What to do when the honeymoon wears off

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Meeting summary

We highlight key messages from a satellite symposium at the International Congress of Parkinson's Disease and Movement Disorders (MDS) 2021, which reviewed the challenges of wearing-off in Parkinson's disease (PD), focusing on both motor fluctuations and – what is often considered the hidden side of wearing-off – non-motor fluctuations (NMF). We consider the catechol-O-methyltransferase (COMT) inhibitor opicapone in the management of motor fluctuations, and consider evidence for a role for COMT inhibition in treating NMF, as well as presenting ongoing studies that may help to elucidate this further. The practicalities of adding opicapone 50 mg to a patient's regimen to treat end-of-dose wearing-off are discussed by the faculty.

KEYWORDS: PARKINSON'S DISEASE, COMT INHIBITORS, OPICAPONE, MOTOR FLUCTUATIONS, NON-MOTOR FLUCTUATIONS

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OFF-time – still a challenge in Parkinson's disease

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A clinical diagnosis of PD relies on the central signs of bradykinesia, rigidity and rest tremor, i.e. the onset of motor symptoms.[1] The vast majority of patients start to experience motor complications including fluctuations (such as end-of-dose wearing off, and levodopa-induced involuntary movements or dyskinesia) as their disease progresses and they have fewer surviving dopaminergic neurons able to store levodopa.[1-3]

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From a patient's perspective, it is the fluctuating response to medication (i.e. wearing-off and ON–OFF states) that has been ranked as the most troublesome of symptoms (after 6 years' disease duration), positioned above drooling, mood and sleep problems.[4] In keeping with this, PD patients who have experienced dyskinesia still have a clear preference for spending time in the ON state and being capable of movement, even if this means a degree of dyskinesia, compared to symptoms of the OFF state.[5] As well as akinesia and rigidity, patients' reluctance to spend time in the OFF state is also influenced by the frequency of NMF, such as anxiety, slowness of thinking, fatigue and pain.[6] As NMF are less visible to clinicians, OFF-time remains a significant challenge for clinicians as well as patients.

There are a number of risk factors associated with the development of motor complications. The speed and degree of neuronal loss is the dominant factor, as reflected in longer disease duration. In patients who receive their first dose of levodopa at an advanced stage of PD, motor fluctuations and dyskinesia may occur within just a few weeks. Levodopa has a short half-life and contributes to the less physiological, pulsatile stimulation of dopamine receptors due to the reduced storage capacity of presynaptic dopaminergic neurons as the neurodegenerative process evolves. According to the concept of continuous dopaminergic stimulation or drug delivery,[7] motor complications may be delayed or ameliorated if dopaminergic medication is delivered in a more continuous manner. In keeping with the concept, the total daily levodopa dose has been found to be associated with the risk of motor complications, whereas the duration of exposure to levodopa therapy is not.[8] Other risk factors for motor complications include young age at onset,[9,10] lower body weight[10] and genetic factors.[11]

The recent double-blind, placebo-controlled LEAP study, in which patients with early PD received either immediate or delayed-start (by 40 weeks) levodopa has contributed to our knowledge; it showed that there is no evidence of a disease-modifying effect over the 80-week study duration, but also no evidence of clinically relevant toxicity.[12] Professor Katzenschlager highlighted that, in addition to the robust evidence for the efficacy and tolerability of levodopa, patients also need to know that its effect on the main motor symptoms will be sustained over the disease course.[13] Some motor symptoms associated with later disease stages, such as postural instability, falls and dysphagia are not due to, or are only partially due to, the dopamine deficit and therefore do not respond as well to levodopa.[14,15]

Targeting motor fluctuations, including their early detection, close monitoring, and treatment adjustments during the disease course, remains a central goal to improving the quality of life of patients with PD. Aiming for a more continuous delivery of levodopa can be achieved by adjusting the way levodopa is administered, such as making dosing intervals shorter, using extended-release formulations where available, and adding COMT inhibitors (such as opicapone), monoamine oxidase-B (MOA-B) inhibitors and, where tolerated, dopamine agonists.

Opicapone for motor fluctuations

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The clinical efficacy and safety of the COMT inhibitor opicapone as an adjunct therapy to levodopa has been demonstrated in two large, Phase III, multinational, randomised, double-blind studies with open-label extension periods. BIPARK-I was a placebo-controlled and active comparator (entacapone) study (n=600), and BIPARK-II was a placebo-controlled study (n=427).[16-18] In both trials, the primary endpoint was change from baseline in absolute OFF-time.[16,18] In BIPARK-I, treatment with opicapone 50 mg was superior to placebo (mean difference in change from baseline: –60.8 min; 95% confidence interval [CI]: –97.2 to –24.4; p=0.0015), and non-inferior to entacapone (–26.2 min; 95% CI: –63.8 to 11.4; p=0.0051 for the non-inferiority test).[16] In BIPARK-II, the adjusted treatment difference versus placebo was significant for opicapone 50 mg (treatment effect: –54.3 min; 95% CI: –96.2 to –12.4; p=0.008).[18]

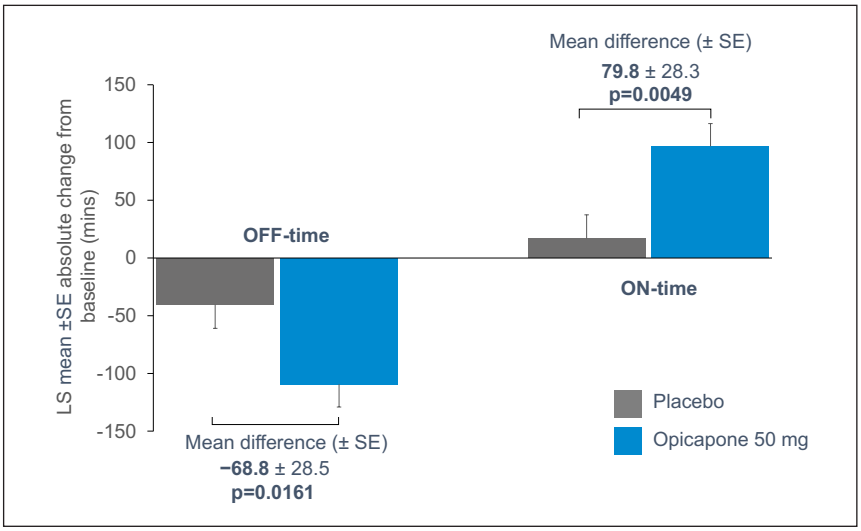
During the open-label extension phase of BIPARK-I, patients who switched from placebo or entacapone to opicapone experienced an additional gain of reduced OFF-time. Entacapone-switch patients presented an improvement in absolute OFF-time of –39.3 minutes (p<0.05).[17]

During BIPARK-I and II, opicapone was generally well tolerated, with dyskinesia being the most common adverse

event (AE) associated with opicapone treatment.[16,18,19] Dyskinesia occurred mainly during the first 2 weeks of opicapone treatment, was managed by levodopa treatment adjustments and did not result in opicapone discontinuations.[19]

Recent post-marketing safety data for opicapone is now available covering more than 4 years (up to June 2021), with a total estimated exposure of 1,310,062 patient-months, corresponding to 109,172 patient-years (BIAL data on file). The majority of reported AEs were considered non-serious. Dyskinesia was the most frequently reported AE (4.1%) (BIAL data on file), which is expected based on the mechanism of action of opicapone.[20]

Figure 1. Opicapone 50 mg as first-line adjunctive therapy versus placebo: mean changes in OFF- and ON-time[21]



LS: least squares; SE: standard error Adapted from Ferreira J et al, 2020[21]

Opicapone as first-line adjunctive therapy in patients with end-of-dose motor fluctuations

A *post hoc* analysis of BIPARK-I and -II evaluated opicapone as first add-on in a subgroup of 127 patients with PD with end-of-dose motor fluctuations treated with levodopa/dopa-decarboxylase (DDCI) only at baseline (i.e. without dopamine agonists or MAO-B inhibitors).[21] Baseline characteristics in the opicapone (n=68) and placebo (n=59) groups were comparable, with mean levodopa doses of 730.3 mg/day and 718.3 mg/day, respectively.[21] Opicapone significantly reduced absolute OFF-time by 68.8 minutes (p=0.0161) and increased ON-time by 79.8 minutes (p=0.0049) compared to placebo **(Figure 1)**,[21] while the incidence of potentially related treatment-emergent AEs leading to discontinuation was similar for opicapone 50 mg (n=5, 7.4%) and placebo (n=5, 8.5%).[21] The most frequently reported potentially related treatment-emergent AE was dyskinesia (opicapone: n=8, 11.8%; placebo: n=1, 1.7%).[21] These data support that opicapone is effective and generally well-tolerated as a first-line adjunctive therapy in levodopa-treated patients with PD and motor fluctuations.[21]

Opicapone efficacy in patients with low levodopa doses (300–400 mg) or less than four levodopa intakes

Further *post hoc* analyses provide evidence for opicapone utility in the treatment of early motor fluctuations. By combining matching efficacy data for opicapone 50 mg and placebo from the pivotal Phase III studies, different levodopa regimens were evaluated in a subgroup analysis (n=239 patients).[22] Improvements in OFF-time were observed for both low-dose and higher-dose levodopa regimens on addition of opicapone 50 mg, with at least a two-fold greater reduction in mean OFF-time versus placebo **(Figure 2)**.[22] Improvements in OFF-time were also observed for <4 and ≥4 levodopa intakes and opicapone 50 mg, with change from baseline in absolute OFF-time of about 60 minutes (–59.7 and –58.6 minutes, respectively) when compared to placebo.[23]

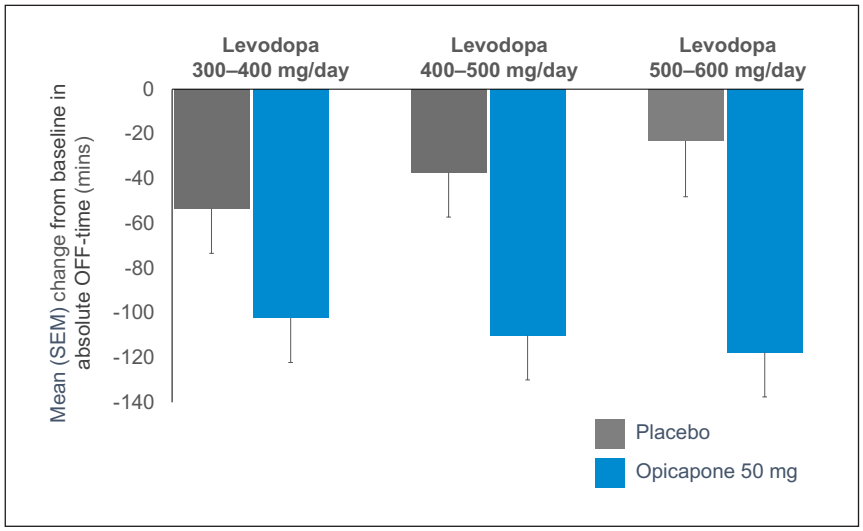
Opicapone efficacy in patients with early morning OFF

Home-diary data from 235 patients with wearing-off in BIPARK-I have also shown that opicapone decreased time-to-ON from first morning levodopa intake by 17.7% compared to 1.9% for patients receiving entacapone.[24] Due to a reduction in morning OFF-time, no pattern of early morning OFF was observed for patients on opicapone in contrast to entacapone.[24]

Opicapone effectiveness in a real-world setting

In a Phase IV, open-label study conducted in the clinical practice setting (OPTIPARK; n=495), the global health status of most patients after 3 months of treatment with opicapone 50 mg improved (71.3% of clinicians and 76.9% of patients reported improvements in the Clinician Global Impression of Change (CGI-C) and the Patient Global Impression of Change (PGI-C) scale, respectively).[25]

Figure 2. Opicapone 50 mg with different levodopa regimens: mean changes in OFF-time[22]



SEM, standard error of the mean. Adapted from LeWitt PA et al, 2020[22]

Ongoing opicapone trials: supporting evidence-based choices in treating motor fluctuations

To enable the development of optimum treatment strategies that can be translated into clinical practice, two studies are ongoing to further elucidate the best use of levodopa and opicapone in treating wearing-off and end-of-dose motor fluctuations.

The aim of the Phase II, open-label pharmacokinetic 203 trial is to assess the effect of opicapone 50 mg on levodopa pharmacokinetics in different levodopa/carbidopa treatment regimens in patients with end-of-dose motor fluctuations.[26] Twenty-four patients will receive five intakes of 100/25 mg levodopa/carbidopa dose for 2 weeks (total of 500/125 mg levodopa/carbidopa). The total amount of levodopa/carbidopa will then be reduced (total of 400/100 mg) and patients randomised 1:1 to either four or five intakes of levodopa/carbidopa plus opicapone 50 mg for 2 weeks. The primary endpoint compares the pharmacokinetics of levodopa at the end of both 2-week treatment periods. Secondary endpoints include tolerability, patient home diary for ON–OFF periods and PGI-C.[26]

The ADOPTION study is a Phase IV, randomised, prospective, open-label exploratory trial in PD patients.[27] The aim of this study is to explore the potential of opicapone to optimise levodopa/DDCI as a first-line approach to treat wearing-off (stable treatment plus addition of opicapone 50 mg versus an additional 100 mg levodopa) in 100 adults with signs of wearing-off for <2 years and treated with 3–4 daily oral levodopa doses up to 600 mg. The primary endpoint is change from baseline in OFF-time at 4 weeks, according to Hauser's diary. Secondary endpoints include tolerability, Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Movement Disorder Society Non-Motor Rating Scale (MDS-NMS), Parkinson's disease Questionnaire-8 (PDQ-8), CGI-C and PGI-C.[27]

Non-motor fluctuations: the hidden side of OFF

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Levodopa-induced NMF remain one of the unmet needs in PD due to poor recognition by clinicians and subsequent under-management.[28] The first depiction of autonomic and cognitive NMF in the 1970s by Marsden and Parkes from King's College in London described a patient reverting to profound akinesia, fear, sweating, flushing and confusion after a period of dyskinetic ON.[29] NMF cover a broad range of symptoms, including neuropsychiatric, sleep, autonomic and sensory domains and affect the majority of PD patients, negatively impacting on health-related quality of life.[30]

In contrast to motor fluctuations, NMF related to ON–OFF states have not been well researched. However, one international NMF study in patients with advanced PD (NoMoFlu-PD) showed that symptoms of dysphagia, anxiety, depression, fatigue and pain were worse during the OFF state.[30] Some NMS were exclusively present in the OFF state while a phenomenon of isolated NMF (happiness, for example) occurring during the ON period was also evident.[30] Non-recognition may lead to erroneous diagnosis of primary behavioural and neuropsychiatric issues with inappropriate treatment. In addition, psychosis, dopamine dysregulation syndrome, metacognition-related worsening of fluctuations[31] and punding, as well as sleep issues, can all masquerade as disease-related or NMF-related symptoms, contributing to the complexity of NMF.[32]

How do we recognise non-motor fluctuations in clinical practice?

The 13-domain Movement Disorder Society's Non-Motor Symptom scale (NMSS) is a valid measure that provides a comprehensive non-motor assessment in patients with PD, with an additional, optional, NMF subscale.[33] A recent study using this rating scale has shown that NMF, such as depression, anxiety, cognition disability and fatigue are evident even in patients with mild PD, through to severe disease.[34] These 'early fluctuations' are associated with NMF as well as motor fluctuations, meaning NMF are almost ubiquitous and can be present when the patient starts experiencing motor fluctuations.[34] Subsequently, a longer and more detailed questionnaire called the NoMoFa questionnaire has also been developed, to "dive deep" in the issue of NMF.[35]

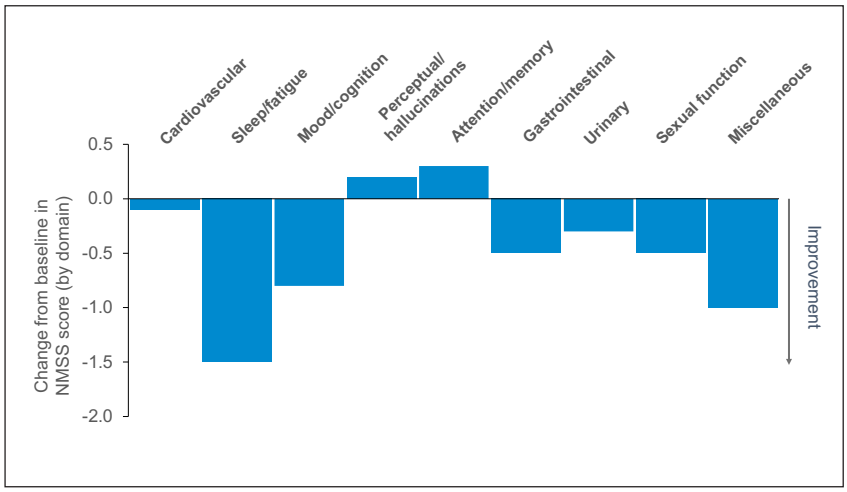
How do we manage NMF in clinical practice?

It is thought that continuous dopaminergic stimulation mimics the normal physiological conditions in the striatum and may facilitate better control of movement.[7,36] Just as importantly, there is some evidence to suggest that continuous dopaminergic stimulation may help to manage NMF.[37]

There are also favourable signs that COMT enzyme inhibition may improve specific NMF symptoms. Two studies have investigated the role of COMT inhibition as an adjunct in the treatment of NMF.[38,39] The use of levodopa/carbidopa and a single entacapone pill at bedtime was found to have a significant ($p<0.001$) therapeutic effect on sleep, with improvements in overall sleep quality, insomnia (sleep onset and maintenance), distressing dreams, and nocturia, which could be an OFF-related phenomenon.[38] Tolcapone was shown to improve two items on the NMSS: sleep/fatigue and mood/cognition, as well as in the miscellaneous domain (which includes pain).[39] While tolcapone is not routinely used due to its hepatic side effects,[40] this study provides an insight into the potential utility of COMT inhibition for NMF.

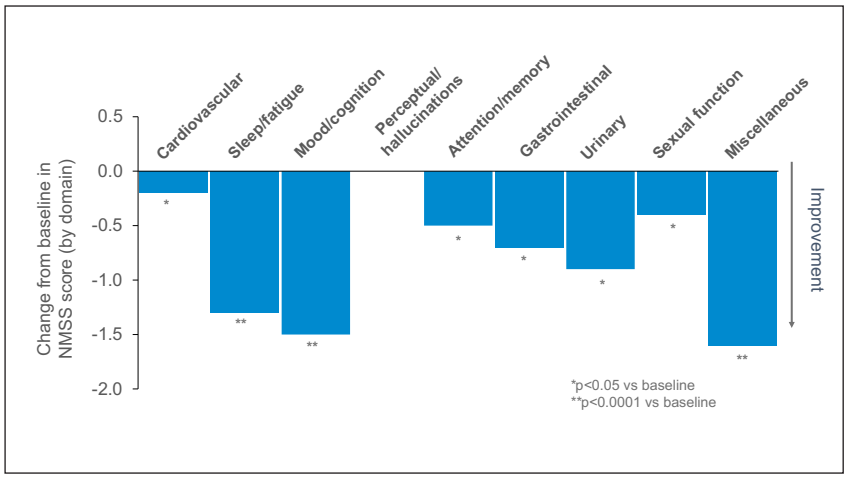
Opicapone has also shown signals of efficacy in the treatment of NMF. In the 1-year, open-label phase of BIPARK-II, improvements in the secondary outcome measure of NMSS in three domains were evident: sleep/fatigue, mood/cognition, pain and sweating (miscellaneous domain) **(Figure 3)**.[41] Together, these studies provide a consistent, robust signal for NMF with COMT inhibitors, which is further validated by NMSS results from the Phase IV, open-label OPTIPARK study.[25] In this real-world study, opicapone significantly improved NMSS domains for sleep/fatigue, mood/cognition, and the miscellaneous domain (which includes pain) (all $p<0.0001$ vs baseline) **(Figure 4)**.[25]

Figure 3. Opicapone 25 & 50 mg: mean change from double-blind baseline to open-label endpoint in NMSS individual domains in BIPARK-II[41]



NMSS, Non-Motor Symptoms Scale Adapted from Oliveira C et al, 2015[41]

Figure 4. Opicapone 50 mg: mean change from baseline in NMSS individual domains in OPTIPARK[25]



NMSS, Non-Motor Symptoms Scale Adapted from Reichmann H et al, 2020[25]

Ongoing opicapone trials: supporting evidence-based choices in treating NMF associated with wearing-off

Two ongoing studies with opicapone aim to examine the concept of COMT inhibition to improve specific non-motor symptoms associated with end-of-dose wearing-off. The OCEAN study is a Phase IV, randomised, double-blind, placebo-controlled trial that aims to evaluate the effect of opicapone 50 mg with levodopa/DDCI in 140 patients with PD with end-of-dose motor fluctuations and associated pain.[42] The primary endpoint is change from baseline in the King's Parkinson's Disease Pain Scale (KPPS) Domain 3 (fluctuation-related pain) at 24 weeks. Secondary endpoints include tolerability, KPPS (including Domain 4 for nocturnal pain), MDS-NMSS (including Domain B for the key endpoint of anxiety), PDQ-8, MDS-UPDRS (including early morning dystonia), patient home diary for ON/OFF periods, CGI-C and PGI-C.[42]

The OASIS study is a Phase IV, open-label, single-arm pilot trial that aims to evaluate the impact of opicapone 50 mg as adjunctive therapy to levodopa/DDCI on PD-associated sleep disorders in 30 patients with wearing-off and sleep disorders.[43] The primary endpoint is change from baseline in Parkinson's Disease Sleep Scale 2 total score at 6 weeks. Secondary endpoints include: the fatigue scale (PFS-16), MDS-NMS, PDQ-8, CGI-C and PGI-C.[43]

Symposium panel discussion session

At the end of this satellite symposium, there was a panel discussion on the practicalities of managing patients with PD. A selection of topics pertinent to the management of both motor and non-motor symptoms and the clinical use of the COMT inhibitor opicapone are presented here.

In response to a question asking: 'How would you detect and manage pain?', Professor Ray Chaudhuri replied that a non-motor symptom questionnaire is used routinely for his PD patients and has a specific question on "unexplained pain". If patients tick 'yes' to this question, a pain assessment pathway using the King's Parkinson's Disease Pain Questionnaire[44] (completed by the patient and taking only a few minutes) should be completed so that the clinician can provide a bespoke personalised management plan for the type of pain the patient describes. It is important to determine whether NMS are constant or fluctuating. If pain is present during wearing-off, dopaminergic treatment rather than analgesics might be more appropriate for pain management (and similarly, dopaminergic therapy vs anti-anxiolytics in the management of fluctuating anxiety). While history taking is paramount, Professor Chaudhuri suggested that use of the MDS-NMS may help to capture NMF and, for some of his patients, NMF are more disturbing than motor fluctuations in the OFF-state.

In reply to the question: 'If you were faced with a patient who has started to develop wearing-off, how would you start treatment with opicapone?', Professor Joaquim Ferreira explained that opicapone is simply administered as a once-daily tablet that the patient should take at bedtime (i.e. titration is not necessary).[45] The key question is identifying which patients would benefit the most from adding opicapone to their treatment regimen. Ideal patients include those who have mild motor fluctuations, some periods of OFF-time, and total daily levodopa doses in the range of 300–600 mg.[20] If they are not already taking an adjunct COMT inhibitor, opicapone can be added to existing medications. If a patient is already taking entacapone and is not responding optimally, or not tolerating this treatment, switching to opicapone is possible by omitting the final entacapone dose of the day and taking opicapone 1 hour after the last levodopa/DDCI dose. Levodopa/DDCI is then taken as usual the next day and opicapone added at bedtime, separated from the final levodopa/DDCI dose by 1 hour.[45] This recommended switching strategy helps to avoid aggravating the OFF state on the day after the patient stops entacapone. If a patient is prone to, or has, dyskinesia, the condition might be aggravated, but an adjustment of levodopa before switching/initiation of opicapone is not recommended. If dyskinesia does occur after switching from entacapone to opicapone, it is useful to let patients know that this usually happens during the first 2 weeks and may settle down,[19,46] and – if there is a need – the levodopa dose can be adjusted.[47]

In response to a question asking: 'In your experience, would you combine opicapone with continuous intestinal levodopa infusion?', Professor Ray Chaudhuri replied that this is a very important practical issue. He highlighted a small, open-label retrospective analysis in 11 PD patients on levodopa-carbidopa intestinal gel (LCIG) with concomitant opicapone.[48] These patients were part of the Non-motor Longitudinal International Study (NILS). The introduction of opicapone led to the LCIG daily dose being reduced by 24.8% (p=0.05)

without any significant worsening of dyskinesia. Two patients discontinued opicapone due to side effects (hallucinations or dizziness) and one discontinued due to lack of efficacy.[48] Professor Chaudhuri added that this adjunctive treatment option warrants further study.

Concluding remarks

In summary, Professors Katzenschlager, Ferreira and Chaudhuri concluded that opicapone is a generally efficacious and well tolerated treatment. Data from four further studies, including opicapone as a first-line adjunct approach to treat early wearing-off, in end-of-dose motor fluctuation-associated pain, and in wearing-off and sleep disorders, aim to consolidate the evidence base for opicapone in routine clinical practice.

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