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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 reduces levodopa metabolism,

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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	Displacement of the tube
		Hallucinations	Weight loss
			Biphasic dyskinesia
	Technical problems or empty battery leading to re-operation	Dopamine dysregulation syndrome and impulse control disorders	Constipation
	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 continuous subcutaneous apomorphine infusion and CLI, there are no daily limitations, not having to carry an external pump	No surgery is required	Many patients are eligible
		Many patients are eligible	Possibility of testing treatment
		Possibility of testing the treatment, easily reversible	

such as an iMAO-Bor 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.

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	+/–	+/–	+/–	+/–	+/–	+/–
Trouble some non-drug 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.

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 refractory 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 electrodes 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 (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 benefits 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 neurostimulation 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.

CONFLICT OF INTEREST

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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.

REFERENCES

[1] de Bie RMA, Clarke CE, Espay AJ, Fox SH, Lang AE (2020) Initiation of pharmacological therapy in Parkinson's disease: When, why, and how. *Lancet Neurol* **19**, 452-461.

[2] Santos-Garcia D, de Deus Fonticoba T, Suarez Castro E, Aneiros Diaz A, McAfee D, Catalan MJ, Alonso-Frech F, Villanueva C, Jesus S, Mir P, Aguilar M, Pastor P, Garcia Caldentey J, Esltelrich Peyret E, Planellas LL, Marti MJ, Caballol N, Hernandez Vara J, Marti Andres G, Cabo I, Avila Rivera MA, Lopez Manzanares L, Redondo N, Martinez-Martin P, Group CS, McAfee D (2020) Non-motor symptom burden is strongly correlated to motor complications in patients with Parkinson's disease. *Eur J Neurol*. doi: 10.1111/ene.14221.

[3] Kim HJ, Mason S, Foltynie T, Winder-Rhodes S, Barker RA, Williams-Gray CH (2020) Motor complications in Parkinson's disease: 13-year follow-up of the CamPaIGN cohort. *Mov Disord* **35**, 185-190.

[4] Bestetti A, Capozza A, Lacerenza M, Manfredi L, Mancini F (2017) Delayed gastric emptying in advanced Parkinson disease: Correlation with therapeutic doses. *Clin Nucl Med* **42**, 83-87.

[5] Fasano A, Bove F, Gabrielli M, Petracca M, Zocco MA, Ragazzoni E, Barbaro F, Piano C, Fortuna S, Tortora A, Di Giacopo R, Campanale M, Gigante G, Lauritano EC, Navarra P, Marconi S, Gasbarrini A, Bentivoglio AR (2013) The role of small intestinal bacterial overgrowth in Parkinson's disease. *Mov Disord* **28**, 1241-1249.

[6] Picconi B, Hernández LF, Obeso JA, Calabresi P (2018) Motor complications in Parkinson's disease: Striatal molecular and electrophysiological mechanisms of dyskinesias. *Mov Disord* **33**, 867-876.

[7] Fox SH, Katzenschlager R, Lim SY, Barton B, de Bie RMA, Seppi K, Coelho M, Sampaio C (2018) International Parkinson and movement disorder society evidence-based medicine review: Update on treatments for the motor symptoms of Parkinson's disease. *Mov Disord* **33**, 1248-1266.

[8] Politis M, Sauerbier A, Loane C, Pavese N, Martin A, Corcoran B, Brooks DJ, Ray-Chaudhuri K, Piccini P (2017) Sustained striatal dopamine levels following intestinal levodopa infusions in Parkinson's disease patients. *Mov Disord* **32**, 235-240.

[9] Okun MS (2012) Deep-brain stimulation for Parkinson's disease. *N Engl J Med* **367**, 1529-1538.

[10] Olanow CW, Kieburtz K, Odin P, Espay AJ, Standaert DG, Fernandez HH, Vanagunas A, Othman AA, Widnell KL, Robieson WZ, Pritchett Y, Chatamra K, Benesh J, Lenz RA, Antonini A (2014) Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: A randomised, controlled, double-blind, double-dummy study. *Lancet Neurol* **13**, 141-149.

[11] Deuschl G, Agid Y (2013) Subthalamic neurostimulation for Parkinson's disease with early fluctuations: Balancing the risks and benefits. *Lancet Neurol* **12**, 1025-1034.

[12] Katzenschlager R, Poewe W, Rascol O, Trenkwalder C, Deuschl G, Chaudhuri KR, Henriksen T, van Laar T, Spivey K, Vel S, Staines H, Lees A (2018) Apomorphine subcutaneous infusion in patients with Parkinson's disease with persistent motor fluctuations (TOLEDO): A multicentre, double-blind, randomised, placebo-controlled trial. *Lancet Neurol* **17**, 749-759.

[13] Dafsari HS, Martinez-Martin P, Rizos A, Trost M, Dos Santos Ghilardi MG, Reddy P, Sauerbier A, Petry-Schmelzer JN, Kramberger M, Borgemeester RWK, Barbe MT, Ashkan K, Silverdale M, Evans J, Odin P, Fonoff ET, Fink GR, Henriksen T, Ebersbach G, Pirtosek Z, Visser-Vandewalle V, Antonini A, Timmermann L, Ray Chaudhuri K (2019) EuroInf 2: Subthalamic stimulation, apomorphine, and levodopa infusion in Parkinson's disease. *Mov Disord* **34**, 353-365.

[14] Krack P, Batir A, Van Blercom N, Chabardes S, Fraix V, Ardouin C, Koudsie A, Limousin PD, Benazzouz A, LeBas JF, Benabid AL, Pollak P (2003) Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med* **349**, 1925-1934.

[15] Schuurman PR, Bosch DA, Bossuyt PM, Bonsel GJ, van Someren EJ, de Bie RM, Merkus MP, Speelman JD (2000) A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor. *N Engl J Med* **342**, 461-468.

[16] Fasano A, Visanji NP, Liu LWC, Lang AE, Pfeiffer RF (2015) Gastrointestinal dysfunction in Parkinson's disease. *Lancet Neurol* **14**, 625-639.

[17] Limousin P, Pollak P, Benazzouz A, Hoffmann D, Le Bas JF, Broussolle E, Perret JE, Benabid AL (1995) Effect of parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. *Lancet* **345**, 91-95.

[18] 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, Starr PA, Simpson R, Baltuch G, De Salles A, Huang GD, Reda DJ (2010) Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. *N Engl J Med* **362**, 2077-2091.

[19] Odekerken VJ, van Laar T, Staal MJ, Mosch A, Hoffmann CF, Nijssen PC, Beute GN, van Vugt JP, Lenders MW, Contarino MF, Mink MS, Bour LJ, van den Munckhof P, Schmand BA, de Haan RJ, Schuurman PR, de Bie RM (2013) Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease (NSTAPS study): A randomised controlled trial. *Lancet Neurol* **12**, 37-44.

[20] Fasano A, Daniele A, Albanese A (2012) Treatment of motor and non-motor features of Parkinson's disease with deep brain stimulation. *Lancet Neurol* **11**, 429-442.

[21] Jakobs M, Helmers AK, Synowitz M, Slotty PJ, Anthofer JM, Schlaier JR, Kloss M, Unterberg AW, Kiening KL (2019) A multicenter, open-label, controlled trial on acceptance, convenience, and complications of rechargeable internal pulse generators for deep brain stimulation: The Multi Recharge Trial. *J Neurosurg*. doi: 10.3171/2019.5.Jns19360.

[22] Boutet A, Hancu I, Saha U, Crawley A, Xu DS, Ranjan M, Hlasny E, Chen R, Foltz W, Sammartino F, Coblentz A, Kucharczyk W, Lozano AM (2019) 3-Tesla MRI of deep brain stimulation patients: Safety assessment of coils and pulse sequences. *J Neurosurg* **132**, 586-594.

[23] Timmermann L, Jain R, Chen L, Maarouf M, Barbe MT, Allert N, Brucke T, Kaiser I, Beirer S, Sejio F, Suarez E,

Lozano B, Haegelen C, Verin M, Porta M, Servello D, Gill S, Whone A, Van Dyck N, Alesch F (2015) Multiple-source current steering in subthalamic nucleus deep brain stimulation for Parkinson's disease (the VANTAGE study): A non-randomised, prospective, multicentre, open-label study. *Lancet Neurol* **14**, 693-701.

[24] Zhang S, Silburn P, Pouratian N, Cheeran B, Venkatesan L, Kent A, Schnitzler A (2019) Comparing current steering technologies for directional deep brain stimulation using a computational model that incorporates heterogeneous tissue properties. *Neuromodulation*. doi: 10.1111/ner.13031.

[25] Contarino MF, Bour LJ, Verhagen R, Lourens MA, de Bie RM, van den Munckhof P, Schuurman PR (2014) Directional steering: A novel approach to deep brain stimulation. *Neurology* **83**, 1163-1169.

[26] Ho AL, Ali R, Connolly ID, Henderson JM, Dhall R, Stein SC, Halpern CH (2018) Awake versus asleep deep brain stimulation for Parkinson's disease: A critical comparison and meta-analysis. *J Neurol Neurosurg Psychiatry* **89**, 687-691.

[27] Zadikoff C, Poewe W, Boyd JT, Bergmann L, Ijacu H, Kukreja P, Robieson WZ, Benesh J, Antonini A (2020) Safety of levodopa-carbidopa intestinal gel treatment in patients with advanced Parkinson's disease receiving >/=2000 mg daily dose of levodopa. *Parkinsons Dis* **2020**, 9716317.

[28] Poewe W, Chaudhuri KR, Bergmann L, Antonini A (2019) Levodopa-carbidopa intestinal gel in a subgroup of patients with dyskinesia at baseline from the GLORIA Registry. *Neurodegener Dis Manag* **9**, 39-46.

[29] Fernandez HH, Boyd JT, Fung VSC, Lew MF, Rodriguez RL, Slevin JT, Standaert DG, Zadikoff C, Vanagunas AD, Chatamra K, Eaton S, Facheris MF, Hall C, Robieson WZ, Benesh J, Espay AJ (2018) Long-term safety and efficacy of levodopa-carbidopa intestinal gel in advanced Parkinson's disease. *Mov Disord* **33**, 928-936.

[30] Poewe W, Bergmann L, Kukreja P, Robieson WZ, Antonini A (2019) Levodopa-carbidopa intestinal gel monotherapy: GLORIA Registry demographics, efficacy, and safety. *J Parkinsons Dis* **9**, 531-541.

[31] Marano M, Naranian T, di Biase L, Di Santo A, Poon YY, Arca R, Cossu G, Marano P, Di Lazzaro V, Fasano A (2019) Complex dyskinesias in Parkinson patients on levodopa/carbidopa intestinal gel. *Parkinsonism Relat Disord* **69**, 140-146.

[32] Ricciardi L, Bove F, Espay KJ, Lena F, Modugno N, Poon YY, Krikorian R, Espay AJ, Fasano A (2016) 24-Hour infusion of levodopa/carbidopa intestinal gel for nocturnal akinesia in advanced Parkinson's disease. *Mov Disord* **31**, 597-598.

[33] Cruse B, Morales-Briceno H, Chang FCF, Mahant N, Ha AD, Kim SD, Wolfe N, Kwan V, Tsui DS, Griffith JM, Galea D, Fung VSC (2018) 24-hour levodopa-carbidopa intestinal gel may reduce troublesome dyskinesia in advanced Parkinson's disease. *NPJ Parkinsons Dis* **4**, 34.

[34] Trenkwalder C, Chaudhuri KR, García Ruiz PJ, LeWitt P, Katzenschlager R, Sixel-Döring F, Henriksen T, Sesar Á, Poewe W, Baker M, Ceballos-Baumann A, Deuschl G, Drapier S, Ebersbach G, Evans A, Fernandez H, Isaacson S, van Laar T, Lees A, Lewis S, Martínez Castrillo JC, Martinez-Martin P, Odin P, O'Sullivan J, Tagaris G, Wenzel K (2015) Expert Consensus Group report on the use of apomorphine in the treatment of Parkinson's disease–Clinical practice recommendations. *Parkinsonism Relat Disord* **21**, 1023-1030.

[35] Bhidayasiri R, Chaudhuri KR, LeWitt P, Martin A, Boonpang K, van Laar T (2015) Effective delivery of apomorphine in the management of Parkinson disease: Practical considerations for clinicians and Parkinson nurses. *Clin Neuropharmacol* **38**, 89-103.

[36] Jenner P, Katzenschlager R (2016) Apomorphine - pharmacological properties and clinical trials in Parkinson's disease. *Parkinsonism Relat Disord* **33 Suppl 1**, S13-s21.

[37] Sesar A, Fernandez-Pajarin G, Ares B, Rivas MT, Castro A (2017) Continuous subcutaneous apomorphine infusion in advanced Parkinson's disease: 10-year experience with 230 patients. *J Neurol* **264**, 946-954.

[38] Perestelo-Pérez L, Rivero-Santana A, Pérez-Ramos J, Serrano-Pérez P, Panetta J, Hilarion P (2014) Deep brain stimulation in Parkinson's disease: Meta-analysis of randomized controlled trials. *J Neurol* **261**, 2051-2060.

[39] Limousin P, Foltynie T (2019) Long-term outcomes of deep brain stimulation in Parkinson disease. *Nat Rev Neurol* **15**, 234-242.

[40] Bhidayasiri R, Phokaewvarangkul O, Boonpang K, Boonmongkol T, Thongchuem Y, Kantachadvanich N, García Ruiz PJ (2019) Long-term apomorphine infusion users versus short-term users: An international dual-center analysis of the reasons for discontinuing therapy. *Clin Neuropharmacol* **42**, 172-178.

[41] Afentou N, Jarl J, Gerdtham UG, Saha S (2019) Economic evaluation of interventions in Parkinson's disease: A systematic literature review. *Mov Disord Clin Pract* **6**, 282-290.

[42] Walter E, Odin P (2015) Cost-effectiveness of continuous subcutaneous apomorphine in the treatment of Parkinson's disease in the UK and Germany. *J Med Econ* **18**, 155-165.

[43] Nijhuis FAP, van den Heuvel L, Bloem BR, Post B, Meinders MJ (2019) The patient's perspective on shared decision-making in advanced Parkinson's disease: A cross-sectional survey study. *Front Neurol* **10**, 896.

[44] Faust-Socher A, Abu Ahmad F, Giladi N, Hilel A, Shapira Y, Klepikov D, Ezra A, Raif L, Gurevich T (2019) Deep brain stimulation as second line advanced treatment for PD after LCIG. *Mov Disord* **34 (Suppl 2)**, S349.

[45] Sesar A, Fernandez-Pajarin G, Ares B, Relova JL, Aran E, Rivas MT, Gelabert-Gonzalez M, Castro A (2019) Continuous subcutaneous apomorphine in advanced Parkinson's disease patients treated with deep brain stimulation. *J Neurol* **266**, 659-666.

[46] Bautista JMP, Oyama G, Nuermaimaiti M, Sekimoto S, Sasaki F, Hatano T, Nishioka K, Ito M, Umemura A, Ishibashi Y, Shimo Y, Hattori N (2020) Rescue levodopa/carbidopa intestinal gel for secondary deep brain stimulation failure. *J Mov Disord* **13**, 57-61.

[47] Antonini A, Nitu B (2018) Apomorphine and levodopa infusion for motor fluctuations and dyskinesia in advanced Parkinson disease. *J Neural Transm (Vienna)* **125**, 1131-1135.

[48] Schuepbach WM, Rau J, Knudsen K, Volkmann J, Krack P, Timmermann L, Halbig TD, Hesekamp H, Navarro SM, Meier N, Falk D, Mehdorn M, Paschen S, Maarouf M, Barbe MT, Fink GR, Kupsch A, Gruber D, Schneider GH, Seigneuret E, Kistner A, Chaynes P, Ory-Magne F, Brefel Courbon C, Vesper J, Schnitzler A, Wojtecki L, Houeto JL, Bataille B, Maltete D, Damier P, Raoul S, Sixel-Doering F, Hellwig D, Gharabaghi A, Kruger R, Pinsker MO, Amtage F, Regis JM, Witjas T, Thobois S, Mertens P, Kloss M, Hartmann A, Oertel WH, Post B, Speelman H, Agid Y, Schade-Brittinger C, Deuschl G (2013) Neurostimulation

for Parkinson's disease with early motor complications. *N Engl J Med* **368**, 610-622.

[49] van Poppelen D, Sisodia V, de Haan RJ, Dijkgraaf MGW, Schuurman PR, Geurtsen GJ, Berk AEM, de Bie RMA, Dijk JM (2020) Protocol of a randomized open label multicentre trial comparing continuous intrajejunal levodopa infusion with deep brain stimulation in Parkinson's disease – the INfusion VErsus STimulation (INVEST) study. *BMC Neurol* **20**, 40.

[50] Apomorphine Pump in Early Stage of Parkinson's Disease (EARLY-PUMP). https://ClinicalTrials.gov/show/NCT02864004.

[51] Gittis AH, Yttri EA (2018) Translating insights from optogenetics to therapies for Parkinson's disease. *Curr Opin Biomed Eng* **8**, 14-19.

[52] Odin P, Ray Chaudhuri K, Slevin JT, Volkmann J, Dietrichs E, Martinez-Martin P, Krauss JK, Henriksen T, Katzenschlager R, Antonini A, Rascol O, Poewe W, National Steering C (2015) Collective physician perspectives on non-oral medication approaches for the management of clinically relevant unresolved issues in Parkinson's disease: Consensus from an international survey and discussion program. *Parkinsonism Relat Disord* **21**, 1133-1144.

[53] Antonini A, Stoessl AJ, Kleinman LS, Skalicky AM, Marshall TS, Sail KR, Onuk K, Odin PLA (2018) Developing consensus among movement disorder specialists on clinical indicators for identification and management of advanced Parkinson's disease: A multi-country Delphi-panel approach. *Curr Med Res Opin* **34**, 2063-2073.