PARKINSON DISEASE PROGRESSION AND THERAPY

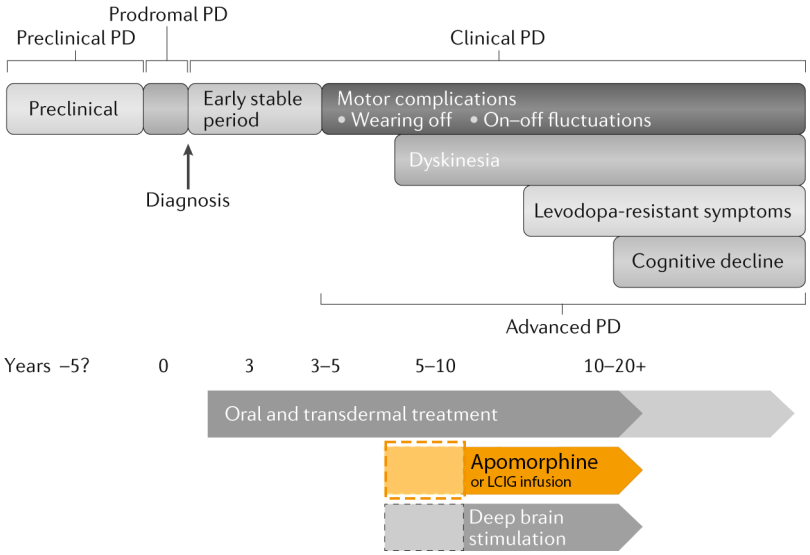

Figure 2: Parkinson disease (PD) stages from prodromal to advanced, including late development of levodopa-resistant symptoms, are shown.
The horizontal arrows indicate current timing of oral and transdermal therapies, Apomorphine infusion or, LCIG infusion, and surgical therapies (solid lines). The lighter shading at the end of the oral and transdermal treatment arrow refers to the period of reduced medication efficacy due to appearance of levodopa-resistant symptoms. The dotted lines indicate the proposed earlier timing for introduction of these therapies in PD management.
(adapted from Antonini et Jenner, 2018)

The TOLEDO study should encourage neurologists to consider implementing Apomorphine infusion or other device-aided therapies early, before patients have deteriorated and have developed severe disability and troublesome dyskinesia. (Antonini et Jenner, 2018)

THE TOLEDO STUDY

The results demonstrated a significant and clinically meaningful reduction in off' time of approximately 2 h more than placebo, and a similar extension of 'on' time without troublesome dyskinesia. The infusion dose was individually optimized between 3 and 8mg/h and administered daily for 16±2h. (Katzenschlager et al., 2018)

Apomorphine infusion is an effective, well tolerated and minimally invasive device-aided treatment for PD, straightforward to administer and can often be started without the need for hospital admission. To be successful it requires concordance from the patient and family, and clinical support from an experienced team of doctors and nurses, particularly in the early months of treatment. (Henriksen et al., 2023)

Apomorphine for subcutaneous continuous infusion can be administered with Dacepton® 5 mg/ml in 20 ml vials and the D-*mine*® Pump (or an adequate syringe driver).

Literature:

1. Antonini et al., Curr Med Research Opin 2018; 34 (12): 2063-2073
2. Antonini A, Jenner P. Apomorphine infusion in advanced Parkinson disease. Nature Reviews Neurology. 2018.
3. Katzenschlager 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. 17,749-759 (2018)
4. Calandrella et al., Parkinsonism Relat Disord. 2012 Jan;18 Suppl 1:S120-2.
5. Schapira et al., Levodopain the treatment of Parkinson's disease. EurJ Neurol. 2009;16:982-989.
6. Olanow et al., Nat Clin Pract Neurol. 2006 Jul;2(7):382-92.
7. Henriksen et al., Journal of Neural Transmission 2023, Volume 130, pages 1475–1484

ABBREVIATED PRESCRIBING INFORMATION: Dacepton 5 mg/ml Solution for infusion. QUALITATIVE AND QUANTITATIVE COMPOSITION: 1 ml contains 5 mg apomorphine hydrochloride hemihydrate, 20 ml contain 100 mg apomorphine hydrochloride hemihydrate. Excipient with known effect: Sodium metabisulphite (E223) 1 mg per ml, Sodium chloride 8 mg per ml. PHARMACEUTICAL FORM: Solution for infusion. Clear and colourless to slightly yellow solution, free from visible particles, pH of 3.3 – 4.0. Osmolality: 290 mOsm/kg. THERAPEUTIC INDICATIONS: Treatment of motor fluctuations ("on-off" phenomena) in patients with Parkinson's disease which are not sufficiently controlled by oral anti-Parkinson medication. POSOLOGY AND METHOD OF ADMINISTRATION: Selection of Patients suitable for Dacepton 5 mg/ml solution for infusion: Patients selected for treatment with Dacepton 5 mg/ml solution for infusion should be able to recognise the onset of their "off" symptoms and be capable of injecting themselves or else have a responsible carer able to inject for them when required. It is essential that the patient is established on domperidone, usually 20 mg three times daily, for at least two days prior to initiation of therapy. Apomorphine should be initiated in the controlled environment of a specialist clinic. The patient should be supervised by a physician experienced in the treatment of Parkinson's disease (e.g. neurologist). The patient's treatment with levodopa, with or without dopamine agonists, should be optimised before starting treatment with Dacepton 5 mg/ml solution for infusion. Adults: METHOD OF ADMINISTRATION: Dacepton 5 mg/ml solution for infusion is a pre-diluted vial intended for use without dilution for subcutaneous use and to be administered as a continuous subcutaneous infusion by minipump and/or syringe-driver. It is not intended to be used for intermittent injection. Apomorphine must not be used via the intravenous route. Do not use if the solution has turned green. The solution should be inspected visually prior to use. Only clear, colourless to slightly yellow and particle free solution should be used. POSOLOGY: Continuous Infusion Patients who have shown a good "on" period response during the initiation stage of apomorphine therapy, but whose overall control remains unsatisfactory using intermittent injections, or who require many and frequent injections (more than 10 per day), may be commenced on or transferred to continuous subcutaneous infusion by minipump and/or syringe-driver as follows: The choice, of which minipump and / or syringe-driver to use, and the dosage settings required, will be determined by the physician in accordance with the particular needs of the patient. DETERMINATION OF THRESHOLD DOSE: The threshold dose for continuous infusion should be determined as follows: Continuous infusion is started at a rate of 1 mg apomorphine hydrochloride hemihydrate (0.2 ml) per hour then increased according to the individual response each day. Increases in the infusion rate should not exceed 0.5 mg at intervals of not less than 4 hours. Hourly infusion rates may range between 1 mg and 4 mg (0.2 ml and 0.8 ml), equivalent to 0.014-0.06 mg/kg/hour. Infusions should run for waking hours only. Unless the patient is experiencing severe night-time problems, 24 hour infusions are not advised. Tolerance to the therapy does not seem to occur as long as there is an overnight period without treatment of at least 4 hours. In any event, the infusion site should be changed every 12 hours. Patients may need to supplement their continuous infusion with intermittent bolus boosts, as necessary, and as directed by their physician. A reduction in dosage of other dopamine agonists may be considered during continuous infusion. ESTABLISHMENT OF TREATMENT: Alterations in dosage may be made according to the patient's response. The optimal dosage of apomorphine hydrochloride hemihydrate varies between individuals but, once established, remains relatively constant for each patient. PRECAUTIONS ON CONTINUING TREATMENT: The daily dose of Dacepton 5 mg/ml solution for infusion varies widely between patients, typically within the range of 3-30 mg. It is recommended that the total daily dose of apomorphine hydrochloride hemihydrate should not exceed 100 mg. In clinical studies it has usually been possible to make some reduction in the dose of levodopa; this effect varies considerably between patients and needs to be carefully managed by an experienced physician. Once treatment has been established, domperidone therapy may be gradually reduced in some patients but successfully eliminated only in a few, without any vomiting or hypotension. Paediatric population: Dacepton 5 mg/ml solution for infusion is contraindicated for children and adolescents under 18 years of age. Elderly: The elderly are well represented in the population of patients with Parkinson's disease and constitute a high proportion of those studied in clinical trials of apomorphine. The management of elderly patients treated with apomorphine has not differed from that of younger patients. However, extra caution is recommended during initiation of therapy in elderly patients because of the risk of postural hypotension. Renal impairment: A dose schedule similar to that recommended for adults, and the elderly, can be followed for patients with renal impairment. CONTRAINDICATIONS: Hypersensitivity to the active substance or to any of the excipients. In patients with respiratory depression, dementia, psychotic diseases or hepatic insufficiency. Apomorphine hydrochloride hemihydrate treatment must not be administered to patients who have an "on" response to levodopa which is marred by severe dyskinesia or dystonia. Dacepton 5 mg/ml solution for infusion is contraindicated for children and adolescents under 18 years of age. Special warnings and precautions for use Apomorphine hydrochloride hemihydrate should be given with caution to patients with renal, pulmonary or cardiovascular disease and persons prone to nausea and vomiting. Extra caution is recommended during initiation of therapy in elderly and/or debilitated patients. Since apomorphine may produce hypotension, even when given with domperidone pre-treatment, care should be exercised in patients with pre-existing cardiac disease or in patients taking vasoactive medicinal products such as antihypertensives, and especially in patients with pre-existing postural hypotension. Since apomorphine, especially at high dose, may have the potential for QT prolongation, caution should be exercised when treating patients at risk for torsades de pointes arrhythmia. Apomorphine is associated with local subcutaneous effects. These can sometimes be reduced by the rotation of injection sites or possibly by the use of ultrasound (if available) in order to avoid areas of nodularity and induration. Haemolytic anaemia and thrombocytopenia have been reported in patients treated with apomorphine. Haematology tests should be undertaken at regular intervals as with levodopa, when given concomitantly with apomorphine. Caution is advised when combining apomorphine with other medicinal products, especially those with a narrow therapeutic range. Neuropsychiatric problems co-exist in many patients with advanced Parkinson's disease. There is evidence that for some patients neuropsychiatric disturbances may be exacerbated by apomorphine. Special care should be exercised when apomorphine is used in these patients. Apomorphine has been associated with somnolence, and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with apomorphine. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore, a reduction of dosage or termination of therapy may be considered. Impulse control disorders: Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including apomorphine. Dose reduction/tapered discontinuation should be considered if such symptoms develop. Dopamine dysregulation Syndrome (DDS) is an addictive disorder resulting in excessive use of the product seen in some patients treated with apomorphine. Before initiation of treatment, patients and caregivers should be warned of the potential risk of developing DDS. Dacepton 5 mg/ml solution for infusion contains sodium metabisulphite which may rarely cause severe hypersensitivity reactions and bronchospasm. Dacepton 5 mg/ml contains 3.4 mg sodium per ml. To be taken into consideration by patients on a controlled sodium diet. Interaction with other medicinal products and other forms of interaction: Patients selected for treatment with apomorphine hydrochloride hemihydrate are almost certain to be taking concomitant medications for their Parkinson's disease. In the initial stages of apomorphine hydrochloride hemihydrate therapy, the patient should be monitored for unusual side-effects or signs of potentiation of effect. Neuroleptic medicinal products may have an antagonistic effect if used with apomorphine. There is a potential interaction between clozapine and apomorphine, however clozapine may also be used to reduce the symptoms of neuropsychiatric complications. If neuroleptic medicinal products have to be used in patients with Parkinson's disease treated by dopamine agonists, a gradual reduction in apomorphine dose may be considered when administration is by minipump and or syringe-driver (symptoms suggestive of neuroleptic malignant syndrome have been reported rarely with abrupt withdrawal of dopaminergic therapy). The possible effects of apomorphine on the plasma concentrations of other medicinal products have not been studied. Therefore caution is advised when combining apomorphine with other medicinal products, especially those with a narrow therapeutic range. Antihypertensive and Cardiac Active Medicinal Products: Even when co-administered with domperidone, apomorphine may potentiate the antihypertensive effects of these medicinal products. It is recommended to avoid the administration of apomorphine with other drugs known to prolong the QT interval. Concomitant use of apomorphine with ondansetron may lead to severe hypotension and loss of consciousness and is therefore contraindicated (see section 4.3). Such effects might also occur with other 5-HT3 antagonists. Fertility, pregnancy and lactation: There is no experience of apomorphine usage in pregnant women. Animal reproduction studies do not indicate any teratogenic effects, but doses given to rats which are toxic to the mother can lead to failure to breathe in the newborn. The potential risk for humans is unknown. Dacepton 5 mg/ml solution for infusion should not be used during pregnancy unless clearly necessary. It is not known whether apomorphine is excreted in breast milk. A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with Dacepton 5 mg/ml solution for infusion should be made taking into account the benefit of breast-feeding to the child and the benefit of Dacepton 5 mg/ml solution for infusion to the woman. Effects on ability to drive and use machines: Apomorphine hydrochloride hemihydrate has minor or moderate influence on the ability to drive and use machines. Patients being treated with apomorphine and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities (e.g. operating machines) where impaired alertness may put themselves or others at risk of serious injury or death until such recurrent episodes and somnolence have resolved. UNDESIRABLE EFFECTS: Very common: (≥1/10), common: (≥1/100 to <1/10), uncommon: (≥1/1,000 to <1/100), rare: (≥1/10,000 to <1/1,000), very rare: (<1/10,000), Not known: (cannot be estimated from the available data). Blood and lymphatic system disorders: Uncommon: Haemolytic anaemia and thrombocytopenia have been reported in patients treated with apomorphine. Rare: Eosinophilia has rarely occurred during treatment with apomorphine hydrochloride hemihydrate. Immune system disorders: Rare: Due to the presence of sodium metabisulphite, allergic reactions (including anaphylaxis and bronchospasm) may occur. Psychiatric disorders: Common: Neuropsychiatric disturbances are common in parkinsonian patients. Dacepton 5 mg/ml solution for infusion should be used with special caution in these patients. Neuropsychiatric disturbances (including transient mild confusion and visual hallucinations) have occurred during apomorphine hydrochloride hemihydrate therapy. Not known: Impulse control disorders: Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including apomorphine. Aggression, agitation. Nervous system disorders: Common: Transient sedation with each dose of apomorphine hydrochloride hemihydrate at the start of therapy may occur; this usually resolves over the first few weeks. Apomorphine is associated with somnolence. Dizziness / light-headedness have also been reported. Uncommon: Apomorphine may induce dyskinesias during "on" periods which can be severe in some cases, and in a few patients may result in cessation of therapy. Apomorphine has been associated with sudden sleep onset episodes, syncope and headache. Vascular disorders: Uncommon: Postural hypotension is seen infrequently and is usually transient: Respiratory, thoracic and mediastinal disorders Common: Yawning has been reported during apomorphine therapy. Uncommon: Breathing difficulties have been reported. Gastrointestinal disorders: Common: Nausea and vomiting, particularly when apomorphine treatment is first initiated, usually as a result of the omission of domperidone. Skin and subcutaneous tissue disorders: Uncommon: Local and generalised rashes have been reported. eneral disorders and administration site conditions: Very common: Most patients experience injection site reactions, particularly with continuous use. These may include subcutaneous nodules, induration, erythema, tenderness and panniculitis. Various other local reactions (such as irritation, itching, bruising and pain) may also occur. Uncommon: Injection site necrosis and ulceration have been reported. Not Known: Peripheral oedema has been reported. Investigations Uncommon: Positive Coombs' tests have been reported for patients receiving apomorphine. Reporting of suspected adverse reactions Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system. Overdose: There is little clinical experience of overdose with apomorphine by this route of administration. Symptoms of overdose may be treated empirically as suggested: Excessive emesis may be treated with domperidone. Respiratory depression may be treated with naloxone. Hypotension: appropriate measures should be taken, e.g. raising the foot of the bed. Bradycardia may be treated with atropine. PHARMACODYNAMIC PROPERTIES: Pharmacotherapeutic group: Anti-Parkinson drugs, dopamine agonists, ATC code: N04B C07. Mechanism of action: Apomorphine is a direct stimulant of dopamine receptors and while possessing both D1 and D2 receptor agonist properties does not share transport or metabolic pathways with levodopa. Although in intact experimental animals, administration of apomorphine suppresses the rate of firing of nigro-striatal cells and in low dose has been found to produce a reduction in locomotor activity (thought to represent pre-synaptic inhibition of endogenous dopamine release) its actions on parkinsonian motor disability are likely to be mediated at post-synaptic receptor sites. This biphasic effect is also seen in humans. Pharmacokinetic properties: After subcutaneous injection of apomorphine its fate can be described by a two-compartment model, with a distribution half-life of 5 (±1.1) minutes and an elimination half-life of 33 (±3.9) minutes. Clinical response correlates well with levels of apomorphine in the cerebrospinal fluid; the active substance distribution being best described by a two-compartment model. Apomorphine is rapidly and completely absorbed from subcutaneous tissue, correlating with the rapid onset of clinical effects (4-12 minutes), and that the brief duration of clinical action of the active substance (about 1 hour) is explained by its rapid clearance. The metabolism of apomorphine is by glucuronidation and sulphonation to at least ten per cent of the total; other pathways have not been described. PRECLINICAL SAFETY DATA: Repeat dose subcutaneous toxicity studies reveal no special hazard for humans, beyond the information included in other sections of the SmPC. In vitro genotoxicity studies demonstrated mutagenic and clastogenic effects, most likely due to products formed by oxidation of apomorphine. However, apomorphine was not genotoxic in the in vivo studies performed. The effect of apomorphine on reproduction has been investigated in rats. Apomorphine was not teratogenic in this species, but it was noted that doses which are toxic to the mother can cause loss of maternal care and failure to breathe in the newborn. No carcinogenicity studies have been performed. LIST OF EXCIPIENTS: Sodium metabisulphite (E223), Sodium chloride, Hydrochloric acid (for pH-adjustment), water for injections: Incompatibilities: In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. SHELF LIFE: Unopened: 30 months. After opening and filling the drug product in syringes attached with infusion sets: chemical and physical in-use stability has been demonstrated for 7 days at 25 °C. From a microbiological point of view, unless the method of opening and further handling precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user. Single use only. Discard any unused contents. Special precautions for storage: Keep the vials in the outer carton in order to protect from light. Do not refrigerate or freeze. NATURE AND CONTENTS OF CONTAINER: Clear glass vials, type I with bromobutyl rubber stopper and a flip-off cap, containing 20 ml solution for infusion, in packs of 1 or 5 vials. Bundle packs: 5 x 1, 10 x 1, 30 x 1, 2 x 5 and 6 x 5. Not all pack sizes may be marketed. Special precautions for disposal and other handling: Do not use if the solution has turned green. The solution should be inspected visually prior to use. Only clear and colourless to slightly yellow solutions without particles in undamaged containers should be used. For single use only. Any unused medicinal product or waste material should be disposed in accordance with local requirements. Continuous infusion and the use of a minipump and or syringe-driver The choice of which minipump and or syringe-driver to use, and the dosage settings required, will be determined by the physician in accordance with the particular needs of the patient. MARKETING AUTHORISATION HOLDER: EVER Neuro Pharma GmbH, Oberburgau 3, 4866 Unterach, Österreich. MARKETING AUTHORISATION NUMBER: AT/H/0364/002/DC. Legal Category: POM. Date of last revision: October 2023.

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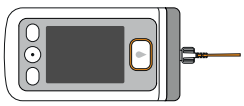
TRANSFER TO CONTINUOUS INFUSION PUMP THERAPY

FLUCTUATIONS AND DYSKINESIA IN PARKINSON´S DISEASE



SUBCUTANEOUS USE

Dacepton®
Apomorphine Hydrochloride

INTRODUCTION

The lack of dopamine makes it impossible to control or direct movement. This is why movement disorders predominate in Parkinson's disease (PD). In addition, the disease can have pronounced non-motor symptoms, such as cognitive dysfunction, depressive symptoms or sensory deficits.

Oral treatments, such as levodopa and dopamine agonists, are effective in treating early motor symptoms in the early or moderate stages of the disease. As the disease progresses, the beneficial effects of oral medications become less predictable.

For a certain period of time progressive symptoms can be controlled by reducing the intervals between the intake of oral medication. However, the motor fluctuations characterized by an "End-of-Dose" phenomenon or "Wearing-Off" become more and more prevalent. Unphysiological pulsatile stimulation of dopamine receptors with levodopa leads to development of levodopa induced dyskinesia with alternating periods of being "On" and being "Off" effective treatment (Calandrella et al., 2012).

CLINICAL LIMITATIONS OF ORAL MEDICATION

Dopaminergic neurons in the basal ganglia normally fire continuously. However, in a dopamine-depleted state, intermittent oral doses of levodopa induce discontinuous stimulation of striatal dopamine receptors, leading to physiological changes in the basal ganglia and the development of motor complications. These effects are reduced when dopaminergic therapies are administered in a more continuous and physiological manner (Olanow, et al., 2006).

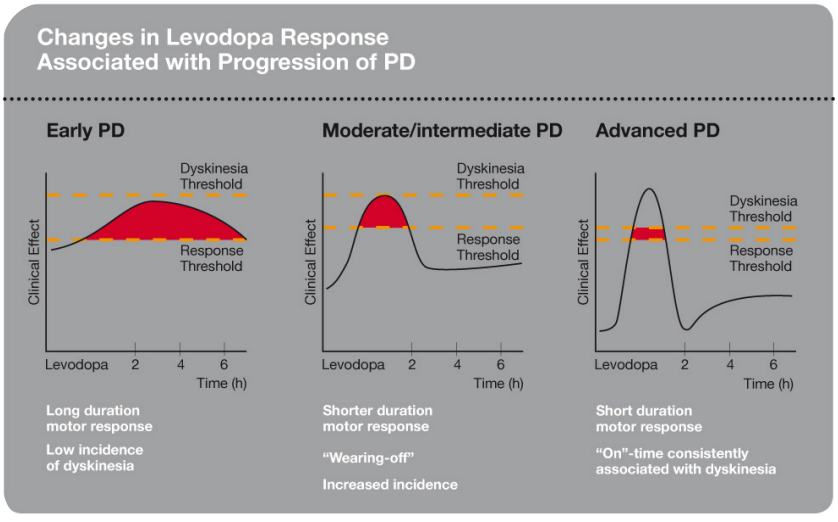


Figure 1: Changes in levodopa Response associated with Progression of PD. (adapted from Schapira et al., 2009)

Several reports and clinical trials have shown that when the loss of physiological dopamine is compensated for by levodopa, the resulting pulsatile stimulation alters the firing patterns of basal ganglia output neurons and leads to complications such as motor fluctuations and dyskinesia. Therefore, continuous drug delivery (CDD) is an important strategy to regulate therapeutic efficacy (Rascol, 2011).

WHEN TO CONSIDER TRANSITION TO CONTINUOUS DEVICE-AIDED THARAPIES?

As PD progresses, patients may become increasingly dependent on caregivers, and disability is dominated by motor symptoms (MS) and non-motor symptoms (NMS), which may be resistant to dopaminergic and/or oral medications. Management of advanced PD symptoms (APD), particularly motor fluctuations, dyskinesia and off-time, may require optimisation of oral therapies (including polypharmacy, dose fractionation and dose tapering) or the use of advanced therapies such as deep brain stimulation (DBS), continuous subcutaneous Apomorphine infusion (CSAI) or levodopa-carbidopa intestinal or subcutaneous infusion.

The lack of global consensus on considerations for the timing of device-based therapies can lead to heterogeneity in care. To **help guide neurologists on key patient characteristics that may indicate the transition and appropriate use of device-based therapies in the management of Parkinson's disease symptoms**, consensus among movement disorders specialists was sought through a modified Delphi study involving 17 leading movement disorders specialists from 10 countries.
The study consisted of four rounds. In the third round, movement disorders specialists were asked to rank the consensus indicators within three discrete symptom groups. In total, consensus was reached on 15 clinically relevant indicators:

Ranking	Clinically important indicators (n = 15)[b]
Motor symptom	
1	Moderate level of troublesome motor fluctuations
2	At least 2h of the waking day with "Off„ symptoms
3	At least 1 h of the day with troublesome dyskinesia
4	Moderate level of dyskinesia
5	Troublesome dysphagia
6	Daily oral levodopa doses "At least 5 times a day"[b]
Non-motor symptom	
1	Mild level of dementia
2	Non-transitory troublesome hallucinations
3	Moderate level of psychosis
4	NMS fluctuations
5	Moderate level of nighttime sleep disturbances
Functional impacts	
1	Repeated falls[c] despite optimal treatment
2	Needs help with ADLs at least some of the time
3	Not able to perform complex tasks at least some of the time
4	Moderate impaired mobility

Table 1: Ranking of most clinically important indicators of patients with suspected APD. ADL, activities of daily living; APD, advanced Parkinson's disease; NMS, non-motor symptoms. (adapted from Antonini et al., 2018)

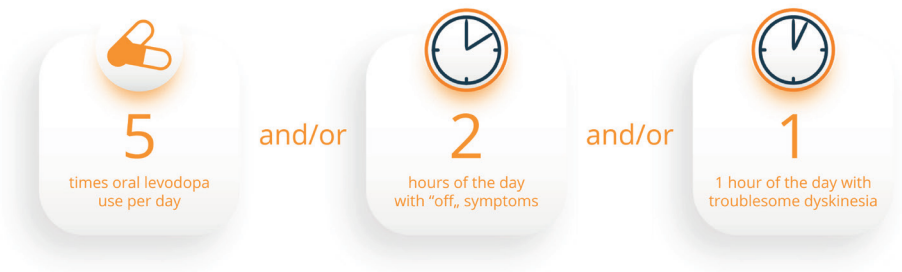
APD = Advanced PD
ADL = Activities of daily living

The panel of movement disorders specialists determined that moderate levels of bothersome motor fluctuations and dyskinesia are indicators that are detectable to the clinician, distressing to the patient, and significantly interfere with daily life.

CONCLUSION

The results of this Delphi model provide a preliminary set of indicators to identify patients transitioning to APD, to identify patients requiring non-oral/device-based therapies, and to make clinical choices between the most widely available device-based therapies.

Algorithm "5-2-1"



Specific descriptive indicators identified in this study by the panel of leading movement disorders specialists provide objective information on indicators of patients who are inadequately controlled on oral medications and who may benefit from transition to device-based therapies.

The 5:2:1 criteria assists neurologists to make decisions about advanced PD and to adjust therapy management in time to improve quality of care and patient outcomes.

WHICH THERAPEUTIC STRATEGY MAY REDUCE TIME SPENT IN "OFF" AND DYSKINESIA?

Advancing Parkinson´s disease stage is generally associated with the development of potentially disabling motor complications (such as motor fluctuations and dyskinesia) and a narrowing therapeutic window.

Continuous dopaminergic stimulation (CDS) has become one of the main concepts in present Parkinson's disease (PD) research.

When strategies of providing more continuous dopaminergic stimulation by adjusting oral medication fail, patients may be candidates for one of three device-aided therapies: continuous subcutaneous Apomorphine infusion, continuous duodenal/jejunal levodopa/Carbidopa pump infusion, or deep brain stimulation (DBS).

A consensus was reached among a group of movement disorders specialists on the key motor, non-motor and functional indicators of PD patients who may be suspected of having APD, and a preliminary profile of PD patients who may be candidates for device-based therapies. (Antonini et al., 2018)

Given the **impact on quality of life** for both patients and caregivers, there is a need for treatment strategies that provide **more continuous dopamine receptor stimulation**.