Satellite Symposium Proceedings

Enhancing Patient Outcomes with Current Therapies – Practical Approaches to Treatment Optimisation in Parkinson's Disease

Proceedings of a Britannia-sponsored symposium held at the 20th International Congress of Parkinson's Disease and Movement Disorders, Berlin, Germany, 19–23 June 2016

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Despite taking multiple oral medications to control the symptoms of Parkinson's disease (PD), many patients experience significant OFF time each day, with troublesome motor fluctuations and dyskinesias, that impact their quality of life. This symposium, chaired by Claudia Trenkwalder (Germany), set out to review the most practical and effective approaches to enhance the outcomes of PD patients across all disease stages using currently available therapies. Stuart Isaacson (US) discussed how to optimise ON time in PD patients once fluctuations start. He highlighted the importance of considering non-oral routes of administration of PD medication to avoid gastrointestinal issues that are common in PD and can affect medication absorption. He reviewed the results of the AM-IMPAKT (Apokyn for Motor IMProvement of morning AKinesia Trial) study, which demonstrated that delayed ON and dose failure due to poor absorption of oral levodopa can be rapidly and reliably overcome with subcutaneous apomorphine injection. Georg Ebersbach (Germany) considered the later stages of disease and the management of patients who require continuous dopaminergic stimulation. Using case study illustrations, he advised how to select the correct form of advanced therapy for patients, highlighting the importance of continuous review and monitoring to optimise their outcomes.

Keywords

Parkinson's disease, motor fluctuations, levodopa, subcutaneous apomorphine injection, subcutaneous apomorphine infusion

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Introduction

Presented by: Claudia Trenkwalder

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Professor Trenkwalder considered that the challenge of how to enhance outcomes for patients was a key focus of clinical care for all clinicians who treated patients with Parkinson's disease (PD). However, despite receiving multiple medications, many patients with PD find that their symptoms are not adequately controlled. Commonly, they complain about experiencing motor OFF periods with akinesia, which impact on their quality of life (QoL) and their ability to undertake their daily activities.[1]

Motor OFF periods that occur upon awakening (early morning OFF [EMO] periods) are often the first manifestation of motor fluctuations. They are known to be common in PD patients[2,3] and can interfere with their ability to undertake their usual morning routine – getting out of bed, having a shower etc. – as well as having a significant negative impact on their QoL.[2] EUROPAR was an international, multicentre, observational study of 320 PD patients receiving dopaminergic therapy that investigated the prevalence and characteristics of EMO periods.[3] The results showed that EMO periods were present in 60% of PD patients in the study and occurred throughout the course of the disease at all stages: mild, moderate and severe. Importantly, at least half of patients who were already being treated with optimised dopaminergic therapy still experienced EMO periods.

Despite the persistence of motor problems, as their PD progresses, many patients remain on oral therapies when in fact their symptoms suggest they would be better suited to a more advanced therapy which would give them continuous dopaminergic stimulation. It seems there is a need for clinicians to give their patients a better explanation of advanced treatment options available to them at this point, such as subcutaneous apomorphine infusion, intrajejunal levodopa infusion and deep-brain stimulation, so that together they can make an informed treatment decision that best suits the individual patient's needs and may reduce their negative feelings or hesitation about trying non-oral treatments.

In an effort to encourage a more 'tailored' approach to treatment, the European Parkinson's Disease Association (EPDA) Inventory has recently been established which aims to identify gaps in the current PD care pathways and to seek out national examples of good practice (www.epda.eu.com/en/projects/my-pd-journey/work-programme/european-inventory/).

The focus of this symposium was therefore to discuss what clinicians can do to better optimise therapy for PD patients in their care, using the currently available treatment options. The presentations focused firstly on how best to manage patients when fluctuations first start and then discussed patients with more advanced disease experiencing severe and frequent OFF periods. In each case the presenters highlighted the practical issues facing clinicians in their daily practice including how to select which treatment is best suited for each patient and, once they are established on therapy, how best to monitor them to ensure the best possible outcomes. ❑

Optimising ON Time When Fluctuations Start

Presented by: Stuart H Isaacson

FIU Herbert Wertheim College of Medicine, Miami, Florida, US; Parkinson Disease and Movement Disorders Center of Boca Raton, Florida, US

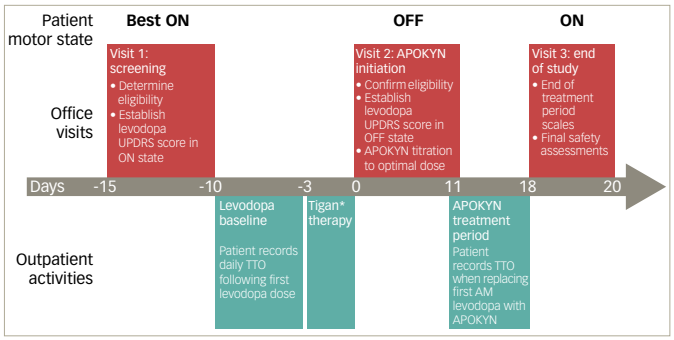
As their disease progresses, many PD patients experience motor fluctuations and increasing periods of OFF time, even though they may be taking a range of different PD medications. In the early stages of levodopa treatment – the 'gold standard' PD therapy – the clinical effect is typically rapid, reliable and sustained, and patients experience excellent benefits in terms of symptom control. However, with long-term treatment and disease progression, the duration of benefit of each levodopa dose becomes progressively shorter and patients begin to experience fluctuations in motor function, alternating between ON responses with a good antiparkinsonian effect and OFF responses when levodopa does not adequately treat their motor symptoms.[4,5] The clinical effects begin to mimic the pharmacokinetics of levodopa and its short half-life in the plasma. Motor fluctuations can include end-of-dose wearing off, a delay in the time taken to turn ON, suboptimal ON, dose failure (no-ON), morning akinesia, postprandial OFF, and nocturnal akinesia. In some cases, patients can experience rapid oscillations between ON and OFF states (ON–OFF phenomena) without an apparent association with the levodopa dose.

Professor Isaacson considered that the development of motor fluctuations is a key limitation to the long-term management of PD with levodopa. Within five years of starting oral levodopa therapy 38–50% of patients develop motor fluctuations[6–8] which can impact significantly on their ability to function and their overall QoL.[2,9] While motor fluctuations are classically associated with the later stages of PD, they also occur in early disease. Patients with early disease, presenting as well controlled, may in fact already be experiencing fluctuations in their response to levodopa and this has consequences for the patient's long-term outcome and choice of therapy.

In addition, up to half of levodopa-treated patients experience involuntary movements or dyskinesias at peak oral doses after five years of therapy and most within 10 years.[10] These typically occur in association with high concentrations of levodopa in the plasma and maximum improvement in the motor response. Dyskinesias can interfere with walking and balance, and lead to social embarrassment for patients and their families.[11]

As reported in the recent EUROPAR study, there is a high incidence of EMO periods in PD patients throughout the course of the disease, including those receiving 'optimised' medication.[3] Motor symptoms are frequent during these EMO periods, which can be prolonged by delayed onset or dose failure of oral medication. The resulting motor complications can

Figure 1: AM IMPAKT study design[25]



Tigan (trimethobenzamide) was used as the anti-emetic in this study for apomorphine initiation as domperidone is not availible in the USA; TTO = Time to ON, UPDRS = Unified Parkinson's Disease Rating Scale

have a significant impact on the patient's overall QoL[2] and affect their ability to get on with their day.

To date, management of these motor fluctuations and OFF periods had focused very much on tackling end-of-dose wearing off of oral PD medication. However, it is now recognised that in addition to end-of-dose wearing off, there are other contributors to total OFF time. Delayed time-to-ON (TTO) is reported to be more than twice the duration of wearing off[12] and can result in morning akinesia, delayed ON and postprandial akinesia. It is important that clinicians recognise the different factors that can result in motor fluctuations and OFF periods, and manage them effectively in order to maintain the patient's QoL and independence.

The objective of treatment in these cases is to reverse the OFF state into an ON state quickly and reliably. Various therapeutic strategies have been employed to try and achieve this including:

- modifying the oral levodopa dosing by giving higher or more frequent doses, administering the dose within 30 minutes of a meal, reducing the amount of protein taken around the time of dosing, or taking the tablets with a carbonated beverage;[13]
- modifying the levodopa formulation by using liquid or dispersible levodopa formulations, however inconsistent results have been observed with this approach;[14,15]
- enhancing the action of levodopa by the addition of adjunctive monoamine oxidase B (MAO-B) inhibitors or catechol-O-methyl transferase (COMT) inhibitors. While this approach may alleviate the severity of the OFF period in morning akinesia it does not result in a reliable ON state; and[16]
- using long-acting dopamine agonists given orally once-daily or administered transdermally have been shown to improve motor symptoms but patients are still not fully in the ON state.[17]

A complicating factor in this clinical picture and a contributor to the problem of delayed ON of oral medication is gastrointestinal (GI) dysfunction, which is common in PD patients and can occur almost a decade or more before PD is clinically diagnosed.[18–20] GI issues can include problems with swallowing, delayed or erratic gastric emptying (gastroparesis), the presence of intestinal protein that competes with levodopa absorption, or bacterial overgrowth in the intestine.[21–23] Delayed gastric emptying is known to affect up to 70–100% of PD patients.[20] This has important consequences for clinical management as delays in turning ON, particularly in the morning when there is unlikely to be any protein in the stomach, are likely to reflect a delay in the delivery of levodopa to, and its absorption from, the small intestine due to gastroparesis.[19,24]

These factors highlight the need for clinicians to consider non-oral routes of administration that are not affected by GI issues and can therefore provide effective symptom control.

In view of this, the efficacy of subcutaneous apomorphine injection was recently evaluated in AM IMPAKT (Apokyn for Motor IMProvement of morning AKinesia Trial), a Phase IV, multicentre, open-label study where PD patients with delayed ON and morning akinesia were treated with subcutaneous apomorphine injection instead of their usual morning dose of oral levodopa.[25] Subcutaneous apomorphine injection is an established PD medication that has been proven in a range of randomised, double-blind trials to provide rapid (effects seen within 4–12 minutes in the majority of patients) and reliable resolution of OFF periods in PD patients, as measured by a decrease in Unified Parkinson's Disease Rating Scale (UPDRS) motor scores[26–28] as well as being well tolerated.[29] It is the only dopamine agonist that has equivalent antiparkinsonian efficacy to orally-administered levodopa and, as it is given subcutaneously, it has the benefit of avoiding the GI route of administration.

The design of the AM IMPAKT study is shown in *Figure 1*. A screening window of up to five days was permitted to allow investigators time to determine patients' eligibility criteria (Visit 1). At this visit, UPDRS total scores were assessed while patients were in their 'best ON' state. Once they entered the study, patients completed a seven-day baseline period recording daily TTO in a diary every five minutes by marking either 'yes' or 'no' until onset of ON up to a maximum of 60 minutes after their regularly scheduled morning dose of levodopa. At the end of the baseline period, patients started trimethobenzamide antiemetic therapy (for three days) and returned to the clinic for apomorphine titration (Visit 2). Optimal doses were identified by the investigator as the apomorphine dose replicating ≥90% of the subject's 'best ON' UPDRS total score within 15 minutes after injection and without intolerable side effects. Once the optimal dose was identified, patients were instructed to self-inject apomorphine at their regularly scheduled levodopa morning dose time during a seven-day treatment period and record TTO as before. At the end of the study, patients returned to the clinic for final assessments (Visit 3).

Subcutaneous apomorphine injection was found to significantly improve the primary endpoint of a reduction from baseline in TTO. Analysis of data for the 88 patients who completed the study found that they achieved an ON state an average of 37 minutes faster with apomorphine injection than with oral levodopa. During the apomorphine treatment period, approximately 96% of patients experienced a rapid and robust clinical improvement in their TTO. Baseline TTO with levodopa was a mean of 60.1 minutes which reduced significantly to a mean of 23.7 minutes with apomorphine injection ($p<0.0001$), representing a mean change from baseline of 37 minutes.

Notably, dose failures were found to be common during the levodopa baseline period while during apomorphine treatment period most patients achieved an ON state (see *Figure 2*). Dose failures (defined as TTO >60 minutes) were reported for 144 of 310 (46%) of completed diary entries during the levodopa baseline period, but were much less frequent during the apomorphine treatment period (20 of 307 [7%] of diary entries).

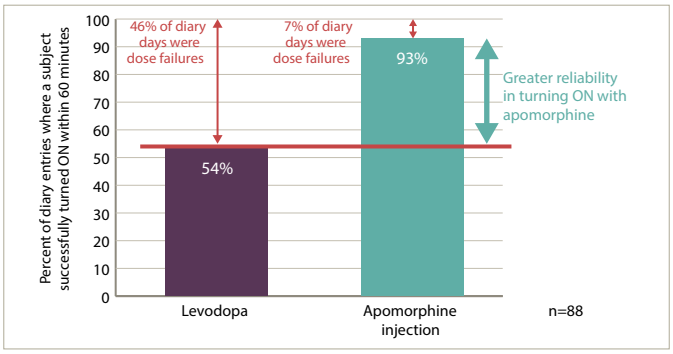
The investigators were also interested in whether these improvements in TTO had any functional impact for patients. Hoehn and Yahr (H&Y) stage is an indicator of postural instability and the risk of falling, Stage 3 being associated with balance impairment. Therefore, any change in H&Y stage could represent an improvement in balance and a reduced risk of

falling. In a secondary analysis, the H&Y stage of patients in the study was compared in the OFF state prior to the first dose of apomorphine and then when ON after an optimal dose of apomorphine. A total of 49 patients had an improved H&Y stage following apomorphine treatment, which may translate into improved function and balance.[25,30]

Further support for the clinical relevance of the significant reduction in TTO with apomorphine was provided by the patients' and clinicians' assessment of overall health status and disease severity. Patients reported a better health status and fewer problems related to mobility, self-care, usual activities, less pain/discomfort and less anxiety/depression when treated with apomorphine injection compared with oral levodopa.[25] Global assessments of disease severity were rated by both patients and clinicians and disease severity found to have significantly improved with apomorphine, and observed after only one week of treatment. Notably, compared with the investigators, patients in the study consistently rated their baseline disease severity as worse and their degree of improvement in disease severity as greater with apomorphine, suggesting patients find morning akinesia a more significant problem than is currently recognised in clinical practice.

Professor Isaacson concluded that the findings of the AM IMPAKT study suggest that delayed ON and dose failure related to impaired GI delivery and/or intestinal absorption of oral levodopa can be significant problems for PD patients, particularly upon awakening. Clinicians therefore need to be more aware of EMO symptoms and take steps to manage them effectively in their patients and should consider medications that avoid the oral route of administration. Apomorphine injection offers an easy, practical way to resolve morning akinesia rapidly and reliably in these patients. ❑

Figure 2: AM IMPAKT study results – a more reliable turning ON was observed with apomorphine injection treatment compared with baseline oral levodopa treatment[25]



The Importance of Patient Selection and Monitoring with Continuous Dopaminergic Therapy

Presented by: Georg Ebersbach

Movement Disorders Clinic, Beelitz-Heilstatten, Germany

For many patients with PD, as their disease progresses they find that motor symptoms can no longer be adequately controlled with oral or intermittent therapy. Despite repeated attempts to optimise medication by adjusting dose and combination, many patients continue to experience ON/OFF motor fluctuations and dyskinesias. In light of this, Professor Ebersbach posed the question: what does it mean to 'optimise' dopaminergic medication and what are realistic goals of pharmacotherapy? By selecting the right dopaminergic treatment strategy, he considered that it should be possible to resolve both ON/OFF-fluctuations and dyskinesias in PD patients. Pharmacoresistant motor problems, however, such as falls or ON freezing, may not resolve with adjustments of dopaminergic therapy.

PD patients general experience increasing duration and severity of OFF episodes with increasing duration of disease. Long-term treatment with levodopa is known to be associated with development of motor fluctuations, with the prevalence increasing alongside the duration of disease and cumulative levodopa exposure: OFF episodes are experienced by up to 50% of patients treated with levodopa for five years or more, and approximately 70% of those treated for nine years or more.[31] Notably, the prevalence of OFF episodes is much higher in patients with young-onset PD (earlier than the age of 40 years): more than 90% of such patients develop OFF episodes after five years of treatment with levodopa.[32]

Different therapeutic approaches have been taken to try and resolve motor complications in fluctuating patients including short intervals between levodopa doses, the use of long-acting dopamine agonists and the addition of COMT-inhibitors or MAO-B-inhibitors. Often these are not sufficient to address the problem in the long term.[13,16,17] In this situation, the clinician may need to consider whether the patient may be better suited to continuous dopaminergic stimulation (CDS) therapy to control PD symptoms. Commonly, this treatment approach is prescribed too late as it is wrongly perceived as only being suitable for patients with end-stage disease.

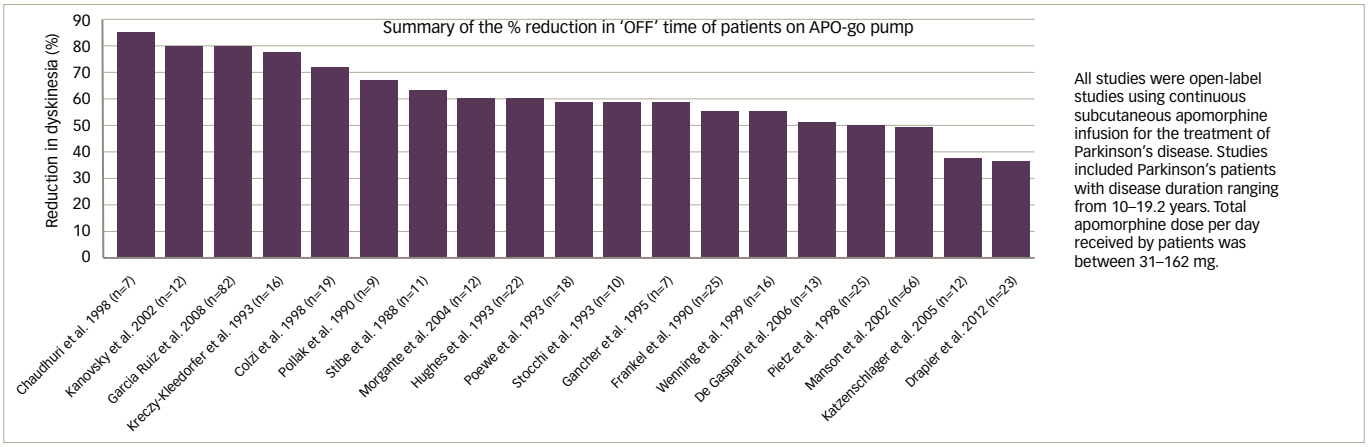
Table 1: Clinical practice recommendations for patients suitable for each of the three continuous dopaminergic stimulation therapy options

	Apomorphine	Levodopa infusion	Deep-brain stimulation
Age >70 years			
Mild to moderate dementia			
Severe dementia			
Tremor (pharmacoresistant)			
Hallucinations			
Suitable for testing			
Independence			
Care/support not available			
Surgical risk			

Adapted from: German Guidelines for Neurology (S2-Leitlinie Parkinson); www.awmf.org/leitlinien/detail/ll/030-010.html

Professor Ebersbach reviewed the profile of patients who might be suitable for CDS. Firstly, they needed to respond well to levodopa – while this seemed counterintuitive, it was in fact the patients who responded well

Figure 3: Combined results from open-label clinical trials of apomorphine infusion showing the percentage reduction in OFF time in Parkinson's disease patients



Adapted from Bhidayasiri R et al., 2015.[37]

to levodopa who obtained optimal benefit from CDS therapies. Patients suitable for CDS should be experiencing response fluctuations despite taking oral PD medications and they should also be willing to at least try an 'invasive' treatment, ideally having support available at home. They should not have severe dementia or psychosis.

There are currently three continuous, non-oral therapies available for the management of motor complications that cannot be controlled sufficiently by standard therapy options, including transdermal patches. These comprise subcutaneous, intrajejunal and surgical interventions. Subcutaneous apomorphine infusion is administered by removable infusion pump and does not require surgery. It also has the benefit of being reversible and can be initiated during inpatient hospitalisation or in a day hospital setting. The second CDS option is administration of levodopa/carbidopa-gel by infusion into the duodenum/jejunum (LCIG). This requires a gastrostomy procedure for the placement of the infusion tube. The third option is deep-brain stimulation (DBS) which requires stereotactic brain surgery.

Correct patient selection is key to the success of CDS therapy and when making a choice, clinicians need to consider the patient's quality of life and complexity of symptoms (irrespective of disease duration), as well as the patient's own preference. This topic has been the subject of several recent reviews and clinical practice recommendations that supplement existing guidelines and aim to aid treatment decisions, including an Expert Consensus Group report on the use of apomorphine in the treatment of PD,[33] the NAVIGATE-PD study, an international consensus on the management of PD patients refractory to non-oral/transdermal PD medications,[34] and an evidence-based review by Volkmann et al. of DBS and infusion therapies.[35] Professor Ebersbach gave an overview of the German Guidelines for Neurology, which outline differential criteria for patients most suited for each of the three CDS options using a 'traffic light' system of coding (www.awmf.org/leitlinien/detail/ll/030-010.html) (see *Table 1*).

He highlighted that apomorphine infusion was the only one of the three options that patients were able to test without any major procedure before committing to long-term treatment, since it was relatively non-invasive and reversible. Head-to-head comparisons of subcutaneous apomorphine infusion and other CDS therapies are, however, limited. The EuroInf study, a large-scale, open-label, multicentre, international, real-life study was undertaken to compare apomorphine infusion (n=43) with LCIG (n=44) at 12 centres throughout the UK, Italy, Sweden, Germany, Slovenia, Austria, and Denmark.[36] Both apomorphine and levodopa infusion showed large effect sizes for total motor and QoL scores. In terms of safety and tolerability, stoma-site irritation and abdominal bloating were more common in the LCIG group while psychiatric adverse events were more common in the apomorphine group.

A recent Expert Consensus Report gave recommendations for patients who are suitable for treatment with apomorphine infusion.[33] The authors considered that apomorphine infusion is suitable for PD patients with troublesome OFF periods despite optimised treatment, in particular those who consider that intermittent apomorphine injections are required too frequently and in cases where dyskinesias limit further therapy optimisation.

Apomorphine infusion can also help simplify complex PD dosing regimens. A range of open-label clinical studies have shown that treatment with apomorphine infusion allows reductions of up to 81% in oral levodopa doses compared with baseline.[33,37] This reduction in the overall pill burden and the requirement for multiple oral PD medications can potentially improve convenience and patient compliance with therapy, and minimise drug–drug interactions.[33] Apomorphine infusion can also be prescribed as an alternative to surgical therapy or LCIG if these are contraindicated, or because of patient preference. As subcutaneous apomorphine infusion bypasses the GI system it is also suitable for cases where absorption of oral levodopa is impaired due to swallowing difficulties or gastric emptying problems.

Professor Ebersbach illustrated these points using a case study of a female PD patient aged 65 years from his clinic. She had had PD for seven years and response fluctuations for three years, including severe non-motor symptoms (NMS) during OFF periods (depression, anxiety and pain). She was taking multiple medications, including controlled-release levodopa, tolcapone, pramipexole and amantadine, but still experienced a significant worsening of motor symptoms and of mood during OFF periods, fragmentation of sleep and daytime sleepiness, as well as slight hyperkinesia during ON periods. She started apomorphine infusion (5 mg/h) from 06:00–22:00 each day and was able to reduce her total daily OFF time by approximately 50% as well as reducing the total daily dose and frequency of her oral medications. As a result of the improvement in ON time she was able to have a greater participation in social activities and became less anxious.

To illustrate the process of initiation, Professor Ebersbach described a second case study of a male PD patient in his clinic aged 64 years who had had PD for nine years. He was taking a complex oral medication regimen comprising amantadine (2 x 150 mg), levodopa (7 x 100 mg), ropinirole (16 mg), safinamide (100 mg) and clozapine (25 mg). Despite this, he experienced bothersome hyperkinesia for 30% of the day and wearing-off with tremor for 20% of the day. He also had mild cognitive impairment with occasional hallucinations. Professor Ebersbach advised there were two possible ways to initiate apomorphine infusion in this patient.

- Stop taking ropinirole and start the apomorphine titration, increasing by 1mg/hour. If hyperkinesias occur, then reduce the levodopa dose.
- A faster approach would be to establish the response threshold with an apomorphine test, then start apomorphine infusion as monotherapy at the hourly threshold dose determined in the test.

The clinical benefits of apomorphine infusion have been confirmed in a range of open-label clinical trials. It has been shown to significantly reduce OFF time in PD patients by up to 85% compared with baseline[33,37] (see *Figure 3*) and to increase ON time by an average of approximately 5.5 hours per waking day.[38] Apomorphine infusion also significantly reduces dyskinesias during ON time by up to 85% compared with baseline and can reduce the severity of dyskinesias that do occur by up to 65% compared with baseline.

Once patients are established on CDS therapy, it is important that they are monitored and regularly reviewed. Ebersbach advised scheduling regular clinics visits and offering unscheduled consultations, including trouble-shooting for both medical and technical problems. Patients should be encouraged to keep a diary recording ON and OFF periods. Medication can then be adapted as needed – for example, the apomorphine infusion pump has a variable flow which be adjusted if required – and should be regularly reassessed.

The beneficial consequences of treatment monitoring and optimisation have been reported in a Dutch study of 65 PD patients whose symptoms were such that they could no longer function in their home setting.[39] The investigators found that 74% of patients were sub-optimally treated with dopaminergic therapy. However, monitoring and optimisation of treatment delayed nursing home admission of these patients by up to 1.5 years and their overall QoL was improved. The delay in nursing home admission may also be potentially cost effective.

Professor Ebersbach concluded by saying that an individualised approach to therapy and correct selection of the most suitable treatment for each patient at the right time in their disease course, was key to the success of therapy. Of the available CDS options, apomorphine infusion is easy to administer, has a good safety profile and is reliably effective against OFF symptoms. Regular patient follow-up and monitoring can enhance patients' adherence and compliance, which can ultimately lead to optimal outcomes. ❑

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When the increasing frequency and severity of daily 'OFFs', dyskinesias or pill burden threaten everything they live for,[1,2,6] it's time to prescribe APO-go PUMP[3] – continuous subcutaneous infusion of apomorphine, delivering smooth, predictable control of motor fluctuations.[3-5]

APO-go® PUMP

apomorphine hydrochloride

Continuous, reliable 'ON'[3-5]

APO-go® Apomorphine hydrochloride. **PRESCRIBING INFORMATION.** Consult Summary of Product Characteristics before prescribing. **Uses:** Treatment of motor fluctuations ('ON-OFF' phenomena) in patients with Parkinson's disease which are not sufficiently controlled by oral anti-Parkinson medication. **Dosage and Administration:** Apomorphine hydrochloride is administered subcutaneously either as an intermittent bolus injection or by continuous subcutaneous infusion. Its rapid onset (4-12 mins) and duration of action (about 1 hour) may prevent an 'OFF' episode which is refractory to other treatments. 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). Please refer to the Summary of Product Characteristics for full details before initiating therapy. Patients treated with apomorphine will usually need to start domperidone at least two days prior to initiation of therapy. The domperidone dose should be titrated to the lowest effective dose and discontinued as soon as possible. Before the decision to initiate domperidone and apomorphine treatment, risk factors for QT interval prolongation in the individual patient should be carefully assessed to ensure that the benefit outweighs the risk. The optimal dosage of apomorphine HCl has to be determined on an individual patient basis; individual bolus injections should not exceed 10mg and the total daily dose should not exceed 100mg. Do not use if the solution has turned green. The solution should be inspected visually prior to use. Only clear, colourless and particle free solution should be used. **Contraindications:** Children and adolescents (up to 18 years of age). Known sensitivity to apomorphine or any other ingredients of the product. Respiratory depression, dementia, psychotic disease or hepatic insufficiency. Intermittent apomorphine HCl treatment is not suitable for patients who have an 'ON' response to levodopa which is marred by severe dyskinesia or dystonia. **Pregnancy and lactation:** Apomorphine should not be used in pregnancy unless clearly necessary. Breast-feeding should be avoided during apomorphine HCl therapy. **Interactions:** Patients should be monitored for potential interactions during initial stages of apomorphine therapy. Particular caution should be given when apomorphine is used with other medications that have a narrow therapeutic window. It should be noted that there is potential for interaction with neuroleptic and antihypertensive agents. It is recommended to avoid the administration of apomorphine with other drugs known to prolong the QT interval. Apomorphine can increase the antihypertensive effects of domperidone. **Precautions:** Use with caution in patients with renal, pulmonary or cardiovascular disease, or who are prone to nausea or vomiting. Extra caution is recommended during initiation of therapy in elderly and/or debilitated patients. Since apomorphine may produce hypotension, care should be exercised in patients with cardiac disease or who are taking vasoactive drugs, particularly when pre-existing postural hypotension is present. 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 whilst driving or operating machines during treatment with apomorphine. Haematology tests should be undertaken at regular intervals, as with levodopa, when given concomitantly with apomorphine. 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. 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. When used in combination with domperidone, risk factors in the individual patient should be carefully assessed. This should be done before treatment initiation, and during treatment. Important risk factors include serious underlying heart conditions such as congestive cardiac failure, severe hepatic impairment or significant electrolyte disturbance. Also medication possibly affecting electrolyte balance, CYP3A4 metabolism or QT interval should be assessed. Monitoring for an effect on the QTc interval is advisable. An ECG should be performed prior to treatment with domperidone, during the treatment initiation phase and as clinically indicated thereafter. The patient should be instructed to report possible cardiac symptoms including palpitations, syncope, or near-syncope. They should also report clinical changes that could lead to hypokalaemia, such as gastroenteritis or the initiation of diuretic therapy. At each medical visit, risk factors should be revisited. Apomorphine has been associated with local subcutaneous effects that can be reduced by rotation of injection sites or use of ultrasound on areas of nodularity and induration. Contains sodium metabisulphite which rarely causes severe allergic reactions and bronchospasm. **Side Effects:** Local induration and nodules (usually asymptomatic) often develop at subcutaneous site of injection, leading to areas of erythema, tenderness, induration and panniculitis. Irritation, itching, bruising and pain may also occur. Rarely, injection site necrosis and ulceration have been reported. Pruritus may occur at the site of injection. Drug-induced dyskinesias during 'ON' periods can be severe, and in a few patients may result in cessation of therapy. Postural hypotension is seen infrequently and is usually transient. Transient sedation following each dose of apomorphine may occur at the start of therapy, but this usually resolves after a few weeks of treatment. Dizziness and light-headedness have also been reported. Nausea and vomiting may occur, particularly when APO-go treatment is initiated, usually as a result of the omission of domperidone. Neuropsychiatric disturbances including transient mild confusion and hallucinations - seeing, hearing or feeling things that are not there have occurred during apomorphine therapy and neuropsychiatric disturbances may be exacerbated by apomorphine. Positive Coombs' tests, haemolytic anaemia and thrombocytopenia have been reported in patients receiving apomorphine. Local and generalised rashes have been reported. Eosinophilia has occurred in only a few patients during treatment with apomorphine HCl. Patients treated with dopamine agonists, including apomorphine, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, compulsive spending or buying, binge eating or compulsive eating, (especially at high doses) and syncope (fainting). Apomorphine is associated with somnolence. Yawning and breathing difficulties have been reported, as has peripheral oedema. Apomorphine has been associated with sudden sleep onset episodes. Prescribers should consult the *Summary of Product Characteristics in relation to other side effects.* **Presentation and Basic NHS Cost:** APO-go PENs (disposable multiple dosage injector system) contain apomorphine hydrochloride 10mg/mL, as follows: 30mg in 3ml - basic NHS cost £123.91 per carton of 5 pens. APO-go Pre-filled syringes contain apomorphine hydrochloride 5mg/mL, as follows: 50mg in 10ml - basic NHS cost £73.11 per carton of 5 syringes. APO-go ampoules contain apomorphine hydrochloride 10mg/ml as follows: 50mg in 5ml - basic NHS cost £73.11 per carton of 5 ampoules. **Marketing Authorisation Numbers:** APO-go Ampoules: PL 04483/0072. APO-go Pens: PL 04483/0073. APO-go Pre filled syringes: PL 04483/0074. **Legal Category:** POM. **Date of last revision:** May 2016. For further information please contact: Britannia Pharmaceuticals, 200 Longwater Avenue, Green Park, READING, Berkshire, RG2 6GP. Version Number: APG.PI.V24.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Medical Information on 0870 851 0207 or dso@britannia-pharm.com

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