Infusion therapies for the treatment of advanced Parkinson's disease

In advanced Parkinson's disease, infusion therapies, including continuous levodopa-carbidopa intestinal gel, continuous levodopa-entacapone-carbidopa intestinal gel and continuous subcutaneous apomorphine infusion, are efficacious and safe treatment options. Infusion therapies are able to significantly reduce time in «off» and time in «on» without troublesome dyskinesia and to improve the quality of life of patients. However, they are not without adverse effects that should be closely monitored and which mostly depend on proper handling of the pump systems. Adequate support and education of patients and caregivers are essential. There is no high quality evidence comparing the different infusion therapies and the choice between the various options is individualized and dependent on the patient's profile and preferences.

Foto: zVg

Andreia D. Magalhães

Foto: zVg

M. Lenard Lachenmayer

Foto: zVg

Paul Krack

Foto: zVg

Ines Debove

Andreia D. Magalhães[1], M. Lenard Lachenmayer[1], Paul Krack[1] and Ines Debove[1]

Introduction

Device-assisted procedures are efficacious and safe treatment options for advanced Parkinson's disease (PD) improving both motor and non-motor symptoms refractory to the best oral treatment and contributing to a better quality of life of patients (1).

As PD progresses, the accumulating loss of nigrostriatal dopaminergic neurons leads to an increasingly impaired ability to store dopamine. At this advanced stage, patients start to experience fluctuating symptoms, which improve and worsen in cycles mimicking the half-life of the orally administered levodopa before its conversion to dopamine (2). Patients developing motor complications that cannot be adequately managed with oral/transdermal dopaminergic medication should be referred to specialized multidisciplinary movement disorders clinics for assessment of eligibility for device-assisted treatments. These device-assisted therapies include deep brain stimulation (DBS) and infusion therapies. Whereas DBS can be considered in PD with early motor fluctuations, the infusion therapies are reserved for refractory fluctuations (3). The «5-2-1» rule (5 intakes of oral levodopa, 2 hours of «off» symptoms and 1 hour of dyskinesia per day) can be used to screen candidates for advanced therapies (4). In this review, we will focus on infusion therapies, which include continuous levodopa-carbidopa intestinal gel (LCIG), continuous levodopa-entacapone-carbidopa intestinal gel (LECIG), continuous subcutaneous apomorphine infusion (CSAI), subcutaneous levodopa-carbidopa and subcutaneous foslevodopa-foscarbidopa infusions (2) (the latter two not being currently available in Switzerland).

The rationale for infusion therapies is to deliver a continuous plasma level of dopaminergic medication in order to decrease time in «off» and improve dyskinesia (2). Generally, infusion therapies do not improve cognition (except for cognitive side effects of high doses of oral dopaminergic medication) or levodopa-resistant axial symptoms such as «on» freezing of gait and postural instability. Patients, who are thought to be candidates for infusion therapies, should be assessed in specialized multidisciplinary movement disorders centers in order to confirm the diagnosis of PD, review the previous dopaminergic medication trials, assess the improvement of symptoms with dopaminergic medication and evaluate cognitive and psychiatric impairment. Importantly, patients and caregivers should also receive education and counselling about the different treatment options, their efficacy, side effects and management in order to ensure realistic expectations of the treatment.

Intestinal Gel Infusion Therapies

Continuous Levodopa-Carbidopa Intestinal Gel Infusion

Efficacy:

Levodopa-carbidopa intestinal gel (LCIG) is an enteral suspension delivered as a continuous infusion through a percutaneous gastrostomy with jejunal tube extension (PEG-J). The first evidence for the efficacy of LCIG in the treatment of motor complications in PD came from a randomized placebo-controlled clinical trial comparing LCIG to oral levodopa-carbidopa for 12 weeks in which both patients' groups underwent gastrojejunos-

[1] Department of Neurology, Bern University Hospital and University of Bern, Bern, Switzerland.

tomy before treatment allocation. LCIG decreased «off» time and increased «on» time without troublesome dyskinesia compared to oral levodopa-carbidopa (5). Specifically in patients with dyskinesia, LCIG treatment was able to reduce not only the duration but also the severity of dyskinesia improving the quality of life of patients (6). Besides its effect on motor symptoms in PD, LCIG treatment was also able to improve non-motor symptoms such as sleep, mood and fatigue thereby also improving the quality of life of patients (7).

Safety:

LCIG is mostly well tolerated and has a low withdrawal rate of about 25% (8). Adverse effects are common, though they are primarily mild in nature. These adverse events are predominantly linked to the percutaneous gastrojejunostomy with reports indicating that they occur in approximately 60–90% of patients (5, 9, 10) with 10-20% being serious adverse events (9, 10). Device-related complications can arise during the insertion procedure and may include skin infection, peritonitis, intestinal tube dislocation and pump malfunction (5, 9) (*Figure 1*). Additionally, axonal polyneuropathy has been reported in 5–10% of patients (11, 12). It has been postulated that levodopa can interfere with B vitamins metabolization and thereby increase the risk of polyneuropathy in PD patients being treated with higher levodopa daily dose or high serum homocysteine levels (11) and low serum vitamin B12 and B6 levels (12).

Practical Considerations:

LCIG is administered using a portable pump strapped around the waist or neck and connected to a PEG-J tube. The available LCIG pump in Switzerland is the Duodopa® pump (*Figure 2*).

Before LCIG installation, patients should be screened for polyneuropathy with electrophysiological neuropathy screening and baseline levels of vitamins B6 and B12 and folic acid (13). LCIG therapy is initiated in an inpatient setting with an initial nasoduodenal test phase for about 5–8 days to evaluate symptom response to treatment. For selected cases such as patients who have already underwent a levodopa challenge test with adequate response and in which a PEG is deemed as necessary for long-term feeding in cases of severe dysphagia, the nasoduodenal test phase can be bypassed. When starting LCIG therapy, the total oral levodopa daily equivalent dose is replaced by LCIG total dose. LCIG infusion is administered as a morning bolus and a continuous maintenance dose. In most cases, a 16 hours a day infusion is sufficient to improve symptoms, but in cases of severe «off» symptoms during the night, LCIG can also be administered overnight (24 hours a day). Extra boluses can also be programmed to further improve symptoms if the continuous maintenance dose in insufficient. The handling of the pump system requires training of the patient and/or caregivers, which includes the daily care of the stoma and the daily flushing of the tube as well as the refrigeration of the drug before use. Patients and caregivers should also be instructed to resume previous oral dopaminergic medication in case of a pump malfunction lasting more than 90 minutes. The pharmaceutical company commercializing the Duodopa® pump offers a hotline for technical support.

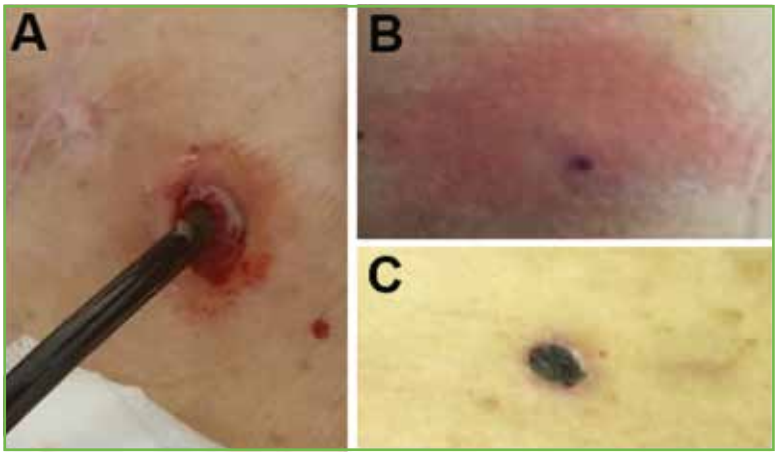

Figure 1: Complications of infusion therapies. A: Local cellulitis and granulomatous tissue at PEG-J site as complication of LCIG. B: Local cellulitis as complication of CSAI. C: Necrotic ulcer as complication of CSAI.
Abbreviations: PEG-J: percutaneous gastrostomy with jejunal tube extension, LCIG: levodopa-carbidopa intestinal gel, CSAI: continuous subcutaneous apomorphine infusion. (Fotos: Universitätsklinik für Neurologie, Inselspital Bern)

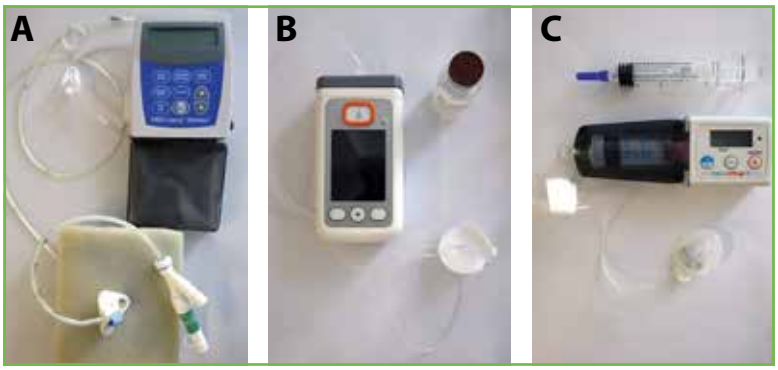

Figure 2: Examples of infusion portable pumps. A: Duodopa® pump. B: D-mine®/ Dacepton® pump. C – APO-GO® pump. (Fotos: Universitätsklinik für Neurologie, Inselspital Bern)

Continuous Levodopa-Entacapone-Carbidopa Intestinal Gel infusion

Efficacy:

Levodopa-entacapone-carbidopa intestinal gel (LECIG) is a novel infusion therapy in which the cathecol-O-methyltransferase (COMT) inhibitor entacapone was added thereby inhibiting the degradation of levodopa to 3-O-methyldopa and increasing the bioavailability of levodopa and decreasing the dose of levodopa needed to treat symptoms (14).

An initial study showed that combining LCIG with oral entacapone was able to reduce the LCIG dose by about 20% while maintaining motor improvement (15) which led to the development of LECIG infusion therapy. Evidence for LECIG treatment efficacy and safety is limited to an open-label crossover trial comparing levodopa exposure in patients with advanced PD treated to LCIG and switched to LECIG, which showed that levodopa dose could be reduced with LECIG without lowering levodopa exposure (15). LECIG is currently only approved in a limited number of European countries and a large multicenter prospective long-term observational

Table 1:
Comparison of device-assisted therapies for Parkinson disease according to different patient characteristics

	Is the patient a candidate for this device-assisted therapy?		
Characteristic	**Deep Brain Stimulation**	**Continuous Subcutaneous Apomorphine Infusion**	**Levodopa-Carbidopa Intestinal Gel Infusion**
Secondary parkinsonism or atypical parkinsonian disorders	No	No	No
Age higher than 70 years-old	Depending on clinical profile	Yes	Yes
Motor fluctuations	Yes	Yes	Yes
Refractory PD tremor	Yes	No	No
Moderate cognitive impairment	No	Yes	Yes
Severe dementia	No	No	No
Severe psychosis and hallucinations	No	No	No
Impulse control disorders	Yes	Yes	Yes
Polyneuropathy	Yes	Yes	No
Frailty/high risk for surgical intervention	No	Yes	Depending on clinical profile

study (ELEGANCE study) is currently ongoing to study the long term effects of LECIG on motor outcomes.

Safety:
Evidence on efficacy, adverse events and clinical experience with LECIG are still limited. Adverse events appear to be similar to LCIG with the additional side effects of entacapone which can frequently induce diarrhea.

Practical Considerations:
The currently available LECIG pump system in Switzerland is the Lecigon® pump. As LCIG, LECIG is delivered as a continuous infusion through a percutaneous gastrojejunostomy tube but because a lower dose of drug is usually needed, the portable pump is smaller. When switching from LCIG to LECIG, the continuous maintenance dose should be reduced by about 30% (2). Most clinicians perform LECIG installation and follow-up similarly to LCIG. A trial of oral entacapone-levodopa (Stalevo®) is recommended to ensure tolerance to the drug formulation.

Subcutaneous Infusion Therapies

Continuous Subcutaneous Apomorphine Infusion (CSAI)

Efficacy:
Apomorphine is a non-narcotic derivate of morphine with a highly potent dopaminergic agonist activity and the only other dopaminergic drug with an efficacy comparable to levodopa. Nowadays apomorphine is used for the treatment of Parkinson's disease, but its first use in the late 1800s was in the treatment of poisoning due to its strong emetic effect (16). Only in the 1950s, apomorphine was first used for the treatment of PD, particularly tremor and rigidity. Due to a strong first-pass effect, apomorphine has a poor oral bioavailability and, therefore, needs to be administered subcutaneously. It is also lipophilic and able to rapidly cross the blood-brain barrier acting on both D1-like (D1 and D5) and D2-like (D2, D3, D4) receptors, even if with a lower affinity for D1-like receptors (16).
The first groundbreaking clinical study of subcutaneous apomorphine in the treatment of motor fluctuations in PD was published in 1988 (17) and it demonstrated that a subcutaneous continuous infusion of apomorphine was able to decrease the mean daily time in «off» by about 6 hours, an effect which was similar in efficacy to that of intravenous levodopa (17). Additionally, this study also further confirmed that the hypotensive and emetic adverse effects of apomorphine administration could be managed with domperidone (17, 18). The TOLEDO study was the first double-blind placebo-controlled clinical trial to provide evidence on the efficacy and safety of CSAI in advanced PD (19). In patients with PD and motor fluctuations not adequately improved by oral drugs, CSAI reduced daily time in «off» (19).

Safety:
The most frequent adverse effects were skin changes at the injection site (59%), but CSAI was considered to be generally well-tolerated (19). Besides reducing daily time in «off», CSAI also reduces dyskinesia, with the improvement of dyskinesia being greater in patients achieving monotherapy with apomorphine (20). Besides its effect on motor symptoms, CSAI is also able to improve non-motor symptoms such as gastrointestinal and urinary symptoms (21). Moreover, in non-demented patients with PD, treatment with apomorphine was able to reduce hallucinations, possibly through allowing a reduction of oral dopaminergic drugs (22). Impulse control disorders, such as pathological gambling and hypersexuality, were also less associated with apomor-

phine than with other dopamine receptor agonists possibly due to its less selective activation of D3 receptors compared to pramipexole and ropinirole (23).
Even if generally well tolerated, CSAI is associated with adverse effects. Skin related adverse effects are most common and range from bruising or nodules to necrosis, subcutaneous abscesses and eosinophilic panniculitis (19) (*Figure 1*). Nausea, vomiting, somnolence and hypotension can also occur, particularly in the beginning of the treatment. Moreover, apomorphine can induce a QT interval prolongation and, rarely, autoimmune hemolytic anemia or eosinophilic reactions (24).

Practical Considerations:
CSAI is available in Europe and is administered using a portable pump device through a fine catheter and a small needle placed in the subcutaneous fatty tissue. The available pump systems in Switzerland are APO-GO® and D-mine®/Dacepton® (*Figure 2*).
Since no surgery is required, CSAI is considered to be less invasive than LCIG/LECIG and installation can be done both in outpatient or inpatient settings. Currently, in Switzerland, installation is mostly done in inpatient or day clinics settings. Usually, CSAI is started at a dose of 1mg/hour and increased daily about 1mg/hour, while at the same time the oral dopaminergic medication is progressively reduced, particularly if dyskinesias occur, usually by first decreasing oral dopamine agonists. The installation phase lasts about 7–15 days, while the daily dose of CSAI and oral dopaminergic drugs is optimized. Usually, CSAI is administered for 16 hours a day (or 24 hours in case of severe night «off» symptoms), at a maximum dose of 100mg/day, and is divided in a morning dose, maintenance dose (usually between 4-7mg/hour) and extra boluses as needed (although their use should be limited due to the risk of aggravating dyskinesia or impulse control disorders). CSAI monotherapy can be aimed but it is less frequently achieved than in LCIG (25) so that oral fractionated levodopa often needs to be maintained.
Before initiation of CSAI, patients should have a basic laboratory evaluation with complete blood count, kidney and liver function tests and Coombs test, ECG to exclude a baseline prolongation of QT interval and baseline Schellong test. Premedication with domperidone 10mg 3 times/day started 3 days before initiation of CSAI and continued until tolerance to nausea, vomiting and hypotension is developed. Ondansetron or other serotonin receptor antagonists are contraindicated during apomorphine treatment due to the risk of severe hypotension. Domperidone as well as apomorphine have been associated with prolongation of QT interval, therefore an ECG should be obtained also after initiation of treatment. During follow-up, every 3–6 months, an ECG to monitor the QT interval as well as complete blood count and a Coombs test should be obtained to monitor for the development of rare but potentially severe autoimmune hemolytic anemia or hypereosinophilia syndrome.
The handling of the pump system requires training of the patient and/or caregivers. This is particularly important because skin-related adverse events can be greatly prevented by adequate hygiene, proper injection technique, rotation of injection site and localized massages.

Key points:

- **For patients with Parkinson's disease and motor complications the current available infusion therapies, in Switzerland, include levodopa-carbidopa and levodopa-entacapone-carbidopa intestinal gel infusions and continuous subcutaneous apomorphine infusion.**
- **Patients who are thought to be candidates for infusion therapies should be assessed in specialized multidisciplinary movement disorders centers.**
- **The choice between the different infusion therapies is individualized and depends on the clinical profile of the patient as well as the values and preferences of patient and caregivers.**

In case of subcutaneous nodules, which impair adequate administration of CSAI, ultrasound treatment can also be tried (26). During CSAI monotherapy, patients and caregivers should be instructed to resume previous oral dopaminergic medication in case of a pump malfunction lasting more than 30 minutes. The pharmaceutical companies commercializing the APO-GO® and D-mine®/Dacepton® pumps offer a hotline for technical support.

Continuous Subcutaneous Levodopa-Carbidopa and Foslevodopa-Foscarbidopa Infusions

Levodopa-carbidopa continuous subcutaneous infusion (LC-CSCI) is a new infusion therapy in which soluble levodopa-carbidopa or foslevodopa-foscarbidopa are delivered through a portable pump infusion similar to that used for CSAI (27). In a phase 3, randomized, double-blind, double-dummy, multicenter trial, ND0612 was shown to increase time in «on» without troublesome dyskinesia and decrease time in "off" compared to oral levodopa-carbidopa (28). Another randomized, double-blind, active-controlled phase 3 clinical trial also showed that ABBV-951 increased time in «on» without troublesome dyskinesia and reduced time in «off» (29). LC-CSCI is a new treatment option approved by FDA and EMA but not by Swissmedic.

The choice between different device-assisted therapies

There are no published clinical trials comparing head-to-head the different device-assisted therapies. An observational study of patients who were treated with CSAI while on a waiting list for STN-DBS showed that CSAI reduced daily «off» time and improved non-motor symptoms, but this improvement was higher after STN-DBS, with STN-DBS allowing a reduction of daily «off» time of 90% compared to 70% of CSAI (30). In another observational study, STN-DBS achieved a greater decrease of dyskinesia duration whereas CSAI was less associated with development of apathy than STN-DBS (31). A meta-analysis which compared over 20 studies of device-assisted therapies suggested that LCIG and DBS were superior in decreasing «off» time compared to CSAI (32). An observational multicenter study comparing LCIG and CSAI concluded that both treatment options were suitable and led to improvement of motor complications and quality of life (33). However, since there is no high quality evidence comparing the different device-assisted therapies, the choice between the

different therapy options for advanced PD is individualized and mostly based on patient profile (34), availability of clinical expertise in managing the different therapies and patient and caregiver values and preferences (see *Table 1*).

Correspondence Address
Andreia D. Magalhães, MD, PhD
Inselspital, Universitätsspital Bern
Universitätsklinik für Neurologie
Zentrum für Parkinson und Bewegungsstörungen
Freiburgstrasse
3010 Bern
E-Mail: andreia.delgadomagalhaes@insel.ch

Conflicts of Interest:

ADM worked as an investigator of the BouNDless trial by Neuroderm.

MLL received a research grant from the Jacques und Gloria Gossweiler Foundation, has served on an advisory board for Bial and received travel expenses to scientific meetings from Bial, Zambon, and Medtronic.

PK reports research or educational grants from Swiss National Science Foundation (FNS23530_177577 / FNS 32003BL_197709-1 / FNS 33IC30_198772), ROGER DE SPOELBERCH Foundation, Fondation Louis-Jeantet, Carigest, Institut National de la Santé et de la Recherche Médicale, France Parkinson, Edmond Safra Philantropic Foundation, Bertarelli Foundation, Annemarie Opprecht Foundation, Parkinson Schweiz, Michael J Fox Foundation, Aleva Neurotherapeutics, Boston Scientific, Medtronic, St. Jude Medical, GE Healthcare, Idorsia, UCB, all paid to employing institutions; lecturing fees to employing institution from Boston Scientific, Bial, Advisis; travel expenses to scientific meetings from Boston Scientific, Zambon, Abbvie, Merz Pharma (Schweiz) AG.

References:

1. Armstrong MJ et al.: Diagnosis and Treatment of Parkinson Disease: A Review. Jama. Feb 11 2020;323(6):548-560. doi:10.1001/jama.2019.22360.
2. Antonini A et al.: Current and novel infusion therapies for patients with Parkinson›s disease. J Neural Transm (Vienna). Nov 2023;130(11):1349-1358. doi:10.1007/s00702-023-02693-8.
3. Deuschl G et al.: European Academy of Neurology/Movement Disorder Society - European Section guideline on the treatment of Parkinson›s disease: I. Invasive therapies. Eur J Neurol. Sep 2022;29(9):2580-2595. doi:10.1111/ene.15386.
4. Antonini A et al.: 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. Dec 2018;34(12):2063-2073. doi:10.1080/03007995.2018.1502165
5. Olanow CW et al.: 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. Feb 2014;13(2):141-149. doi:10.1016/s1474-4422(13)70293-x.
6. Poewe W et al.: Levodopa-carbidopa intestinal gel in a subgroup of patients with dyskinesia at baseline from the GLORIA Registry. Neurodegener Dis Manag. Feb 2019;9(1):39-46. doi:10.2217/nmt-2018-0034.
7. Chaudhuri KR et al.: Effects of Levodopa-Carbidopa Intestinal Gel on Dyskinesia and Non-Motor Symptoms Including Sleep: Results from a Meta-Analysis with 24-Month Follow-Up. J Parkinsons Dis. 2022;12(7):2071-2083. doi:10.3233/jpd-223295.
8. Garrì F et al.: Long-term safety, discontinuation and mortality in an Italian cohort with advanced Parkinson›s disease on levodopa/carbidopa intestinal gel infusion. J Neurol. Oct 2022;269(10):5606-5614. doi:10.1007/s00415-022-11269-7.
9. Lang AE et al.: Integrated safety of levodopa-carbidopa intestinal gel from prospective clinical trials. Mov Disord. Apr 2016;31(4):538-546. doi:10.1002/mds.26485.
10. Freire-Alvarez E et al.: Levodopa-Carbidopa Intestinal Gel Reduces Dyskinesia in Parkinson›s Disease in a Randomized Trial. Mov Disord. Nov 2021;36(11):2615-2623. doi:10.1002/mds.28703.
11. Merola A et al.: Peripheral neuropathy associated with levodopa-carbidopa intestinal infusion: a long-term prospective assessment. Eur J Neurol. Mar 2016;23(3):501-509. doi:10.1111/ene.12846.
12. Uncini A et al.: Polyneuropathy associated with duodenal infusion of levodopa in Parkinson›s disease: features, pathogenesis and management. J Neurol Neurosurg Psychiatry. May 2015;86(5):490-495. doi:10.1136/jnnp-2014-308586.
13. Höglinger G et al.: Diagnosis and treatment of Parkinson´s disease (guideline of the German Society for Neurology). Neurol Res Pract. Jun 6 2024;6(1):30. doi:10.1186/s42466-024-00325-4.
14. Jost WH: Apprends-moi l›art des petits pas: Levodopa, Carbidopa Intestinal Gel plus Entacapone. J Neural Transm (Vienna). Nov 2023;130(11):1379-1382. doi:10.1007/s00702-023-02625-6.
15. Senek M et al.: Levodopa-entacapone-carbidopa intestinal gel in Parkinson›s disease: A randomized crossover study. Mov Disord. Feb 2017;32(2):283-286. doi:10.1002/mds.26855.
16. Carbone F et al.: Apomorphine for Parkinson›s Disease: Efficacy and Safety of Current and New Formulations. CNS Drugs. Sep 2019;33(9):905-918. doi:10.1007/s40263-019-00661-z
17. Stibe CM et al.: Subcutaneous apomorphine in parkinsonian on-off oscillations. Lancet. Feb 20 1988;1(8582):403-406. doi:10.1016/s0140-6736(88)91193-2
18. Agid Y et al.: Bromocriptine associated with a peripheral dopamine blocking agent in treatment of Parkinson›s disease. Lancet. Mar 17 1979;1(8116):570-572. doi:10.1016/s0140-6736(79)91003-1.
19. Katzenschlager R et al.: Apomorphine subcutaneous infusion in patients with Parkinson›s disease with persistent motor fluctuations (TOLEDO): a multicentre, double-blind, randomised, placebo-controlled trial. Lancet Neurol. Sep 2018;17(9):749-759. doi:10.1016/s1474-4422(18)30239-4.
20. Manson AJ et al.: Apomorphine monotherapy in the treatment of refractory motor complications of Parkinson›s disease: long-term follow-up study of 64 patients. Mov Disord. Nov 2002;17(6):1235-41. doi:10.1002/mds.10281.
21. Martinez-Martin P et al.: Chronic subcutaneous infusion therapy with apomorphine in advanced Parkinson›s disease compared to conventional therapy: a real life study of non motor effect. J Parkinsons Dis. 2011;1(2):197-203. doi:10.3233/jpd-2011-11037.
22. Ellis C et al.: Use of apomorphine in parkinsonian patients with neuropsychiatric complications to oral treatment. Parkinsonism Relat Disord. Apr 1997;3(2):103-107. doi:10.1016/s1353-8020(97)00009-6.
23. Moore TJ et al.: Reports of pathological gambling, hypersexuality, and compulsive shopping associated with dopamine receptor agonist drugs. JAMA Intern Med. Dec 2014;174(12):1930-1933. doi:10.1001/jamainternmed.2014.5262.
24. Pot C et al.: Apomorphine-induced eosinophilic panniculitis and hypereosinophilia in Parkinson disease. Neurology. Jan 25 2005;64(2):392-393. doi:10.1212/01.Wnl.0000149757.47854.6f.
25. Rožanković PB et al.: Monotherapy with infusion therapies - useful or not? J Neural Transm (Vienna). Jul 5 2024;doi:10.1007/s00702-024-02801-2.
26. Poltawski L et al.: Ultrasound treatment of cutaneous side-effects of infused apomorphine: a randomized controlled pilot study. Mov Disord. Jan 15 2009;24(1):115-118. doi:10.1002/mds.22316.
27. Aubignat M et al.: Continuous Subcutaneous Foslevodopa-Foscarbidopa in Parkinson›s Disease: A Mini-Review of Current Scope and Future Outlook. Mov Disord Clin Pract. Jul 11 2024;doi:10.1002/mdc3.14161.
28. Espay AJ et al.: Safety and efficacy of continuous subcutaneous levodopa-carbidopa infusion (ND0612) for Parkinson›s disease with motor fluctuations (BouNDless): a phase 3, randomised, double-blind, double-dummy, multicentre trial. Lancet Neurol. May 2024;23(5):465-476. doi:10.1016/s1474-4422(24)00052-8.
29. Soileau MJ et al.: 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. Dec 2022;21(12):1099-1109. doi:10.1016/s1474-4422(22)00400-8.
30. Fernández-Pajarín G et al.: Continuous Subcutaneous Apomorphine Infusion before Subthalamic Deep Brain Stimulation: A Prospective, Comparative Study in 20 Patients. Mov Disord Clin Pract. Nov 2021;8(8):1216-1224. doi:10.1002/mdc3.13338.
31. Antonini A et al.: A 5-year prospective assessment of advanced Parkinson disease patients treated with subcutaneous apomorphine infusion or deep brain stimulation. J Neurol. Apr 2011;258(4):579-85. doi:10.1007/s00415-010-5793-z.
32. Antonini A et al.: Comparative Effectiveness of Device-Aided Therapies on Quality of Life and Off-Time in Advanced Parkinson›s Disease: A Systematic Review and Bayesian Network Meta-analysis. CNS Drugs. Dec 2022;36(12):1269-1283. doi:10.1007/s40263-022-00963-9.
33. Martinez-Martin P et al.: EuroInf: a multicenter comparative observational study of apomorphine and levodopa infusion in Parkinson›s disease. Mov Disord. Apr 2015;30(4):510-516. doi:10.1002/mds.26067.
34. Brinker D et al.: How to Use the New European Academy of Neurology/Movement Disorder Society European Section Guideline for Invasive Therapies in Parkinson›s Disease. Mov Disord Clin Pract. Mar 2024;11(3):209-219. doi:10.1002/mdc3.13962.