Treatment with levodopa infusions in patients with Parkinson's disease

A Scandinavian Movement Disorder Society, ScandMODIS, consensus document April 2024

Patients with Parkinson's disease (PD) in advanced stage of the disease should be referred to a Movement Disorders Clinic where a comprehensive and unbiased evaluation can be made by a neurologist specialized in movement disorders with a vast experience of adjusting peroral medication and in the use of deep brain stimulation (DBS), continuous subcutaneous administration of apomorphine, foslevodopa and continuous intestinal administration of levodopa.

Background
Levodopa-treatment in combination with a dopamine agonist is the golden standard of treatment in PD. As the disease progresses oral medication only to a certain degree can control symptoms and upcoming fluctuations and dyskinesias will dominate. Continuous dopaminergic stimulation is thought to be a basic principle in the optimal treatment of these problems. There are presently two approved drugs for intestinal levodopa infusion; (Duodopa® and Lecigon®) and one for subcutaneous foslevodopa infusion (Produodopa®).

The development of a carboxymethyl-cellulose gel with levodopa/carbidopa (Duodopa®, AbbVie, USA) in the 1990s in Uppsala made intraduodenal infusion of levodopa/carbidopa possible. The concentration of levodopa is 20 mg/ml, with a cassette containing 100 ml which is a sufficient daily total dose for most patients. The cassette is attached to a portable pump (CADD-Legacy-Duodopa, Smiths Medical, MN, USA).

Lecigon® (Lobsor, Sweden) was developed in Uppsala in the late 2010s and includes the cathecol-O-methyltransferase inhibitor entacapone, 20 mg/ml, in the gel. The gel is contained in syringes of 47 ml, and is administered via a portable pump (Cane, Italy). The addition of entacapone increases the bioavailability of levodopa and thereby allows the use of lower doses and volumes of levodopa and carbidopa. Thus, the addition of entacapone in Lecigon® enables the use of a smaller primary container as well as a smaller and lighter pump. Lecigon® is approved by the medical authorities in Sweden, since 2018, and in Denmark, Finland and Norway since 2019.

The tube of the cassette/syringe is connected to a PEG (Percutaneous Endoscopic Gastrostomy) tube, containing a smaller bore intestinal tube, where the end of the tube is placed in the duodenum or the proximal jejunum, after Treitz' ligament. In this position administration of Duodopa®/Lecigon® is given continuously allowing immediate absorption of the medication across the intestinal mucosa.
It is possible to switch directly from Duodopa® to Lecigon® pump treatment, or vice versa, using the same PEG tube, but an ENFit-adapter is required for Lecigon®.
The clinical response of this type of levodopa administration can be tested before establishing a PEG, by temporary Duodopa/Lecigon treatment through a naso-jejunal tube allowing clinicians to evaluate the degree of response and possible side effects.

Produodopa® (AbbVie, USA) is the first formulation for subcutaneous levodopa delivery. It contains foslevodopa and foscarbidopa, i.e. phosphorylated levodopa/carbidopa, and was approved in Europe in 2023. Foslevodopa and foscarbidopa are prodrugs and are used for subcutaneous infusion over 24 hours. One randomized controlled trial is available with

similar efficacy of response fluctuations compared to DBS and intestinal levodopa infusion. Available data for long-term therapy or for clinical practice are limited so far.

General indications

- Treatment of levodopa-responsive PD in the advanced and complicated phase, with motor fluctuations, “off”-periods and/or hyper-/dyskinesias despite optimized oral/patch/injection treatment
- A condition with sufficiently severe symptoms to necessitate initiation of advanced treatment.

Special conditions that may be successfully treated

- When treatment of advanced symptoms by means of DBS is contraindicated, ineffective or otherwise unsuitable
- When treatment of advanced symptoms by means of continuous subcutaneous infusion with apomorphine is contraindicated, ineffective or otherwise unsuitable
- Elderly people, as there is no strict age limit
- Duodopa/Lecigon treated patients with a severe sleep disturbance that is unresolved by oral therapy, as the patient may benefit by extending the pump treatment to 24 hours. Produodopa is designed for 24 hour-infusion.
- Patients with mild to moderate Parkinson dementia if support from a spouse or caregiver is permitted and the patient does not manipulate the infusion equipment.

Secondary prerequisites that must be taken into consideration when evaluating the patient for treatment.

- The patient’s level of independence and general condition
- The patient’s social situation, relation to spouses and other relatives and general living conditions
- Care-giver assistance to cognitively impaired patients may be required in the daily handling of the equipment, e.g. starting and stopping the pump.

A well-planned setting in terms of logistics and support with regular, scheduled checkups is necessary for successful treatment. A dedicated experienced Parkinson team at a university hospital or Movement Disorder Clinic should be involved in initiation and follow-up of treatment. Ideally, specialized units and PD nurses should be available for training, consultation and general education of patients and caregivers.

Each patient should have a tailor-made "optimal" peroral treatment “rescue” schedule in case of interruptions in the infusion due to problems with the pump or tubing.

Contraindications

- Hypersensitivity to levodopa or carbidopa (or entacapone in Lecigon)
- Narrow angle glaucoma
- Serious liver and kidney disease
- Severe heart failure
- Acute myocardial infarction
- Severe cardiac arrhythmias
- Recent or acute stroke
- Contraindications for adrenergic effects; pheochromocytoma, hyperthyroidism, Cushing's syndrome
- Other contraindications for abdominal surgery (regarding Duodopa/Lecigon)
- Other contraindications for subcutaneous infusion (regarding Produodopa)

Relative contraindications

- Significant dementia, which makes the treatment more difficult to perform and leads to less favorable outcomes
- Patients with non-compliance or no care-giver support
- Patients with levodopa-resistant Parkinsonism
- Ongoing treatment with unselective MAO inhibitors or selective MAO-A inhibitors (to be withdrawn at least two weeks before the start of treatment)
- Therapy resistant psychosis due to dopaminergic medication
- Polyneuropathy.
- Previous malignant-like neuroleptic syndrome and/or non-traumatic rhabdomyolysis
- Suspected melanoma

Pre-treatment period

After considering a patient for levodopa infusion treatment, the patient and also the spouse must be adequately informed about the treatment and the expected results of treatment. The patient must also be given information about the surgical procedures of the PEG operation or the subcutaneous infusion system. Information about long-term experiences with Duodopa/Lecigon/Produodopa and the circumstance of living with a pump and the complications must be shared. There must be an agreement with informed consent to treatment. The patient should be given a schedule of the procedures during the stay in the neurological department. Selected blood samples should be taken in advance. Neurophysiology should be considered in risk-patients concerning polyneuropathy.

Start of Duodopa/Lecigon treatment

A temporary naso-jejunal tube may be applied. The initial dosage of the levodopa/carbidopa gel or the levodopa/entacapone/carbidopa gel is calculated on the basis of the previous dose of oral levodopa or levodopa equivalents. Both morning dose and infusion rate are titrated and fine-tuned over the course of a few days in order to find the optimal dose that produces a continuous "on" state without troublesome dyskinesia. The infusion rate can be adjusted in small increments of for example 0.2 ml/h.

After titrating an individual morning bolus, usually 1-10 ml levodopa/carbidopa or levodopa/entacapone/carbidopa gel is used to rapidly achieve steady-state, after which the concentration can be kept constant by the individualized infusion rate. The continuous daily levodopa dose is normally between 20-120 ml/day levodopa/carbidopa or levodopa/entacapone/carbidopa intestinal gel. An individually set extra bolus dose on demand is possible (normally, 10-40 mg levodopa). After a few days of treatment, the clinical effect and possible side effects are evident. If indication, the permanent PEG-tube can then be established.
Normally, the total length of admission for levodopa pump start is less than 1.5 weeks.

The patient is discharged from the hospital a few days after the PEG surgery, when an optimal dose is found, and the patient or a relative or a caregiver has learnt how to operate the infusion system. The titration period may continue at home using telemedicine. Follow-up should be carried out by a PD nurse or at an outpatient clinic visit a few weeks later, but more frequent visits may be needed. The dosage may need to be adapted after some weeks to months, probably due to long-term plasticity changes in the brain. The levodopa infusion may be used as monotherapy, but can be combined with other drugs, especially for treatment of non-dopaminergic symptoms. Initially the treatment is only administered during the day, and a long-acting levodopa preparation and/or peroral/patch dopamine agonist is given at bedtime.

Start of Produodopa treatment
Initiation of subcutaneous foslevodopa infusion can be performed in an outpatient setting, or by home-titration. Adequate training of handling pump and infusion system is required.

Special circumstances
Continuous administration of the levodopa gel smoothens plasma concentrations, which probably accounts for the clinical effect on fluctuations. Improvements can be seen in dyskinesias and dopaminergic side effects in spite of an unchanged or even increased total daily levodopa dose. Psychotic side effects due to dopaminergic stimulation may improve on infusion with levodopa. Also other non-motor symptoms such as sleep/fatigue, pain gastrointestinal and urinary problems together with sexual dysfunction may improve after switching to pump therapy.
Duodenal levodopa infusion for long-term Deep Brain Stimulation-refractory symptoms as axial symptoms can be used in advanced PD.

Pharmacological side effects
The adverse events of the levodopa infusions are the same as in oral medication, and should be handled in accordance to the same principles, as when dealing with oral treatment adverse events.

Polyneuropathy, sometimes severe, has been reported in patients on Duodopa. It is still unclear if this relates to the Duodopa treatment, to L-dopa treatment in general or to the disease process. These reported cases are generally of type sensorimotor polyneuropathy with both subacute and chronic onsets, often associated with vitamin B12 deficiency. They have often responded to vitamin supplementation, often without need for Duodopa cessation. It is advisable to monitor vitamin B6/B12/Folic acid status, by analysing S-Homocystein, before and after patients start a levodopa infusion (after 1, 3 and 6 months and thereafter annually). It is also important to be vigilant for signs of polyneuropathy. Another alternative is to substitute both vitamine B6, B12 and folic acid as a routine but S-Homocystein must be monitored as above.

Some patients experience weight loss due to levodopa treatment. It is therefore important to monitor the weight at each clinical control and if weight loss contact a dietician for prescription of energy subsidies.

Some patients report long-term sedation due to levodopa treatment. In addition, sudden sleep episodes (the sudden onset of sleep without prior tiredness or warning signals) can occur as in other PD treatments. Patients treated with levodopa infusions should therefore be informed to take care when driving or operating machines.

Diarrhea is a well-known potential side-effect from oral entacapone, and present experience is that this risk is the same (around 10%) when using Lecigon®.

If bothersome hyperkinesias to the levodopa pump treatment, 50 mg peroral Ongentys® (opicapone), a new COMT-inhibitor, at nighttime after stopping the pump, can be tried, if the continuous levodopa dose on the pump at the same time is reduced.

Technical issues with intestinal infusion
The most frequent problems with levodopa infusion relate to technical aspects of the therapy such as dislocation of the small intestinal catheter, which occurs in 3-4 % of patients. These problems are now less prominent than in the beginning of the treatment with Duodopa® because of technical improvements. Displacement of the catheter into the stomach, may lead

to reappearance of the fluctuating symptoms and decline in the efficacy of the medication. In such cases the catheter position must be corrected under radiographic control.

The intestinal catheter may also become blocked or kinked. Blockage can usually be eliminated by flushing the catheter with tap water, or introduction of a guide wire. Kinks may need to be eliminated by repositioning the catheter. In rare cases the PEG or the intestinal catheter can become disconnected from the coupling and may be detached in the stomach or small intestine. If the inner catheter becomes disconnected it normally exits with defecation without any problem. A broken PEG entails a risk of complications, such as perforation of the stomach or intestine, which can necessitate open surgery. In such a case a gastroenterologist must be consulted.

If persistent abdominal pain, a gastroscopy should be performed. Some complications are not visible on CT. If signs of gastrointestinal infection, antibiotics should be given according to the clinical condition and local guidelines.

The stoma usually heals without significant complications. However, there may be abdominal pain, infection and discharge of gastric juice shortly after the operation. In rare cases bacterial peritonitis occurs in connection with the PEG application (in 1% of patients). The most common chronic local complications are secretion and the formation of hypertrophic granulation tissue. Local infection around the stoma is treated with soap and water, or disinfectant, and antibiotic therapy is rarely necessary. Hypertrophic granulation can be treated with class 1-3 steroid ointment.

Technical problems may often require immediate contact by telephone or visit to an outpatient clinic to be solved. Patients must therefore be able to have access to an immediate contact to a PD nurse or department.

Technical issues with subcutaneous infusion
Skin reactions, including infections, seem to be the most frequent side effects. It is probably advisable to change infusion site daily. Due to the limited clinical experience with this treament, no specific consensus can be reported yet.

Efficacy variables from treatment (mainly based on data from studies on Duodopa®)

- When responding to the levodopa/carbidopa or levodopa/entacapone/carbidopa treatments, motor symptoms, fluctuations and dyskinesias are alleviated to a large degree
- Some non-motor symptoms are often effectively treated and become less prominent
- Quality of life and quality of sleep have shown to be improved
- Levodopa/carbidopa treatment can be administered with equal beneficial efficacy for a variable time range up to 24 hours. 24-hours treatment may require different dosages during daytime and at nights (normally 2/3 of the daytime dose at nights).

There is no evidence of the development of tolerance to daytime levodopa/carbidopa or levodopa/entacapone/carbidopa gel therapy. On the contrary, the dose can be reduced in many patients after the first few weeks or months. The situation is less clear-cut with 24-hour therapy, as there have been sporadic reports of the possible development of tolerance that was reversible when 16-hour therapy was resumed. Most patients undergoing 24-hour therapy do not, however, show any signs of tolerance.

Long term experience with Duodopa® treatment is good with an unchanged efficacy and tolerability to treatment. A typical length of treatment is 8 years, and for many patients this becomes a life-long therapy. The experience of Lecigon® is much shorter, starting in Sweden, in 2019.

End of treatment
In the case where the patient develops severe dementia, advanced malignancy or other serious medical conditions, where the patient is not benefiting from treatment, has no active motor ability and perhaps no ability to communicate, termination of levodopa pump treatment should be considered. Ethical aspects in decision making must be taken into consideration. Patients should after termination of treatment, be offered optimal standard oral treatment, palliative care and regular consultations.

Socioeconomics
Levodopa pump treatments are rather expensive, so the total cost for society as well as the benefit for the patient must be taken into consideration, when evaluating a patient for the treatment. Factors that can contribute to make the therapy cost-effective:

- Significant improvement in motor ability with reductions in fluctuations and hyperkinesias
- Independence of gait and mobility
- Significant benefit in non-motor symptoms
- Significant increase in patient autonomy and independency measurable with standard ADL scores
- Care-giver burden will be reduced, since independency in patients will improve
- Aspects of quality of life for the patient as for the spouses/relatives must be considered as an operational measure for treatment
- Nursing costs for the care of the patient will be reduced. Need for nursing homes reduced
- The reduction in total costs due to withdrawal of the oral medication must be in calculated
- Different possible therapy strategies must be considered.

Name of the products
Duodopa® (levodopa/carbidopa enteral gel, 20mg/ml+5 mg/ml).
Lecigon® (levodopa/carbidopa/entacapone enteral gel, 20mg/ml+5 mg/ml+20mg/ml)
Produodopa® (foslevodopa/foskarbidopa solution for infusion, 240 mg/ml + 12 mg/ml)

References

1. Shoulson I, Glaubiger GA, Chase TN. On-off response. Clinical and biochemical correlations during oral and intravenous levodopa administration in parkinsonian patients. Neurology 1975;25: 1144-48.

2. Quinn N, Marsden CD, Parkes JD. Complicated response fluctuations in Parkinson's disease: response to intravenous infusion of levodopa. Lancet. 1982;2:412-15.

3. KurIan R, Rubin AJ, Miller C, Rivera-Calimlim L, Clarke A, Shoulson I. Duodenal delivery of levodopa for on-off fluctuations in parkinsonism: preliminary observations. Ann Neurol 1986;20:262-5.

4. Nilsson D, Hansson LE, Johansson K, Nystrom C, Paalzow L, Aquilonius SM. Long-term intraduodenal infusion of a water based levodopa-carbidopa dispersion in very advanced Parkinson's disease. Acta Neurol Scand 1998; 97:175-83
   Evidence Level: 4

5. Nilsson D, Nyholm D, Aquilonius SM. Duodenal levodopa infusion in Parkinson's disease-long-term experience. Acta Neurol Scand 2001;104:343-48.
   Evidence Level: 4

6. Stocchi F, Vacca L, Ruggieri S, Olanow CW. Intermittent vs continuous levodopa administration in patients with advanced Parkinson disease: a clinical and pharmacokinetic study. Arch Neural 2005; 62: 905-10

7. Antonini A. Continuous dopaminergic stimulation - From theory to clinical practice. Parkinsonism Relat Disord. 2007 Volume 13, Supplement 1, September 2007, Pages S24-S28

8. Samanta J, Hauser RA. Duodenal levodopa infusion for the treatment of Parkinson's disease. Expert Opin Pharmacother. 2007; 8(5):657-64.

9. Odin P, Wolters E, Antonini A. Continuous dopaminergic stimulation achieved by duodenal levodopa infusion. Neurol Sci. 2008 Dec;29 Suppl 5:S387-8.

10. Fernandez HH, Odin P. Levodopa-carbidopa intestinal gel for treatment of advanced Parkinson's disease. Curr Med Res Opin. 2011 May;27(5):907-19.

11. Hilker R, Antonini A, Odin P. What is the best treatment for fluctuating Parkinson's disease: continuous drug delivery or deep brain stimulation of the subthalamic nucleus? J Neural Transm. 2011 Jun;118(6):907-14.

12. Kurth MC, Tetrud JW, Tanner CM, et al. Double-blind, placebo-controlled, crossover study of duodenal infusion of levodopa/carbidopa in Parkinson's disease patients with "on-off" fluctuations. Neurology 1993 ;43: 1698-1703.
    Evidence Level: 1b

13. Olanow CW, Schapira AHV, Rascol O. Continuous dopamine receptor stimulation in early Parkinson’s disease. Trends in Neurosciences 2000;23(10) (Supl. Basal Ganglia, Parkinson’s disase and levodopa therapy) S117-S126.

14. Nyholm D, Askmark H, Gomes- Trolin C, Knutson T, Lennemas H, Nystrom C, Aquilonius SM. Optimizing levodopa pharmacokinetics: intestinal infusion versus oral sustained-release tablets. Clin Neuropharmacol 2003 May-Jun;26(3):156-63.
Evidence Level: 1b

15. Nyholm D, Aquilonius SM. Levodopa infusion therapy in Parkinson disease: state of the art in 2004. Clin Neuropharmacol 2004;27:245-56.
Evidence Level: 5

16. Nyholm D, Nilsson Remahl AI, Dizdar N, Constantinescu R, Holmberg B, Jansson R, Aquilonius SM, Askmark H. Duodenal levodopa infusion monotherapy vs oral polypharmacy in advanced Parkinson's disease. Neurology 2005;64:216-23.
Evidence Level: 2b

17. Nutt JG. Continuous dopaminergic stimulation:is it the answer to the motor complications of levodopa? Mov disord 2007;32:1-9

18. Volkmann J, Albanese A, Antonini A, Chaudhuri KR, Clarke CE, de Bie RM, Deuschl G, Eggert K, Houeto JL, Kulisevsky J, Nyholm D, Odin P, Ostergaard K, Poewe W, Pollak P, Rabey JM, Rascol O, Ruzicka E, Samuel M, Speelman H, Sydow O, Valldeoriola F, van der Linden C, Oertel W. Selecting deep brain stimulation or infusion therapies in advanced Parkinson's disease: an evidence-based review. J Neurol. 2013 Jan 5.
Evidence level: 3a

19. 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 Committees. (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, 1133-44.
Evidence level 5

20. Antonini A, Chaudhuri KR, Martinez-Martin P, Odin P. Oral and infusion levodopa-based strategies for managing motor complications in patients with Parkinson's disease. CNS Drugs. 2010 Feb;24(2):119-29.

21. Meiler B, Andrich J, Muller T. Rapid switch from oral antiparkinsonian combination drug therapy to duodenal levodopa infusion. Mov. Disord. 2008;23:145-46

22. Syed N, Mmphy J, Zimmerman T Jr, Mark MH, Sage n. Ten years' experience with enteral levodopa infusions for motor fluctuations in Parkinson's disease. Mov Disord 1998;13:336-38.

23. Nyholm D, Lewander T, Johansson A, LeWitt P A, Lundqvist C, Aquilonius SM. Intraduodenal infusion of a gel suspension of levodopa/carbidopa, Duodopa, in advanced Parkinson’s disease: safety, tolerability, efficacy and dosage. Mov, disord. (2004) 19; S177
vidence Level: 4

24. Nyholm D, Jansson R, Willows T, Remahl IN. Long-term 24-hour duodenal infusion of levodopa: outcome and dose requirements. Neurology 2005;65:1506-7
Evidence Level: 4

25. Chapuis S, Ouchchane L, Metz O, Gerbaud L, Durif F. Impact of the motor complications of Parkinson's disease on the quality of life. Mov Disord 2005;20:224-30

26. Chaudhuri KR, Healy DG, Schapira AH. Non-motor symptoms of Parkinsons's disease: diagnosis and management Lancet Neurol 2006;5:235-45

27. Antonini A, Isaias IV, Canesi M, Zibetti M, Mancini F, Manfredi L, Dal Fante M, Lopiano L, Pezzoli G. Duodenal levodopa infusion for advanced Parkinson's disease: 12-month treatment outcome. Mov Disord. 2007 Jun 15;22(8):1145-49.
Evidence Level: 3b

28. Antonini A, Mancini F, Canesi M. Duodenal levodopa infusion improves quality of life in advanced Parkinson's disease. Neurodegener Dis 2008;5:244-46
Evidence Level: 4

29. Eggert K., Schrader C., Hahn M., Stamelou M., Rüssmann A., Dengler R., Oertel W., Odin P. (2008) Continuous jejunal levodopa infusion in patients with advanced Parkinson´s disease: Practical aspects and outcome of motor and non-motor complications. *Clininical Neuropharmacology*, 31, 151-66
Evidence Level: 4

30. Nyholm D, Levander T, Johansson A, LeWitt PA, Lundquist C Aquilonius S-M. Enteral levodopa/carbidopa infusion in advanced Parkinson disease: long-term exposure. Clin Neuropharmocol 2008;31:63-73.
Evidence Level: 4

31. Nyholm D, Constantinescu R, Holmberg B, Dizdar N, Askmark H. Comparison of apomorphine and levodopa infusions in four patients with Parkinson's disease with symptom fluctuations. Acta Neurol Scand. 2009;119(5):345-8.
Evidence Level: 3b

32. Elia AE, Dollenz, Soliveri P, Albanese A. Motor features and response to oral levodopa in patients with Parkinson's disease under continuous dopaminerg infusion or deep brain stimulation. Eur J Neurol 2012;19(1):76-83.
Evidence Level: 3b

33. Honig H, Antonini A, Martinez-Martin P, Forgacs, Faye GC, Fox T, Fox K, Mancini F, Canesi M, Odin P, Dhaudhuri KR. Intrajejunal levodopa infusion in Parkinson's disease: a pilot multicenter study of effects on nonmotor symptoms and quality of life. Mov Disord 2009 under publication
Evidence Level: 3b

34. Reddy P, Martinez-Martin P, Rizos A, Martin A, Faye GC, Forgacs I, Odin P, Antonini A, Chaudhuri KR. Intrajejunal levodopa versus conventional therapy in Parkinson disease: motor and nonmotor effects. Clin Neuropharmacol. 2012 Sep-Oct; 35(5):205-7.
Evidence level: 3b

35. Olanow C.W., Kieburtz K., Odin P., Espay A.J., Standaert D.G., Fernandez H.H., Vanagunas A., Othman A.A., Widnell K.L., Robieson W.Z., Pritchett Y., Chatamra

K., Benesh J., Lenz R.A., Antonini A.; LCIG Horizon Study Group. (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, 141-9.
Evidence level 1b

36. Martinez-Martin P, Reddy P, Katzenschlager R, Antonini A, Todorova A, Odin P, Henriksen T, Martin A, Calandrella D, Rizos A, Bryndum N, Glad A, Dafsari HS, Timmermann L, Ebersbach G, Kramberger MG, Samuel M, Wenzel K, Tomatschger V, Storch A, Reichmann H, Pirtosek Z, Trost M, Svenningsson P, Palhagen S, Volkmann J, Chaudhuri KR.
EuroInf: A Multicenter Comparative Observational Study of Apomorphine and Levodopa Infusion in Parkinson's Disease. Mov Disord. 2015 Apr;30(4):510-6.
Evidence level 3b

37. Fernandez HH, Standaert DG, Hauser RA, Lang AE, Fung VS, Klostermann F, Lew MF, Odin P, Steiger M, Yakupov EZ, Chouinard S, Suchowersky O, Dubow J, Hall CM, Chatamra K, Robieson WZ, Benesh JA, Espay AJ. (2015) Levodopa-carbidopa intestinal gel in advanced Parkinson's disease: Final 12-month, open-label results. Mov Disord. 30, 500-9.
Evidence level 2b

38. Antonini A, Yegin A, Preda C, Bergmann L, Poewe W. Global long-term study on motor and non-motor symptoms and safety of levodopa-carbidopa intestinal gel in routine care of advanced Parkinson's disease patients; 12-month interim outcomes. Parkinsonism Relat Disord. 2015;21(3): 231-5.
Evidence level 2b

39. Lang AE, Rodriguez RL, Boyd JT, Chouinard S, Zadikoff C, Espay AJ, Slevin JT, Fernandez HH, Lew MF, Stein DA, Odin P, Fung VS, Klostermann F, Fasano A, Draganov PV, Schmulewitz N, Robieson WZ, Eaton S, Chatamra K, Benesh JA, Dubow J. (2015) Integrated safety of levodopa-carbidopa intestinal gel from prospective clinical trials. Mov Disord. 31(4), 538-46.
Evidence level 2a

40. Todorova A, Samuel M, Brown RG, Chaudhuri KR. Infusion therapies and development of impulse control disorders in advanced Parkinsons disease: clinical experience after 3 years follow-up. Clin Neuropharm. 2015;38(4):132-4.
Evidence level 4

41. Devigili G, Rinaldo S, Lettieri C, Eleopra R. Levodopa/carbidopa intestinal gel therapy for advanced Parkinson Disease: An early toxic effect for small nerve fibers? Muscle Nerve 2016 Nov;54(5):970-2.

42. Willows T, Diztar N, Nyholm D, Widner H, Grenholm P, Schmiauke U, Urbom A, Groth K, Larsson J, Permert J, Kjellander S. Initiation of Levodopa-Carbidopa Intestinal Gel Infusion Using Telemedicine (Video Communication System) Facilitates Efficient and Well-Accepted Home Titration In Patients with Advanced parkinson's Disease. J Parkinsons Dis. 2017;7(4):719-728.

43. Rispoli V, Simioni V, Capone JG, Golfré Andreasi N, Preda F, SetteE, Tugnoli V, Sensi M. Peripheral neuropathy in 30 duodopa patients with vitamins B supplementation. Acta Neurol Scand. 2017 Dec;136(6):660-667.
Evidence Level 4.

44. Ezat B, Pihlstrøm L, Aasly J, Tysnes OB, Egge A, Dietrichjs E. Use of advanced therapies for Parkinson's disease in Norway. Tidsskr Nor Laegeforen. 2017 May 2;137(9):619-623.
Evidence Level 4.

45. Regidor I, Benita V, Del Alamo de Pedro M, Ley L, Martinez Castrillo JC. Duodenal Levodopa Infusion for Long-Term Deep Brain Stimulation-Refractory Symptoms in Advanced Parkinson Disease. Clin Neuropharmacol 2017 May/Jun;40(3):102-197.
Evidence level 4.

46. Senek M, Nielsen EI, Nyholm D. Levodopa-entacapone-carbidopa intestinal gel in Parkinson's disease: A randomized crossover study. Mov Disord. 2017;32(2):283–286.
Evidence level 1b.

47. Öthman M, Widman E, Nygren I, Nyholm D. Initial Experience of the Levodopa-Entacapone-Carbidopa Intestinal Gel in Clinical Practice. J Pers Med. 2021 Mar 31;11(4):254.
Evidence level 4.

48. Rosebraugh M, Stodtmann S, Liu W, Facheris MF. Foslevodopa/foscarbidopa subcutaneous infusion maintains equivalent levodopa exposure to levodopa-carbidopa intestinal gel delivered to the jejunum. Parkinsonism Relat Disord. 2022 Apr;97:68-72.
Evidence level 1b

49. Soileau MJ, Aldred J, Budur K, Fisseha N, Fung VS, Jeong A, Kimber TE, Klos K, Litvan I, O'Neill D, Robieson WZ, Spindler MA, Standaert DG, Talapala S, Vaou EO, Zheng H, Facheris MF, Hauser RA. Safety and efficacy of continuous subcutaneous foslevodopa-foscarbidopa in patients with advanced Parkinson's disease: a randomised, double-blind, active-controlled, phase 3 trial. Lancet Neurol. 2022 Dec;21(12):1099-1109.
Evidence level 1b

Level of Evidence	Type of Study
1a	Systematic review of (homogeneous) randomized controlled trials
1b	Individual randomized controlled trials (with narrow confidence intervals)
2a	Systematic review of (homogeneous) cohort studies of "exposed" and "unexposed" subjects
2b	Individual cohort study / low-quality randomized control studies
3a	Systematic review of (homogeneous) case-control studies
3b	Individual case-control studies
4	Case series, low-quality cohort or case-control studies
5	Expert opinions based on non-systematic reviews of results or mechanistic studies