

8-2015

Non-Oral Drug Delivery Strategies: From Early Diagnosis to Advanced Treatments

Claudia Trenkwalder

University Medical Centre of Göttingen

Werner Poewe

Innsbruck Medical University

Fabrizio Stocchi

Institute of Research and Medical Care

Stuart H. Isaacson

Herbert Wertheim College of Medicine, Florida International University, sisascso@fiu.edu



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Recommended Citation

EMJ Neurol. 2015;3[1]:40-49.

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NON-ORAL DRUG DELIVERY STRATEGIES: FROM EARLY DIAGNOSIS TO ADVANCED TREATMENTS

Summary of presentations from the Britannia-sponsored
symposium held at the 1st Congress of the European Academy of
Neurology (EAN), Berlin, Germany, on 21st June

Chairpersons

Claudia Trenkwalder,¹ Werner Poewe²

Speakers

Werner Poewe,² Fabrizio Stocchi,³ Stuart H. Isaacson⁴

1. University Medical Centre of Göttingen, Göttingen;
and Paracelsus Elena Klinik, Center of Parkinsonism and Movement Disorders, Kassel, Germany
2. Department of Neurology, Innsbruck Medical University, Innsbruck, Austria
3. Institute of Research and Medical Care, IRCCS San Raffaele, Rome, Italy
4. Florida International University, Herbert Wertheim College School of Medicine, Miami;
Parkinson's Disease and Movement Disorders Center of Boca Raton, Boca Raton;
and Marcus Neuroscience Institute, Boca Raton Regional Hospital, Boca Raton, Florida, USA

Disclosure: C. Trenkwalder has received personal fees for advisory boards from Mundipharma, UCB, Vifor Pharma, Britannia Pharmaceuticals, and Novartis; she has also received payments for lectures from UCB, AstraZeneca, and Desitin; and has received royalties from Schattauer Verlag. W. Poewe has received personal fees from Britannia for consultancy and lecture fees in relation to clinical drug development programmes for Parkinson's disease (PD); he has also received personal fees from AbbVie, AstraZeneca, Britannia, Lundbeck, Teva, Novartis, GSK, Boehringer-Ingelheim, UCB, Orion Pharma, Zambon, and Merz Pharmaceuticals for consultancy and lecture fees in relation to clinical drug development programmes for PD, outside of the submitted work; and has received royalties from Thieme, Wiley Blackwell, and Oxford University Press. F. Stocchi has received honoraria for participation in scientific advisory boards for GSK, Teva, Boehringer Ingelheim, Newron, Merck Serono, Novartis, Lundbeck, Impax, Schering-Plough, MSD, and UCB; and has received speaker fees for educational lectures for GSK, Teva, Boehringer Ingelheim, Merck Serono, Novartis, Lundbeck, UCB, and Britannia. S. H. Isaacson has received honoraria for CME activities, research grants and/or consultant and promotional speaker fees from AbbVie, Acadia, Adamas, Addex, Allergan, Allon, AstraZeneca, Biotie, Britannia, Chelsea, Civitas, Eisai, GE, GSK, Impax, Ipsen, Kyowa, Lilly, Merck Schering-Plough, Medtronics, Merz, Michael J. Fox Foundation, Novartis, Neurocrine, National Institutes of Health (NIH), Novartis, Orion, Parkinson Study Group, Phytopharm, Purdue, Roche, Santhera, Serono, Shire, Teva, UCB, and US World Meds.

Acknowledgements: Writing assistance was provided by Dr Karen Wolstencroft, Helen Lawn Associates PR Limited.

Support: This symposium and the publication of this article was funded by Britannia Pharmaceuticals Limited. The views and opinions expressed are those of the authors and not necessarily of Britannia Pharmaceuticals Limited.

Citation: EMJ Neurol. 2015;3[1]:40-49.

MEETING SUMMARY

This educational symposium, sponsored by Britannia Pharmaceuticals Limited, was held during the 1st Congress of the European Academy of Neurology (EAN), which took place from 20th-23rd June 2015 in Berlin, Germany. The symposium reviewed the role of non-oral drug delivery strategies in patients with Parkinson's disease (PD) and how they can overcome problems that occur with the gastrointestinal (GI) route of administration in many patients. GI dysfunction is recognised as a common problem in PD and may in fact be a preclinical marker of the disease. It can affect the absorption of oral medication resulting in OFF periods and unreliable control of motor symptoms, which in turn can have a negative impact on quality of life (QoL). Delayed time-to-ON (TTO) after an oral levodopa dose and dose failures are known to be significant contributors to total OFF time. Results of the recently completed

AM-IMPAKT trial in patients with morning akinesia due to a delay in the onset of oral levodopa effect demonstrate that apomorphine intermittent injection (penject) is able to provide rapid and effective resolution of such complications, restoring patients to the ON state quickly and allowing them to get on with their daily activities.

Gastrointestinal Dysfunction in Parkinson's Disease

Professor Werner Poewe

Prof Poewe reminded delegates that while PD is traditionally considered to be primarily a movement disorder, it is in fact a multi-system disease and affects areas of the brain that are not directly involved in motor control, for example the hypothalamus, locus coeruleus, and raphe nuclei of the brainstem.^{1,3} PD pathology also extends into the peripheral autonomic nervous system involving sympathetic ganglia, cardiac sympathetic efferents, and the enteric nervous system (ENS).

The PRIAMO study⁴ was a multicentre survey that interviewed 1,072 consecutive PD patients at different stages of disease (treatment-naïve, stable, and complex) over a period of 12 months at 55 centres in Italy to assess the prevalence of non-motor symptoms (NMS) in PD and their impact on QoL. The results found that 98.6% of patients with

PD reported the presence of NMS. They occurred across all disease stages and many patients experienced multiple symptoms - the mean number of NMS per patient in the survey was 7.8. Notably, GI symptoms were present in 45% of newly diagnosed, untreated patients, 60% of those with stable disease, and 72% of those with complex disease (Figure 1).

Prof Poewe commented that, in many cases, if patients were not specifically asked about these symptoms, they might be overlooked. He highlighted the results of a study of 89 PD patients who undertook a validated NMS questionnaire (NMSQ), which was compared with standard neurology clinic reporting in case notes.⁵ Results of NMSQ found a mean of 11 different NMS per patient. In contrast, chart review showed a mean of 4.8 NMS per patient, suggesting that some symptoms remain under-reported by patients unless questioned. In this study, constipation was reported by 48%, highlighting that GI problems are a frequent non-motor issue in PD.

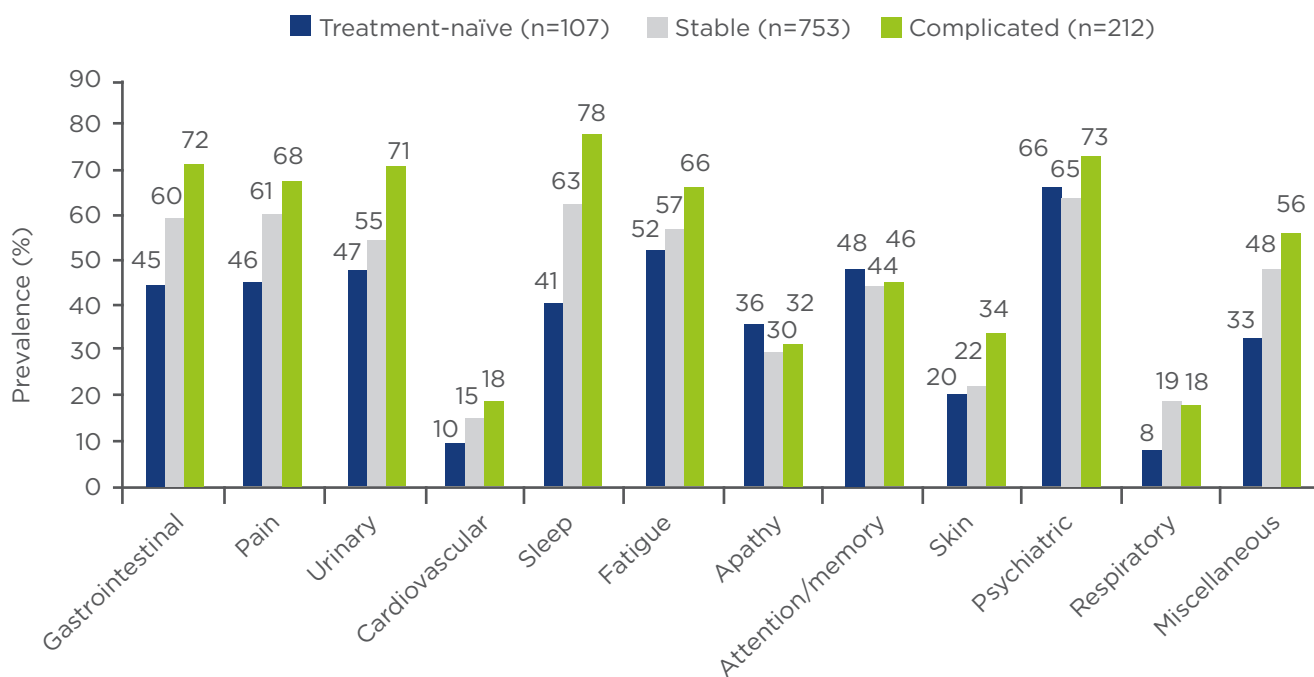


Figure 1: Prevalence of non-motor Parkinson's disease symptoms in patients with treatment-naïve, stable, and complex disease: results of the PRIAMO study.⁴

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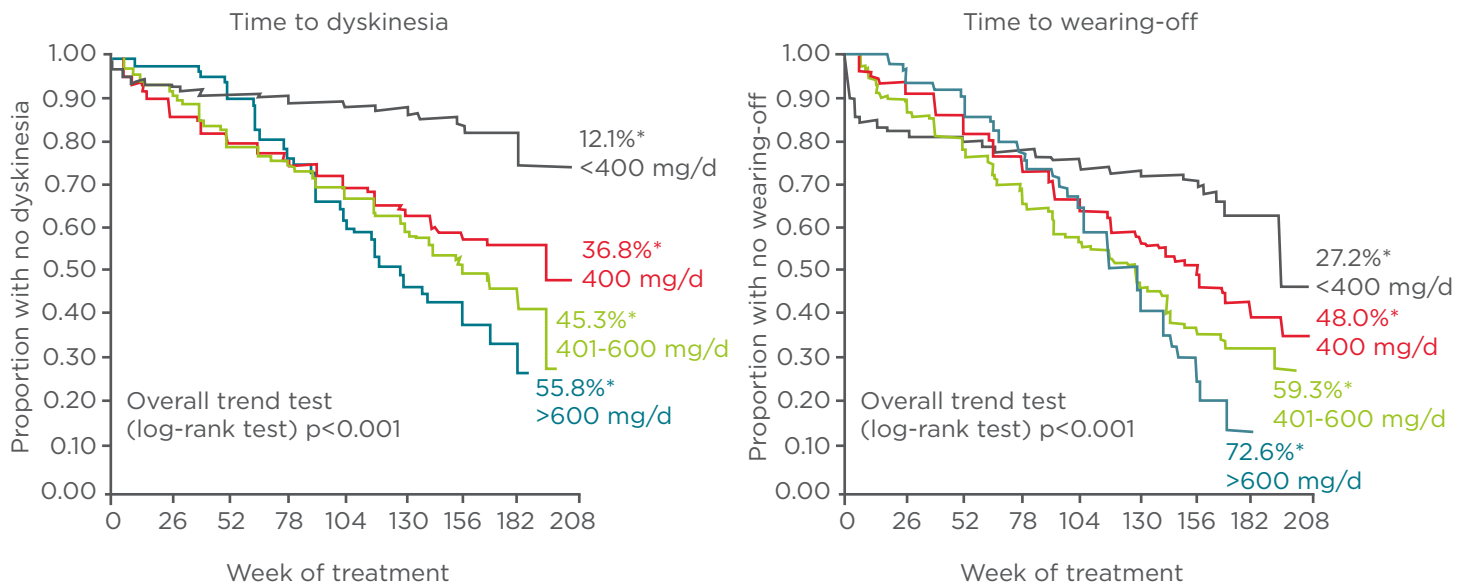


Figure 2: Levodopa dose is predictive of the development of dyskinesia and wearing-off: results of the STRIDE-PD study.¹⁷

*Rates at study termination.

Reproduced with permission of Movement Disorders.

GI dysfunction in PD patients is now known to occur at all levels of the GI tract.^{6,7} Common clinical features include sialorrhoea (drooling), dysphagia, gastroparesis, colonic dysmotility (constipation), and anorectal dysfunction. These symptoms have a range of clinical consequences for patients, and in some cases can be a burden for their caregivers too, resulting in social embarrassment, reduced appetite, weight loss, aspiration of food, and impact on effective absorption of oral PD medication.

It is now recognised that development of NMS can precede the onset of motor symptoms in PD. A recent study was undertaken to investigate the timing of onset of NMS in PD and the possible association with motor phenotype using a custom-made questionnaire in 109 newly diagnosed, untreated PD patients and 107 age and sex-matched healthy controls from 11 centres in Spain and Austria.⁸ Seventeen of 31 different NMS were found to be more common in PD patients than in controls (p < 0.05). Notably, in >50% of PD patients, NMS preceded the onset of motor symptoms. The symptoms reported more frequently in the 2-10-year premotor period were smell loss, mood disturbances, taste loss, excessive sweating, fatigue, and pain. Constipation, dream-enacting behaviour, excessive daytime sleepiness, and postprandial fullness were frequently perceived more than 10 years before motor symptoms occurred.

The natural history of PD is characterised by a gradual decline in striatal dopamine through the preclinical and prodromal stages, eventually reaching an 80% deficit which is indicative of a diagnosis of PD and represents a 50% loss of neurons in the substantia nigra. The identification and characterisation of prodromal NMS of PD is the subject of considerable research. In the case of GI dysfunction, studies by Abbott and colleagues⁹ found that constipation and infrequent bowel movements were associated with a significantly elevated risk of future PD (p = 0.005). Further studies by this group found evidence that constipation can predate the extrapyramidal signs of PD and could be one of the earliest markers of the beginning of the PD process. The preclinical phase of PD is often characterised by the presence of incidental Lewy bodies (ILB). Assessment of bowel movement frequency in 245 men, aged 71-93 years without clinical evidence of PD who later received post-mortem examinations, found that the percentage of brains with ILB declined with increasing bowel movement frequency (p = 0.013).¹⁰

There is a substantial need for an accurate early diagnostic test for PD, and with this in mind, researchers have been focussing on the potential link between ENS pathology and preclinical or prodromal PD. Alpha-synuclein is the primary structural component of Lewy bodies and its aggregation is thought to play a critical role in the

development of PD. Alpha-synuclein pathology has been found in body tissues outside of the brain not usually associated with PD. A recent study has suggested that alpha-synuclein may be present in colonic biopsy tissue in early or even prodromal PD before the development of characteristic PD motor symptoms, and may therefore be a potential diagnostic biomarker for pre-motor PD.¹¹ Archival colon biopsy samples obtained 2-5 years before PD onset were analysed for three patients with PD. All patients showed immunostaining for alpha-synuclein at least 2 years before the first motor PD symptom occurred. In contrast, no corresponding alpha-synuclein immunostaining was seen in 23 healthy controls.

Prof Poewe concluded by highlighting that many aspects of GI dysfunction in PD are now recognised to have a significant potential impact on oral drug delivery and hence clinical efficacy.¹² Difficulties in swallowing can lead to adherence problems in patients receiving oral medication. Delayed gastric emptying (gastroparesis) can lead to a reduction in the speed of oral levodopa delivery to its site of absorption in the small intestine, resulting in a 'delayed ON' or even dose failure. Competition between levodopa and proteins for transport across the GI mucosa can result in unpredictable drug responses. The OFF periods that the patient experiences will result in motor and non-motor fluctuations that have a negative impact on their QoL, and so Prof Poewe considered that it was important that alternative therapeutic interventions were sought in such cases.

Wearing OFF and Delayed ON – Motor and Non-Motor Fluctuations

Professor Fabrizio Stocchi

Prof Stocchi described how 'ON-OFF' fluctuations in PD patients receiving chronic oral levodopa therapy were first described by Marsden and Parkes in 1976.¹³ Motor complications include both motor fluctuations and dyskinesias. Motor fluctuations can include predictable end-of-dose 'wearing-off' phenomena, peripheral problems such as delayed ON (for example morning akinesia) or 'no ON' (dose failure), and unpredictable ON-OFF periods. Dyskinesias may be peak-dose effects, distressing and painful diphasic dyskinesias, or painful OFF-period dystonia. He highlighted how debilitating and distressing these different motor complications can be in the real-life setting with a

series of patient videos. In addition to classical motor fluctuations, many PD patients also experience non-motor fluctuations, such as anxiety, panic attacks, pain, fatigue, mood changes, urinary urgency, and swallowing difficulties.¹⁴

Wearing-off is commonly associated with the later stages of PD. However, a review of preclinical and clinical data suggest that fluctuations in the response to levodopa may appear much earlier than previously thought, and can be present in patients with early disease.¹⁵ Prof Stocchi presented the results of the DEEP study (Early DEtection of wEaring off in Parkinson disease),¹⁶ which was undertaken to assess the frequency of wearing-off in PD patients and its impact on QoL using a validated screening tool, WOQ-19. These results showed that the frequency of wearing-off increased with duration of disease such that, after 10 years, around 80% of PD patients experienced wearing-off phenomena.

Prof Stocchi went on to highlight some of the risk factors underlying complications in PD. He reviewed a secondary analysis of the STalevo Reduction In Dyskinesia Evaluation in Parkinson's Disease (STRIDE-PD) study that had investigated the effect of levodopa dose and other risk factors on the development of dyskinesias and wearing-off. The results demonstrated that time to development of dyskinesias and time to wearing-off both correlated with the dose of oral levodopa (Figure 2).¹⁷ Multivariate analyses showed that factors predictive of dyskinesia included young age at onset, higher levodopa dose, low body weight, female gender, and more severe Unified Parkinson's Disease Rating Scale (UPDRS) Part III scores. Predictors of wearing-off included higher baseline UPDRS scores, higher levodopa dose, and the female gender.

Motor complications in PD patients are recognised to have a significant impact on QoL.¹⁸ This was investigated in 143 patients with PD who were evaluated using the Hoehn and Yahr scale and the motor part of the UPDRS. In addition, a specific PD QoL questionnaire (39-item version, PDQ-39) was used. Motor complications, including early morning akinesia, nocturnal akinesia, end-of-dose fluctuations, paradoxical fluctuations, and unpredictable OFFs, were found to significantly worsen the PDQ-39 Summary Index of patients with PD. The dimensions of mobility, activities of daily living, stigma, and communication were most strongly affected.

Prof Stocchi described an ongoing study, the Time to ON Questionnaire in PD (TOQ-PD), which is a survey being undertaken in PD patients attending a routine clinical appointment to help characterise their early morning OFF problems (unpublished data). This pilot study is a non-interventional, outpatient study being conducted in 90 consecutive patients treated in movement disorders centres. As part of the inclusion criteria, patients, in the opinion of the prescribing physician, had to be able to understand and describe the changes in ON and OFF clinical status. A total of 25% of patients felt that their medication was taking >1 hour to work. Almost 52% of patients found it troublesome when their first daily dose of levodopa took longer than usual to work (delayed ON), did not work well (suboptimal ON), or did not work at all (dose failure). In the case of the mealtime dose of levodopa, this figure was 56%. Patients also described a range of problematic symptoms that occurred while waiting for their levodopa to work, including slowness, stiffness, and difficulty walking.

Prof Stocchi also recognised the contribution of peripheral factors to delayed ON and dose failure with oral levodopa, for example swallowing difficulties which he clearly illustrated with a series of endoscopic videos. Swallowing abnormalities in PD patients include abnormal lingual control of swallowing, lingual festination, delayed swallowing reflex (a tendency of parkinsonian patients to swallow during the inspiration phase increasing the possibility of aspiration), and repetitive or involuntary reflux from the vallecula and piriform sinuses into the oral cavity. These troublesome symptoms need careful management and might require a change in the type of food and diet consumed. Dopaminergic drugs may improve swallowing; however, alternative routes of administration such as transdermal therapy, subcutaneous infusion, or intraduodenal infusion should be considered.

Gastroparesis, or delayed gastric emptying, is common in PD, resulting in postprandial fullness, nausea, vomiting, and impaired drug absorption that in turn leads to delayed ON or no ON.¹⁹ Recently, delayed TTO and dose failures have been recognised as a significant proportion of total OFF time, comprising more than twice the duration of wearing-off in PD patients.²⁰ This was illustrated clearly in a pharmacokinetic study of levodopa given every 4 hours undertaken by Prof Stocchi, which revealed a substantial proportion of OFF

time over the day, and particularly delayed ON (unpublished data).

In view of the high prevalence of GI dysfunction in PD patients and its impact on the efficacy of oral medication, a range of alternative PD medication formulations and routes of administration have been investigated in this setting with varying degrees of success. These include liquid levodopa, transdermal dopamine agonists, subcutaneous apomorphine, and intraduodenal levodopa infusion.

Prof Stocchi also reviewed the strategies that had been investigated to tackle the phenomenon of wearing-off.²¹ Standard oral formulations of levodopa result in pulsatile dopaminergic stimulation and are not able to maintain steady plasma levels throughout the day. Therefore, continuous dopaminergic stimulation (CDS) has been proposed to more closely mimic the physiological situation and help overcome the motor complications that occur with standard oral therapy.²²⁻²⁵ Other options include modifying the timing or formulation of levodopa, modifying the actions of levodopa by using catechol-O-methyltransferase (COMT) inhibitors (entacapone, tolcapone), the use of longer-acting dopamine agonists (such as pramipexole, ropinirole, rotigotine, apomorphine, or pergolide), or by modifying the actions of dopamine at the synaptic level by using a monoamine oxidase B (MAO-B) inhibitor (rasagiline).

One option for CDS that is backed by considerable clinical experience is continuous apomorphine infusion: it has proven efficacy for PD patients with motor fluctuations that are uncontrolled by conventional oral or transdermal medication and is well tolerated. In a recent review, the data for 390 patients from 21 open-label uncontrolled studies were pooled.²⁶ The results showed a 58.2% average OFF time reduction (range 38-80%) and a levodopa-sparing effect with a 45.9% reduction in levodopa-equivalent dose during an observation period of 24.8 months (6-57 months). In the case of dyskinesias, 6 of 11 long-term studies showed ~50% reduction in duration and ~45% reduction in severity of dyskinesias with continuous apomorphine infusion.²⁷ Biphasic and peak-dose dyskinesias showed the best response to therapy. A study by Prof Stocchi's own research group showed a significant and sustained reduction in the severity of dyskinesias with long-term use of continuous apomorphine infusion over a period of 5 years.²⁸

As with all therapeutic interventions, Prof Stocchi noted that it was important to select the right patient in order to maximise the success of treatment. He advised that continuous apomorphine infusion should be considered in all PD patients who develop features of complicated disease irrespective of their age or disease duration. This should include patients who have become progressively disabled, those who experience increasing or long OFF periods, those who have moderate-to-severe dyskinesias, and those who are already suffering with motor complications or who have developed levodopa-induced dyskinesias. PD patients who might not be suitable for this treatment option include those with a poor response to levodopa; those with severe cognitive impairment; patients with contraindications such as hepatic insufficiency, pregnancy, or lactation; patients without support to help them manage the infusion device; and those with excessive skin problems.

Prof Stocchi concluded his presentation by noting that continuous apomorphine infusion has several advantages over other CDS options for PD patients who experience motor fluctuations despite optimised oral medication. Importantly, it is the least invasive of the three advanced therapies (apomorphine infusion, intrajejunal levodopa infusion, and deep brain stimulation) and is completely reversible. Apomorphine infusion is practical to use – it can be initiated during inpatient hospitalisation or in a day-hospital setting – and does not induce tolerance.²⁸

Apomorphine Penject – AM-IMPAKT Trial Results and Best Clinical Practice

Professor Stuart Isaacson

Prof Isaacson noted that over the past two decades the issue of motor fluctuations and OFF periods in PD patients had focussed very much on end-of-dose wearing-off of oral PD medication. However, it is now becoming increasingly recognised that in addition to end-of-dose wearing off there are many other contributors to total OFF time, including nocturnal akinesia, morning akinesia, postprandial akinesia, delayed TTO, and dose failure (no ON). Studies have now shown that delayed TTO is in fact a major contributor to OFF time, being more than twice the duration of wearing-off.²⁰ He acknowledged that when oral levodopa is first used to treat PD patients, the clinical effect

of each levodopa dose is rapid, reliable, and sustained with an onset of around 20 mins and a long-duration response. However, with chronic treatment, the long-duration response is replaced by a short-duration response and OFF periods, such as wearing-off and delayed TTO, become more frequent.

Levodopa has been the recognised ‘gold standard’ treatment for PD for the past 50 years but it is an oral treatment that must be swallowed and therefore its efficacy may be affected if the patient also suffers from GI tract dysfunction. The GI tract is known to be dysfunctional in many PD patients and this can occur almost a decade or more before PD is clinically diagnosed. In addition, medications used to treat PD may also contribute to GI dysfunction, including levodopa, dopamine agonists, anticholinergics, amantadine, and inhibitors of MAO-B and COMT. GI symptoms, such as gastroparesis, can impact on the effectiveness of oral levodopa by delaying its delivery to, and absorption in, the small intestine,^{19,29} resulting in delayed ON or even dose failure.³⁰ Absorption of levodopa can be affected by competition with ingested protein for the amino acid transporter. In addition, recent studies have confirmed a high prevalence of small intestinal bacterial overgrowth in PD, which may also affect levodopa absorption, and have reported an association with poor motor function, longer daily OFF time, and more episodes of delayed ON and no ON.^{31,32}

An investigation of the prevalence of delayed gastric emptying of solids in PD was undertaken in 22 healthy subjects and 36 patients at different clinical stages of PD using a ¹³C-sodium octanoate breath test (OBT).²⁹ The OBT was able to detect a significant delay in gastric emptying of a solid test meal in patients with PD that was associated with disease severity, illustrating how common gastroparesis is across all disease stages. While liquids are able to empty from the stomach quicker than solids, in PD patients there may still be a delay in gastric emptying. In the case of oral levodopa, Doi and colleagues¹⁹ demonstrated a significant relationship between levodopa pharmacokinetics and gastric emptying in PD patients, suggesting that delayed gastric emptying is a causative factor for producing the delayed ON.

The high prevalence of early morning OFF (EMO) periods has been demonstrated in the results of the international, multicentre EUROPAR study.³³ EMO periods occur when the first morning dose

of oral levodopa has a delayed onset of action and were found in this study to be present in 59.7% of the 320 patients, occurring throughout the course of PD in mild, moderate, and severe disease. Prof Isaacson highlighted that EMO periods are often an early sign of emerging motor fluctuations and the loss of the long-duration levodopa response, and can occur despite attempts to optimise oral therapy and the use of multiple medications. During episodes of morning akinesia the patient can experience impaired mobility and function until the oral levodopa takes effect, and this is known to have a negative effect on patient QoL.¹⁸ Although morning akinesia represents the motor component of EMO periods, both motor and NMS are frequent in PD patients at these times.

A range of treatment strategies have been employed in an attempt to resolve the issue of morning akinesia, for example the use of long-

acting dopamine agonists or MAO-B inhibitors, or by aiming to improve delivery of levodopa to the proximal small intestine by using liquid, dispersible, modified, or higher-dose levodopa. However, none of these approaches addressed the problem of PD patients who have gastroparesis where emptying of both solids and liquids may be impaired,²⁹ and in whom a delayed onset of levodopa effect may still occur. This has been illustrated in a study by Chaná and colleagues,³⁰ who assessed the pharmacokinetics of levodopa in 19 patients with advanced PD with and without a delayed onset of first levodopa dose in the morning. The results confirmed that the difference in plasma concentrations of levodopa between the two groups was most likely due to delayed gastric emptying, and this phenomenon probably underlies the delayed clinical response to oral levodopa in many PD patients.³⁰



Figure 3: Apomorphine pen injection.

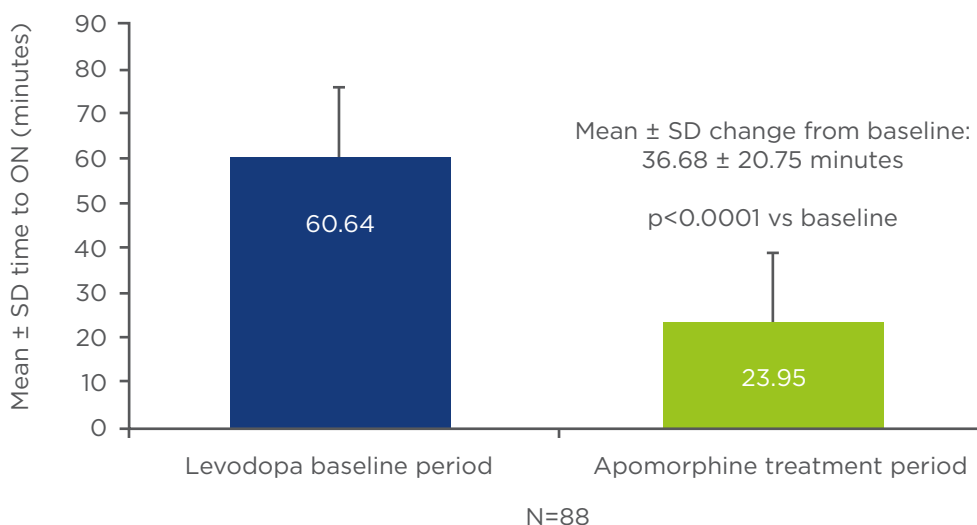


Figure 4: Change from baseline in time-to-ON following apomorphine injection: results of AM-IMPACT [unpublished data].

SD: standard deviation; vs: versus.

These problems highlight the need to consider non-oral therapies to manage motor symptoms in this setting. The potent dopamine agonist apomorphine administered subcutaneously has provided clinicians with an effective option for the rapid resolution of the parkinsonian symptoms for over 25 years. Prof Isaacson considered that subcutaneous apomorphine intermittent injection offered an easy and practical therapeutic option for managing EMO as it avoided the oral route of administration that could be affected by delayed gastric emptying or impaired intestinal absorption. The clinical efficacy of apomorphine infusion has been confirmed in a range of randomised, controlled clinical trials undertaken in the USA. In the APO202 study of 29 PD patients with motor fluctuations and prolonged OFF time despite aggressive oral therapy, apomorphine injection was able to reverse 95% of OFF episodes over a 4-week period when used as needed.³⁴ The APO302 study undertaken in 62 patients at 26 USA centres demonstrated that apomorphine injection was able to achieve rapid and reliable improvements in UPDRS motor scores compared with placebo.³⁵

These significant improvements in mean UPDRS motor scores were seen 20 mins after administration of apomorphine injection. In addition, apomorphine injection significantly and rapidly improved mobility as early as 7.5 mins after dosing, and this effect persisted for at least 40 mins after dosing. Apomorphine injection was found to be effective over the long term, with efficacy being maintained in patients with an average therapy duration of 14.5 months. The APO303 study of 56 apomorphine-naïve patients with advanced PD at 17 USA centres provided further confirmation of the ability of apomorphine injection to provide rapid, effective relief of OFF episodes in PD patients already receiving optimised oral medication.³⁶ Mean changes from pre-dose in UPDRS motor were significantly improved following apomorphine injection (4 mg) versus placebo at 20 mins ($p=0.0002$), 40 mins ($p<0.0001$; maximum improvement), and 90 mins ($p=0.0229$) post-administration.

Prof Isaacson described how the use of apomorphine pen injection (Figure 3) has been investigated in the recently completed Phase IV, 10-centre, open-label, efficacy and safety study – AM-IMPAKT (Apokyn for Motor IMProvement of morning AKinesia Trial).³⁷⁻³⁹ AM-IMPAKT aimed to investigate whether subcutaneous apomorphine injection given upon awakening was able to provide

rapid and reliable improvement in motor symptoms in PD patients with morning akinesia due to delayed onset of the first oral levodopa dose. During the 7-day baseline study period, each morning following their first oral levodopa dose, patients recorded their TTO in a diary every 5 mins for up to 60 mins by checking boxes either 'yes' or 'no' until onset of ON. Patients subsequently initiated treatment with the apomorphine pen and used this for another 7 days upon awakening, completing the same TTO diary each morning. The primary endpoint was a comparison of TTO between the levodopa study period and the apomorphine injection period.

Morning akinesia was found to be common in the study population and occurred throughout the course of PD, even at relatively early stages. Over half of the PD patients who entered the study were in the first decade of their disease and, despite a range of oral therapies, had experienced persistent morning akinesia for an average of 4 years. The final analysis of data for 88 patients found that apomorphine pen injection significantly improved the primary endpoint of TTO: mean baseline TTO with levodopa averaged 60.64 mins, which reduced significantly to a mean of 23.95 mins with apomorphine injection ($p<0.0001$; Figure 4), representing a mean change from baseline of 36.7 mins. UPDRS motor scores were also significantly reduced within 15 mins of apomorphine compared with baseline (35.5 versus 17.3; $p<0.0001$), representing a mean change in UPDRS score of 18.2.

Analysis of individual data for each patient was very revealing and demonstrated the reliability of the response to apomorphine injection. Approximately 98% of patients experienced a rapid and robust clinical improvement in TTO with apomorphine injection. Dose failures were found to be common during the levodopa baseline period; however, most of these patients achieved an ON state with apomorphine injection, the majority within 20 mins.

Significant improvements were also found for the secondary patient-reported outcomes following treatment with apomorphine injection. Patients and investigators were asked to rate their global impression of severity of illness relative to akinesia/motor function before and after apomorphine therapy, measured on a 7-point scale from 'normal' to 'extremely ill'. In both cases significant improvements were recorded ($p<0.0001$). Measures of health-related QoL also showed improvement

with apomorphine injection. EQ-5D-3L is a patient-reported health outcome scale related to mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and each dimension is ranked from 1 (no problem) to 5 (extreme problem), so lower scores indicate a more favourable rating. EQ-5D-3L index scores were significantly reduced from a mean of 3.30 at baseline to a mean of 2.18 at the end of the 1-week apomorphine treatment period ($p < 0.0001$). Using the EQ-5D Visual Analogue Scale, subjects rate their health state relative to akinesia on a scale of 0 (worst imaginable) to 100 (best imaginable), so higher scores indicate a more favourable rating. In AM-IMPAKT, scores also showed significant improvement from a mean of 50.38 at baseline to 65.67 at the end of the apomorphine treatment period ($p = 0.0001$). An exploratory analysis of the number of patients who had at least one dose failure (failure to turn ON within 60 mins) found a total of 46% of patients during the levodopa baseline period compared with 7% during apomorphine injection period.

Prof Isaacson concluded by highlighting the importance of addressing not only end-of-dose wearing-off but also delayed TTO in PD patients, since this comprises the majority of total OFF time. Commonly, oral levodopa onset is impaired or absent due to GI dysfunction and therefore there

is a need for effective non-oral PD medication to return patients to the ON state quickly. Results from the AM-IMPAKT study confirm that morning akinesia is a common but under-recognised symptom of PD and that subcutaneous apomorphine pen injection meets the need for an effective, rapid, and reliable solution to this problem. Notably, the observed reduction in TTO in the study is clinically relevant since there were significant improvements across a range of subjective measures, including UPDRS motor scores, QoL, and clinician and patient global impression of severity.

Summary

Prof Trenkwalder concluded the symposium by noting that an Expert Consensus Group Report on the use of subcutaneously administered apomorphine for the management of PD had just been accepted for publication in *Parkinsonism & Related Disorders*. The publication provided both a review of the published literature on the use of apomorphine and also consensus recommendations prepared by 26 advisors from 13 countries to help guide healthcare professionals in the optimal application of apomorphine therapy in clinical practice.

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