Dyskinesia	++	–	+	–	+	–
Levodopa resistant tremor	++	–	–	–	–	–
Nighttime motor symptoms	+	–	+ [¶]	–	+ [¶]	–
Drug-related hallucinations/delusions	+	–	+/-	+/-	+	–
Slight non-drug related hallucinations	+/-	+/-	+/-	+/-	+/-	+/-
Troublesome non-drug related hallucinations/psychosis	–	++	–	++	–	++
Impulse control disorders	+	+/-	+/-	+	+	+/-
Severe therapy refractive depression	+/-	++	+/-	–	+/-	–
Apathy	–	+	+/-	–	+/-	–
Drug related day time somnolence	+	–	–	+	+/-	+/-
Restless legs	+/-	–	+	–	+	–
Postural instability	+ [‡]	+	+ [‡]	–	+ [‡]	–
Dysarthria	–	+	–	–	–	–
Peripheral neuropathy	–	–	–	–	–	+
Orthostatic hypotension	+/-	–	–	+	+/-	–
Non-motor fluctuations*	+	–	+	–	+	–
Mild cognitive impairment	–	–	–	–	–	–
Dementia	–	++	–	+	–	+/-

NA, not applicable. Potential symptom improvement: ++very likely; +probable; +/- unclear; – probably not; very unlikely. Contra-indication: ++absolute contra-indication; +relative contra-indication; +/- unclear; – no contra-indication. *e.g., anxiety, pain, clouded thinking, apathy; [‡]if levodopa responsive; [¶]continuation of therapy during the night. Adapted from Odin et al. [52] and Antonini et al. [53]. This information is based largely upon clinical experience and expert opinion in the absence of robust published evidence from comparative studies.

tory to changes in oral medications, or standard DRT leads to bothersome symptoms, for example dyskinesia, but also impulse control disorders [10–12]. Although motor symptoms are the main indication for the advanced treatments, NMS may contribute to the indication and selection of one or more of the advanced therapies (Table 2) [13]. The available advanced therapies are symptomatic, none have an impact on the progression of the underlying neurodegenerative process. All three treatments can match and extend the peak levodopa effect or best ON-drug state achieved with standard DRT but not improve upon it. There are two exceptions to this rule of thumb, namely 1. when there is a lack of medication effect due to gastrointestinal absorption problems and 2. medication-resistant tremor where DBS can be efficacious [14, 15]. Greater magnitude of benefits to

advanced therapies are seen in patients with a large difference in disability between OFF and ON periods (i.e., a large levodopa response). In a small proportion of patients, gastric problems limiting absorption of oral pharmacotherapy is the indication for an advanced treatment, here all three therapies can be considered [16].

WHAT: CURRENTLY AVAILABLE ADVANCED THERAPIES

Deep brain stimulation

DBS has been available for 25 years with efficacy established by several large randomized clinical trials, although never against a blinded control group [11, 17]. For DBS, a neurosurgeon places two elec-

trodes with the tip bilaterally in the subthalamic nucleus (STN) or globus pallidus internus (GPi) [18, 19]. The electrodes are connected to an implantable pulse generator placed just below the clavicular bone. Following surgery, the DBS parameters have to be programmed to optimize response, sometimes requiring adjustment in DRT, specifically after STN DBS. Patients treated with DBS still need DRT, although the dosage can be reduced by a mean of 60% after STN DBS [20]. DBS of both GPi and STN significantly reduces daily OFF time. The daily ON time without troublesome dyskinesias similarly increases considerably, either due to a direct antidyskinetic effect (GPi) or indirectly through the reduction in DRT (STN) [20]. Adverse effects include dysarthria, balance problems and there is a small risk of intracerebral hemorrhage. In some patients, re-surgery is required because of implanted device problems. In recent years several developments were introduced, such as rechargeable pulse generators [21], MRI compatible hardware [22], multiple independent current pulse generators (instead of one source for all contacts on the electrode) [23, 24], and constant-current instead of constant-voltage stimulation. The conventional ring-mode electrode has ring-shaped contact points, which emit electrical current to the surrounding tissue omnidirectionally. Newer electrodes with steering capabilities allow a more directional shape of the current field activated by each contact, which can correct small inaccuracies in electrode placement, may lessen or avoid stimulation-induced side-effects and reduce battery drainage [25]. Advances in imaging techniques have made it possible to visualize the DBS target directly permitting electrode implantation under general anesthesia [26].

Levodopa-carbidopa intestinal gel

LCIG provides continuous levodopa delivery bypassing the stomach through an intrajejunal percutaneous tube connected to an externally carried pump. This allows safe titration of levodopa to high doses, even more than 2000 mg/day [27], and leads to more stable levodopa plasma concentrations. LCIG has been shown to substantially reduce OFF time and increase ON time without troublesome dyskinesia [10, 28]. In general, standard DRT is fully replaced by LCIG. The most common complications of LCIG are device- and tubing-related failures, including infection and tube kinking and dislocation [29]. Peritonitis has been reported. Medical complications include weight loss and abdominal pain [30], with a variable

incidence of peripheral neuropathy, in part related to levodopa metabolism [30]. Approximately 15% of LCIG-treated patients develop diphasic dyskinesia, which manifest as leg-predominant ballistic choreiform movements [31]. Higher LCIG doses or adding a dopaminergic medication may improve this complication. Diphasic dyskinesia can become particularly troublesome at night, after pump discontinuation, affecting sleep. Preliminary evidence suggests LCIG infusion over 24 h can improve sleep, nocturnal akinesia [32], and even daytime troublesome dyskinesia [33].

Continuous apomorphine infusion

Apomorphine is a rapid-onset, subcutaneously-administered dopamine agonist with affinity to all dopamine agonist receptor subtypes as well as serotonergic and adrenergic receptors [34, 35]. Despite its name, it does not share pharmacological properties with morphine [36]. When used continuously, via an externally worn mini-pump system, apomorphine markedly reduces daily OFF time and increases daily ON time without troublesome dyskinesia [12]. With CAI, the dosage of the daytime oral levodopa is reduced and in some patients no additional DRT is needed [37]. Nocturnal OFF symptoms can benefit from 24 h use. Adverse effects include skin changes (mostly nodules and erythema), nausea, somnolence, neuropsychiatric issues and there is a small risk of drug-induced immune hemolytic anemia [36]. Following the initial adjustments to the doses of apomorphine and concomitant DRT, patients who tolerate the treatment well often continue on stable doses, in some cases for many years [34, 35]. As a subcutaneous delivery system, this treatment does not require a surgical procedure and is easily reversible.

Comparison of the three

Unfortunately, no head-to-head randomized controlled trials comparing DBS, LCIG, and CAI have been performed. Therefore, only indirect comparisons can be made and these should be interpreted with caution. Compared to patients on standard DRT, DBS was shown to increase the ON time without troublesome dyskinesia by 3.3 h per day (95% CI 1.8–4.7; follow-up (FU) 3–24 months) [38], LCIG by 1.9 h (95% CI 0.6–3.2; FU 3 months) [10] and CAI by 2.0 h (95% CI 0.7–3.4; FU 3 months) [12]. Improvement in quality of life has been shown in randomized trials for DBS and LCIG [10, 12, 38]. Long-term ben-

efits remain for up to 10 years in STN DBS, although with decline over time [39]. One longer term follow-up study in patients treated with LCIG showed that after a mean treatment duration of 4.1 years, 34% of patients had discontinued due to adverse events [29]; and a study in CAI showed that after a median treatment duration of 15 months, 50% of the surviving patients had discontinued mainly due to side effects and a decline in benefits [37]. Regarding the mean attrition rates, it is important to take into account that the reversibility of the procedures differs, making it easier to start and discontinue CAI than treatments involving surgery [40], where discontinuation means removal of implanted material.

Advanced therapies for PD are costly, and costs differ between countries. In most health care systems, LCIG is associated with substantially higher costs for increase of quality-adjusted life years (QALY) than the other therapies, followed by DBS for which the costs are highest in the first year and drop thereafter. CAI has the lowest costs in countries where generic companies distribute it without infrastructure [41, 42].

Making a choice

A proportion of patients is only eligible for one of the advanced treatment options, mainly due to absolute contra-indications for the others and sometime because one of the therapies is superior (e.g., DBS in medication refractory tremor). Still, because all three advanced treatments have roughly the same indications, that is disability accompanying motor fluctuations, most patients are eligible for more than one of the advanced treatments. Then, a choice needs to be made. Besides local availability and idiosyncrasies related to treatment centers, reimbursement, regulations and clinical experience, tailoring each of the advanced therapies for individual patients is based on limited clinical trials, registries, and assumptions regarding individualized efficacy and adverse effects profiles (Table 2). Additional elements to consider include potential effects on nonmotor symptoms, device characteristics (e.g., pump to carry), and cosmetic issues. The choice is preferably made collaboratively between the treating physician and the patient [43], reviewing the pros and cons of each therapy and taking possible caregiver support into account. The multiple elements to consider without direct comparative evidence makes the selection challenging. Patients are best advised by a movement disorders specialist familiar

with all available advanced treatments in order to prevent bias from (absence of) experience with the individual therapies in the decision-making process. If the chosen therapy does not provide enough symptom reduction, eligible patients may be offered an alternative advanced therapy [37, 44–46].

WHEN: TIMING OF ADVANCED THERAPIES

Advanced treatments were once reserved as a last resort. Although they all carry a small risk of severe adverse effects and the use of the devices can be bothersome, their efficacy can be so dramatic that there is a tendency to initiate these treatments earlier in the disease course, before motor complications generate marked disability [47]. A major contribution to this discussion was the EARLYSTIM trial, which confirmed that patients with a disease duration of at least four years, fluctuations or dyskinesia for three years or less, and mild-to-moderate impairment in social and occupational functioning, may benefit from STN DBS [48]. Advanced therapies should only be initiated once other causes of Parkinsonism have been ruled out with relative certainty, which typically requires 3–4 years of disease duration. Still it is advisable to start discussing advanced therapies early in the disease course, preferably when motor fluctuations start to occur, but can still be managed by alterations in standard DRT. This reassures patients that further options remain available, gives them time to get acquainted with the advanced therapies and may facilitate decision making later on.

FUTURE PERSPECTIVES

While controlled trials for comparative efficacy assessments of the advanced therapies may be very difficult, the currently ongoing INVEST trial in which DBS and LCIG are compared in an RCT combined with ancillary patient preference observational arms, may provide some of the essential directly comparative information [49]. Important knowledge gaps include the differential effect of the advanced therapies on non-motor features of PD (e.g., anxiety, depression, pain), criteria for discontinuation (e.g., severe dementia), and predictors of long-term complications. A study investigating early use of CAI (in patients similar to those in EARLY-STIM) is currently ongoing [50]. DBS techniques likely will continue to evolve, such as with adaptive neurostim-

ulation by which local neurophysiological signals are used to continuously adjust the amount of current delivered. Another interesting development is optogenetics; stimulation of specific neuronal cell types using light-sensitive ion channels introduced through gene-therapy may provide knowledge to optimize DBS treatment [51]. For both levodopa and apomorphine, efforts are underway to develop easier and less invasive methods of continuous drug delivery compared to the currently used pump systems. Both drugs are currently being investigated as transdermal systems, such as patch pumps. Future understanding of the biological subtypes of PD may allow pharmacogenomics and other bioassay-based tailoring of medical and surgical treatments. It is conceivable that improvements in individualized pharmacotherapy with disease-modifying properties may favorably alter the course of disease for certain PD subtypes and, with that, reduce the need for advanced symptomatic therapies.

CONCLUSIONS

Over the last two decades, DBS, LCIG, and CAI greatly expanded the therapeutic options for PD. These advanced treatments are deployed when standard DRT no longer controls motor complications or leads to major adverse effects, and should preferably be initiated before disability occurs. Currently, the choice between the treatments remains dependent on a mix of device characteristics, indirect evidence on comparative efficacy for particular symptoms, availability, individual risk factors for adverse effects, patient preference and possible caregiver support. Patients are best advised early in the disease course, by a movement disorders specialist familiar with all the advanced treatments available in their country. Future research stands to improve the efficacy of each of the treatments and also address the knowledge gaps regarding the choice between the possible options to improve individual decision making.

Panel: Take home information

- Deep brain stimulation, continuous levodopa-carbidopa intestinal gel and continuous subcutaneous apomorphine infusion are accepted advanced treatments for persistent motor fluctuations in Parkinson's disease.

- When motor fluctuations appear, continuous vigilance is warranted to determine timing of an advanced treatment – before severe fluctuations and loss of functioning create difficulties in reversing the disability.
- Patients should be informed about the advanced treatments early in the disease course.
- The choice between the advanced treatments is tailor-made and patients are best advised by a movement disorders specialist familiar with the treatments available in their country.

CONFLICT OF INTEREST

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