ADVANCED THERAPIES FOR PARKINSON'S DISEASE

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DISCLOSURES

- **Advisory board: Sunovion**
- **Honoraria: Paladin Labs**
- **Travel Support: AbbVie, Parkinson Canada**

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OBJECTIVES

- Review candidacy for device assisted therapies
- Review of advanced therapies that are, or will soon be, available in Canada
- Review selection of optimal therapy for a given individual

WHAT ARE ADVANCED THERAPIES?

- Device-assisted therapies used for the management of *motor complications* in patients with *advanced Parkinson's disease* that are disabling despite optimization of oral medications
  - Deep brain stimulation
    - GPi
    - STN
    - (VIM)
  - Infusion therapies
    - (Fos)Levodopa/(fos)carbidopa
    - (Apomorphine)

WHO SHOULD BE CONSIDERED FOR ADVANCED THERAPIES?

- Ideally, advanced therapies should be used to *prevent or delay* disability in people with PD, not to *salvage* disability

- Early identification of individuals who may be candidates for advanced therapies is important

WHO SHOULD BE CONSIDERED FOR ADVANCED THERAPIES?

- Patients with advanced Parkinson's disease who, despite optimal treatment, have:
  - Disabling motor fluctuations
  - Bothersome dyskinesias
- Patients with medically refractory tremor
- Patients who are interested in advanced therapies
- Patients with realistic expectations
- Patients with adequate supports

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DEFINING ADVANCED PARKINSON'S DISEASE

CURRENT MEDICAL RESEARCH AND OPINION
2018, VOL. 34, NO. 12, 2063–2073
https://doi.org/10.1080/03007995.2018.1502165
Article FT-0310.R1/1502165

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Developing consensus among movement disorder specialists on clinical indicators for identification and management of advanced Parkinson's disease: a multi-country Delphi-panel approach

Angelo Antonini[a], A. Jon Stoessl[b], Leah S. Kleinman[c], Anne M. Skalicky[c], Thomas S. Marshall[d], Kavita R. Sail[d], Koray Onuk[d] and Per Lars Anders Odin[e,f]

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Table 3. Round 3 final results on indicators for suspected APD.

Question ($n = 22$)[a,b]	Domain	Consensus result (total questions)		
		Final Round 3 result[c]	Consensus	Clinically important (Yes/No)
Does troublesome dysphagia make you suspect APD?	MS	Definite	93%	Yes[h]
For optimally treated patients, how many hours of the waking day with "off" symptoms indicate a patient is suspected to have APD?	MS	At least 2 h	86%	Yes[h]
In your opinion, how many hours of the day with troublesome dyskinesia indicate a patient is suspected to have APD?	MS	At least 1 h	84%	Yes[h]
What level of troublesome motor fluctuations indicates a patient is suspected to have APD?	MS	Moderate	81%	Yes[h]
What is the frequency of daily oral levodopa dosing that indicates suspected to have APD?	MS	At least 5-times/day	79%	Yes[h]
Does a good "on" response to medication indicate a stable stage of PD?	MS	Yes	79%	No
For optimally treated patients, what level of troublesome dyskinesia indicates that a patient is suspected to have APD?	MS	Moderate	77%	Yes[h]
What is the frequency (in hours) of "off" symptoms that indicates that a patient is suspected to have APD?	MS	Every 3 h	75%	Yes[f]

Adapted from Antonini *et. al.* 2018

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5-2-1 CRITERIA

- At least 5 doses of medication per day
- At least 2 hours of off time per day
- At least 1 hour of troublesome dyskinesias per day

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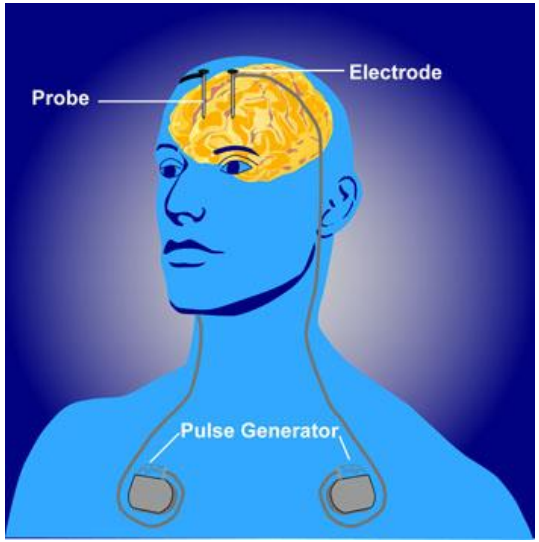
DEEP BRAIN STIMULATION (DBS)

- Implantation of electrodes into deep grey matter structures along with an implantable pulse generator allowing stimulation of subcortical networks involved in PD

- Targets used in treatment of people with PD
  - Subthalamic nucleus (STN)
  - Globus pallidus pars interna (GPi)
  - (VIM thalamus)



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STN DBS

- Mimics the effect of levodopa
  - Off-state motor scores improve by 25-60% compared to pre-op
  - Medication dose is reduced by ~50%
  - No change in non-motor symptoms
  - Best effect = best “on” with levodopa
- Dyskinesia will improve due to reduction in dopaminergic medications
- Improves tremor amplitude by ~80%
- Symptoms that don’t improve with levodopa don’t improve with DBS

GPI DBS

- Provides direct anti-dyskinetic and anti-dystonic effect

- Motor scores improve by 30-50%
    - 50% improvement in rigidity
    - 80% improvement in tremor

- No change in medication dose

- Most studies fail to show a difference in outcome between the two targets, but some studies show a benefit of STN over GPi
    - Most centres perform STN surgery unless there is a contraindication

THALAMIC DBS

- Results in 80-90% improvement in tremor amplitude
- No effect on other parkinsonian symptoms
- May be a consideration for patients with contraindication to other surgical targets
  - Older age
  - Cognitive impairment
  - Mood symptoms
- In some cases may go on to have STN/GPi electrodes implanted later

ELIGIBILITY

- People being considered for DBS should have:
  - Disease duration of at least 5 years
  - At least 30% improvement in UPDRS motor score with levodopa
  - Disabling motor fluctuations and/or dyskinesias; or
  - Medically-refractory tremor

CONTRAINDICATIONS TO DBS

- Contraindications to DBS include:
  - Dementia
  - Severe levodopa-resistant symptoms
  - Severe depression
  - Concern for atypical parkinsonian syndrome
  - Unrealistic expectations
  - Older age is a relative contraindication
  - Lack of caregiver is a relative contraindication, especially for STN DBS

DBS ASSESSMENT

- Patients are assessed to ensure that they meet criteria – by movement disorder neurologist/neurosurgeon

- Reviewed by the neurosurgeon to ensure they have no contraindications to surgery

- Undergo a number of standardized assessments
    - Levodopa challenge
    - Screening for mood disorders
    - Cognitive testing

- Many centres have multidisciplinary rounds to review candidacy and target selection

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COMPLICATIONS OF DBS

- STN:
  - Worsened verbal fluency
  - Worsened speech
  - Depression and suicidality
  - Worsened gait/balance
  - Impulse control disorders
  - Mania
  - Apathy
  - Weight gain

COMPLICATIONS OF DBS

- GPi
  - Overall similar side effect profile to STN
  - Possibly less effect on speech and gait

- Surgical risk
  - Hemorrhage – up to ~3%
  - Infection 2.2 – 4.5% (rarely intracranial)

- Hardware malfunction – up to ~5%

LONG-TERM OUTCOMES OF DBS

- STN
  - Durable improvements in tremor, rigidity and bradykinesia up to at least 10 years post-op
  - Durable improvement in fluctuations and dyskinesias for at least 5 years
  - Quality of life initially improves compared to baseline, but this effect may be lost by 5 years post-op
  - No effect on the development of dementia
    - Verbal fluency worse
  - Variable effect on psychiatric symptoms

- Bottom line: STN DBS offers a durable benefit to motor complications, but does not affect disease progression

LONGTERM OUTCOMES OF DBS

- GPi
  - Limited data with contradictory results
  - Variable effects on severity of off-period symptoms
  - Durable improvement in levodopa-induced dyskinesias, tremor and rigidity

TARGET SELECTION

- Factors favouring STN DBS:
  - Medication side effects
  - More prominent motor fluctuations
  - Absence of significant cognitive or psychiatric symptoms

- Factors favouring Gpi DBS:
  - Dyskinesias are most prominent symptom
  - Levodopa-responsive mood symptoms?

DBS – USE IN CANADA

- The overall rate of DBS surgery in Canada is ~ 10/1,000,000 per year (Honey *et. al.* 2018)
    - This compares favourably to estimated rates in other countries
    - The rate in BC is 80% of the national rate

- Only 1.2% of PD patients diagnosed in Ontario between 1995 – 2009 underwent DBS (Crispo *et. al.,* 2020)

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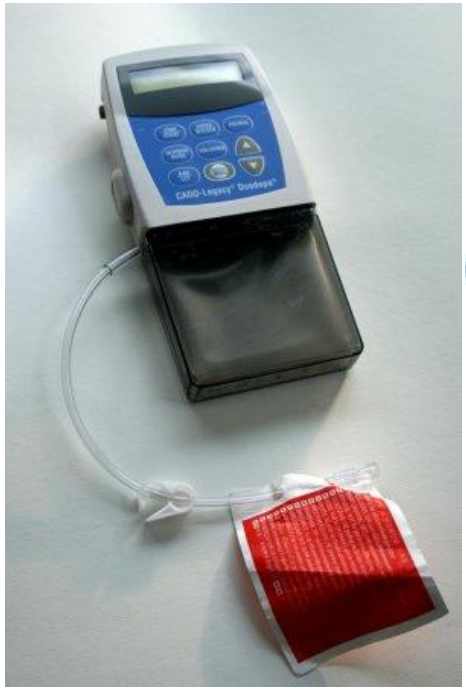
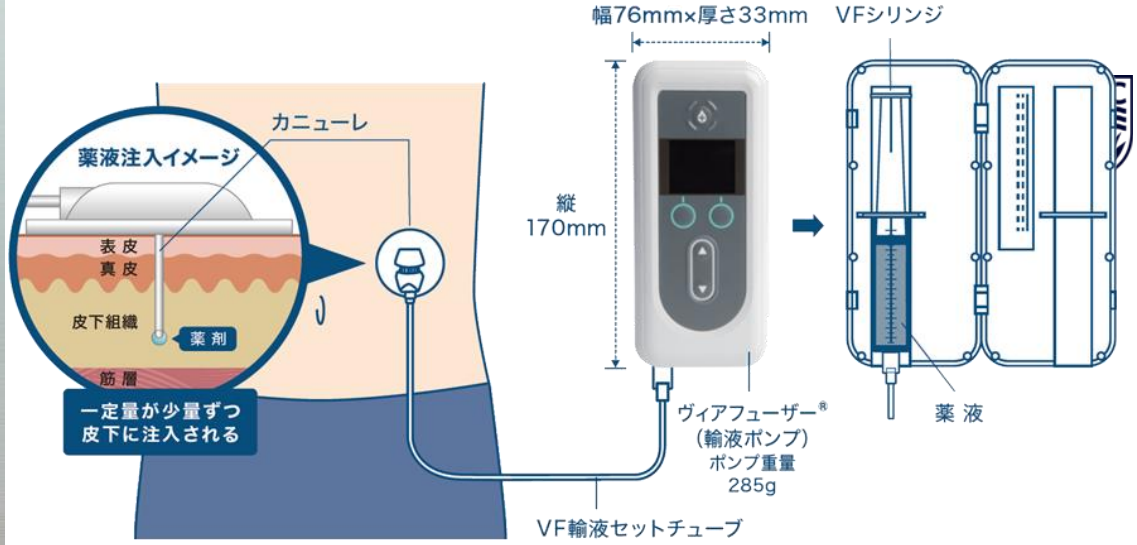
- Only a small minority of PD patients are ever candidates for DBS
  - 1.6 – 4.5% of patients may be eligible, depending on criteria used (Morgante *et. al.*, 2007)

- Other therapies are needed for these patients as their condition worsens

INFUSION THERAPIES





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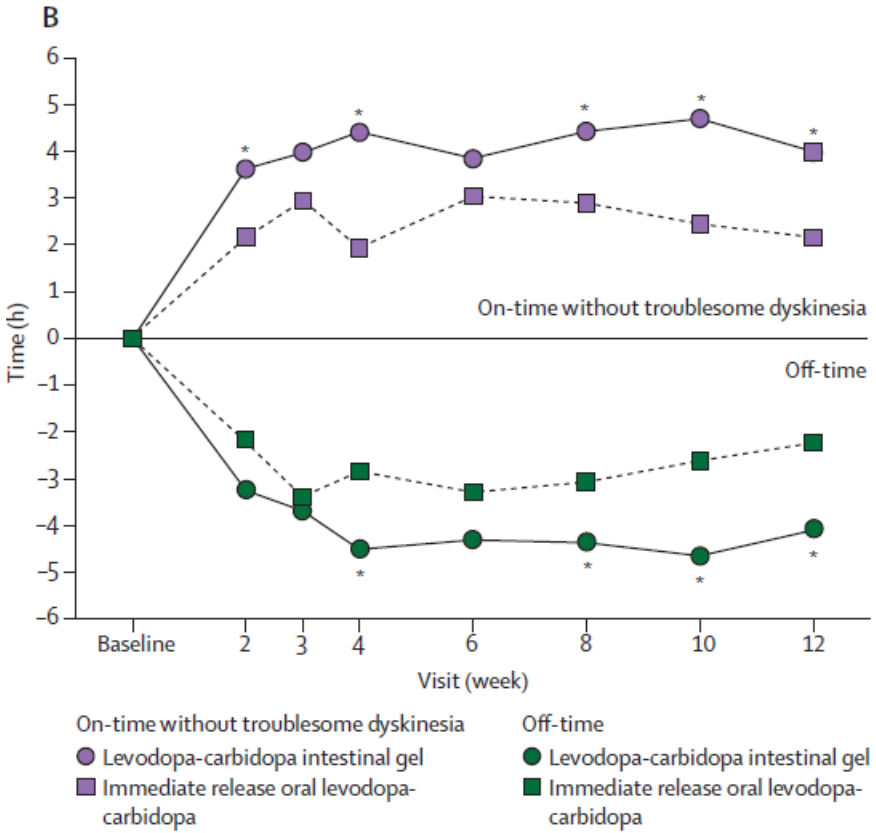
INFUSION THERAPIES

- Provide continuous administration of dopaminergic medication, helping to maintain more stable dopamine concentrations.

- Available options:
  - Levodopa/carbidopa intestinal gel (Duodopa)
  - SC foslevodopa/foscarbidopa (Vyalev)
  - (SC Apomorphine)

LEVODOPA/CARBIDOPA INTESTINAL GEL (LCIG)

- Intrajejunal infusion of levodopa/carbidopa administered during waking hours
- Approved in 2004 in the EU, 2015 in North America
- Patients receive a bolus dose in the morning followed by a continuous infusion with additional PRN boluses during waking hours (16 hours/day)
- Requires insertion of a proprietary PEG-J tube
- Bypasses the stomach → improved absorption



Lancet Neurol 2014; 13: 141–49

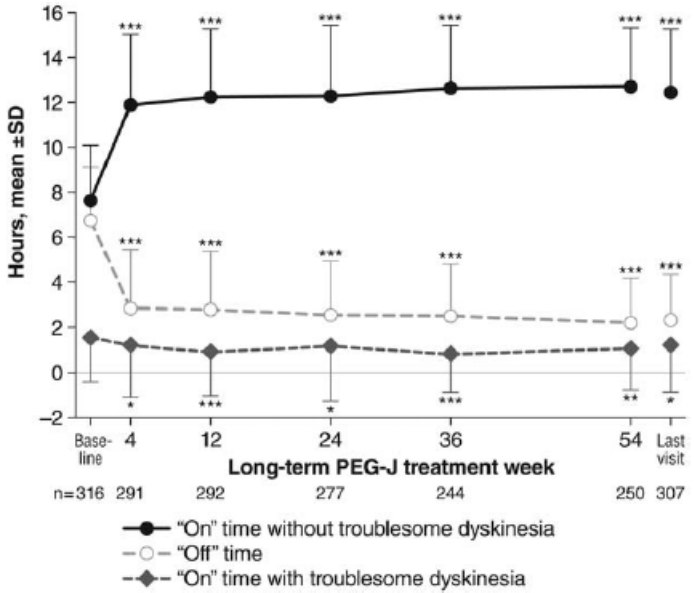


FIG. 2. Mean ± SD daily "off" and "on" times as assessed by a Parkinson's disease diary. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$ versus baseline.

Movement Disorders, Vol. 30, No. 4, 2015

Adv Ther (2021) 38:2854–2890
https://doi.org/10.1007/s12325-021-01747-1

REVIEW

The Long-Term Impact of Levodopa/Carbidopa Intestinal Gel on 'Off'-time in Patients with Advanced Parkinson's Disease: A Systematic Review

Angelo Antonini · Per Odin · Rajesh Pahwa · Jason Aldred · Ali Alobaidi · Yash J. Jalundhwala · Pavnit Kukreja · Lars Bergmann · Sushmitha Inguva · Yanjun Bao · K. Ray Chaudhuri

SAFETY

- Complications and side effects are quite common, and are related to:
  - Insertion of the PEG-J
    - Abdominal pain
    - Bloating
    - Wound infection
    - Peritonitis (very rare)
  - Long-term tube complications
    - Fracture/dislocation/migration
    - GI ulceration/erosion
    - Bezoar formation
  - Medication-related
    - Weight loss
    - Polyneuropathy (10-15%)
    - Biphasic dyskinesia
  - Most adverse effects are minor and transient

CONTRAINDICATIONS TO LCIG

- Contraindications to abdominal surgery
- Severe psychosis (hallucinations/paranoia) or dementia
- Lack of supportive care partner
- Living in LTC*
- Individual not interested

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BC EXPERIENCE

- Titrations have been ongoing since about 2016
- Initially coverage was limited to 5 patients/year. Currently no cap
- Titrations carried out in Vancouver, Surrey and Kelowna
- Current active patients
  - UBC – 15
  - Surrey – 4
  - Victoria – 10
  - Kelowna – 8

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PHARMACARE COVERAGE CRITERIA FOR LCIG

- Severe, disabling fluctuations and or dyskinesias refractory to oral medications
    - Patients must try at least one drug from each class

- Severe disability with at least 25% of the day in the off state or severe dyskinesias despite at least 5 doses of levodopa/day

- Adequate clinical response to levodopa

- Absence of severe psychosis or dementia

- DBS is contraindicated or the wait list is >1 year

ELIGIBILITY ASSESSMENT AT UBC

- Following referral, charts are reviewed by the LCIG nurse to identify any contraindications
- Patients undergo allied health assessment with OT, PT, SW to review goals and identify barriers to the therapy
- If no obvious contraindication is identified, patients are assessed by the neurologist
- If deemed eligible, patients are referred to GI for PEG-J insertion
- In-person titration for 2-4 days

FOSLEVODOPA/FOSCARBIDOPA (VYLEV)

- Prodrug of levodopa/carbidopa
- Administered as a continuous SC infusion over 24 hours
- Received Health Canada Approval in May 2023 (drug) and Feb 2024 (pump)
- Has received a positive CADTH review

EFFICACY

- Average increase in on time without troublesome dyskinesia = 3.8 hours
- Improvement in morning akinesia (77.7% at the start of the study, 19.2% at the end)
- Quality of life measures improved
- *However* 107/244 participants dropped out of the study early
  - 23% due to side effects
  - 11% due to inefficacy
  - Equipment was modified and increased training resulted in significant reduction in side effects

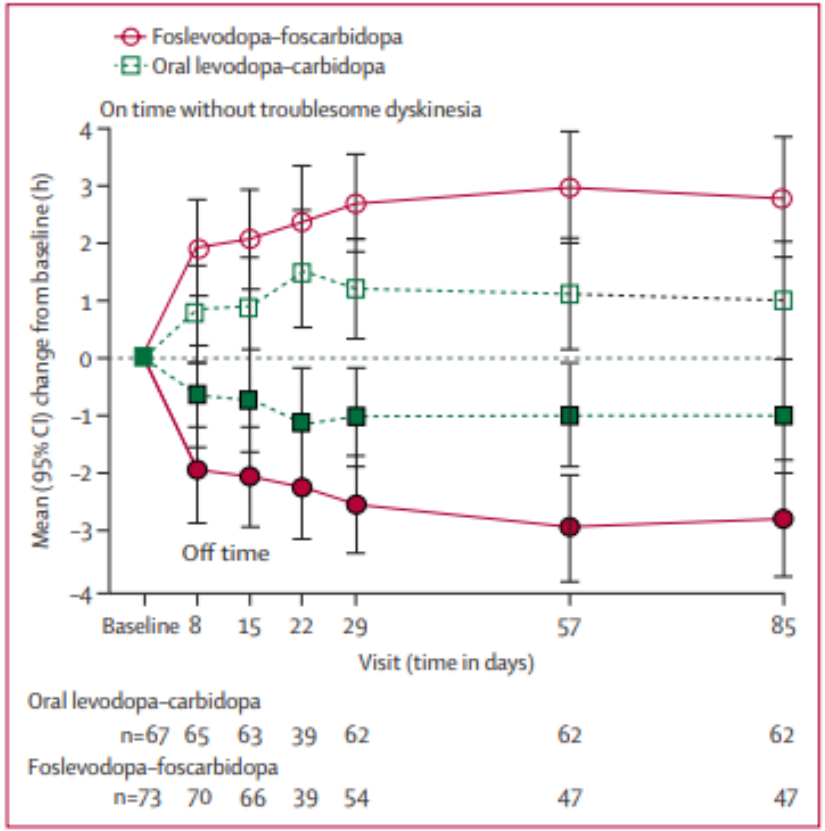

***Figure 2*: Least squares mean (95% CI) of change from baseline in average daily on time without troublesome dyskinesia and off time (full analysis set)**

Lancet Neurol 2022;
21: 1099–109

	Oral levodopa-carbidopa group (n=67)	Foslevodopa-foscarbidopa group (n=74)
Adverse events	42 (63%)	63 (85%)
Deaths	1 (1%)	0
Serious adverse events	4 (6%)	6 (8%)
Severe adverse events	1 (1%)	7 (9%)
Any adverse event leading to death	1 (1%)*	0
Any adverse event leading to premature study drug discontinuation†	1 (1%)	16 (22%)
Any adverse event considered related to study drug	15 (22%)	52 (70%)
Adverse events of special interest		
Infusion site events	8 (12%)	53 (72%)
Hallucinations or psychosis	2 (3%)	11 (15%)
Falls and associated injuries	17 (25%)	13 (18%)
Somnolence	1 (1%)	1 (1%)
Polyneuropathy	2 (3%)	2 (3%)
Weight loss	1 (1%)	1 (1%)

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Most frequent adverse events†		
Infusion site erythema	1 (1%)	20 (27%)
Infusion site pain	1 (1%)	19 (26%)
Infusion site cellulitis	0	14 (19%)
Infusion site oedema	0	9 (12%)
Dyskinesia	4 (6%)	8 (11%)
Fall	12 (18%)	6 (8%)
Infusion site bruising	2 (3%)	6 (8%)
Infusion site haemorrhage	0	6 (8%)
Infusion site nodule	0	6 (8%)
On and off phenomena	0	6 (8%)
Hallucination	1 (1%)	5 (7%)
Balance disorder	0	4 (5%)
Constipation	0	4 (5%)
Hallucination, visual	0	4 (5%)
Infusion site induration	0	4 (5%)
Infusion site infection	0	4 (5%)
Infusion site pruritus	0	4 (5%)
Peripheral swelling	0	4 (5%)

Data are n (%). Preferred terms classified according to the Medical Dictionary for Regulatory Activities version 24·0. *Considered by the investigator to have no reasonable possibility of being related to study drug. †Adverse events were one of the reasons for discontinuation, irrespective of whether it was the primary reason. ‡Occurring in ≥5% of patients. Further details are included in the appendix (pp 13–14) for serious and severe adverse events.

Table 3: **Overview of treatment-emergent adverse events (safety analysis set)**

LIMITATIONS OF INFUSION THERAPIES

- Need for engaged caregiver
- Cost (about $60k per year!)
- Titration is quite labour intensive
- Difficult to manage for those who live remotely
- Lack of comfort with GI/skin complications

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CHOICE OF THERAPY

- Some individuals may be a candidate for more than one therapy
- Other than personal preference, several disease-specific factors can help guide choice of therapy.

	DBS	Infusion therapy
Lack of caregiver	+/-	-
Older age (>70)	-	+
Fluctuations	++	++
Dyskinesia	++	+
Refractory tremor	++	-
Medication S/E	+	-
Dementia	-	+/-
Lives remotely	+	+/-
Dysarthria	+/-	+

Adapted from Dijk *et. al.* 2020

ADVANCED THERAPIES ARE UNDERUTILIZED

Table 2 DAT-eligible patients and ongoing DAT in the OBSERVE-PD and PARADISE studies: insights into international heterogeneity

References	Country	Proportions of ongoing DAT in eligible advanced PD patients	Most used DAT
Fasano et al. (2019) (OBSERVE-PD)	18 countries	43.6% (DBS, CSAI or LCIG)	DBS (57%)
Takáts et al. (2020) (OBSERVE-PD)	Hungary	75% (unspecified)	Unspecified
Martínez-Castrillo et al. (2021) (PARADISE)	Spain	15.2% (DBS, CSAI, LCIG)	Unspecified
Szasz et al. (2021) (OBSERVE-PD)	Romania	45.7% (DBS, LCIG)	Unspecified
Evans et al. (2021) (OBSERVE-PD)	Australia	68% (DBS, CSAI, LCIG)	DBS
Möller et al. (2021) (OBSERVE-PD)	Switzerland	79% (DBS, CSAI, LCIG)	DBS
Stefani et al. (2022) (OBSERVE-PD)	Italy	41% (DBS, LCIG)	DBS
Pedrosa et al. (2022) (OBSERVE-PD)	Germany	40.8% (unspecified)	Unspecified

CSAI continuous subcutaneous apomorphine infusion, *DAT* device-aided therapies, *LCIG* levodopa/carbidopa intestinal gel, *PD* Parkinson's disease

M. Auffret *et. al.* 2023

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BARRIERS TO ACCESS

- Racialized communities and individuals of lower socioeconomic status are consistently noted to be less likely to be considered for DBS
- Women are less likely to be referred for DBS
- Patients may be resistant to more invasive therapies

SUMMARY

- Consider advanced therapy when motor complications start to interfere with quality of life
- Ideally, these therapies should be initiated prior to the development of significant disability
- Access remains a challenge due to resource limitations
- SC levodopa infusion is a promising therapy, but there is currently no Pharmacare coverage

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