Changing the paradigm for treating motor fluctuations in Parkinson's: advancements in COMT inhibition

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Meeting summary

We highlight the satellite symposium at the International Congress of Parkinson's Disease and Movement Disorders (MDS) 2020 reviewing the clinical manifestations and impact of the range of motor fluctuations in patients with Parkinson's disease (PD). We focus on the pharmacology and role of catechol-O-methyltransferase (COMT) inhibition in the management of these motor fluctuations. Efficacy and safety data, including real-world experience for opicapone ▼ 50 mg as an adjunct to levodopa/dopa-decarboxylase inhibitor (DDCI) in the management of OFF episodes in patients with PD are then presented. Delegates' questions are answered in a panel discussion.

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

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Impact and management of motor fluctuations in PD

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It is universally accepted that the central pathological feature of PD is the loss of dopaminergic neurons in the substantia nigra; yet, it is not until 70–80% of dopamine is depleted that motor function is disrupted and motor symptoms start to appear.[1–3] While levodopa remains the most efficacious, oral pharmacotherapeutic option in PD,[4] limitations in its use become apparent with progression from early to advanced/late stage disease.[1] With disease progression and fewer surviving dopaminergic neurons that are able to store levodopa for later use, patients start to experience motor

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fluctuations, such as end-of-dose wearing-off, as well as levodopa-induced involuntary movements or dyskinesia.[5,6] Dyskinesia is most commonly associated with high plasma levels of levodopa, while the OFF state (akinesia and rigidity) is associated with low levels of levodopa.[7,8] With the long-term complications of this disease, as well as increasing levodopa dose, it is not really a matter of *if*, but *when*, patients with PD develop motor and non-motor fluctuations.[1]

Despite the wide spectrum of motor fluctuations observed in PD, *wearing-off*, the re-emergence of PD symptoms before the next levodopa dose, is the most common type and one of the first to appear.[6,9] Another type of motor fluctuation that appears early in the disease course, and is often under-appreciated, is *early-morning akinesia*, where patients have prolonged symptoms of rigidity, bradykinesia and tremor before their first levodopa dose of the day.[9]

As the disease progresses, wearing-off may become more prominent, with patients experiencing fluctuating ON and OFF periods that require more frequent levodopa dosing. Moreover, during OFF periods, painful dystonia may be present alongside the resurgence of rigidity, bradykinesia and tremor. In the advanced stage, more complex fluctuations become evident with *sudden OFFs* (i.e. OFF periods without warning), *unpredictable OFFs* that do not occur at the end of the dose, and *dose failures* (where there is no appreciable benefit from a particular dose).[9]

Motor fluctuations and OFF periods impact considerably on day-to-day activities and quality of life. In a large survey by The Michael J Fox Foundation for Parkinson's Research, in which over 3000 patients in different disease stages responded, more than 90% reported at least one OFF episode per day.[10] Nearly 65% of respondents claimed to experience OFF periods for ≥2 hours per day and 20% of respondents were OFF for ≥4 hours per day. For nearly half of all respondents, OFF times were reported as having a moderate to severe effect on their daily life, resulting in patients avoiding or stopping their normal activities.[10]

Motor symptoms in the OFF state have generally been considered to be a re-emergence of the cardinal symptoms of PD, including slowness, rest tremor, rigidity, and stiffness;[11] however, data from this survey supports previous findings that defining the OFF state is not straightforward.[10,11]

When patients were asked, 'What do you feel when your medication starts wearing-off?', a wide spectrum of motor symptoms and non-motor symptoms, unique to individual patients, emerged. These included difficulty walking, falling, difficulty swallowing, and speech difficulties.[10] This variation in patient experiences has been shown in a previous study, where patient experiences during OFF periods ranged from muscle cramps, weakness, slowness of movement, balance problems, difficulty getting out of a chair, and non-motor symptoms, such as urinary problems, cognitive slowing, depression, anxiety and panic attacks.[11]

This variability and uniqueness of motor fluctuations and their impact on an individual patient's life was highlighted at a 2015 US Food & Drug Administration 'Voice of the Patient' public meeting.[12] Perspectives from 55 patients with PD, caregivers and other patient representatives included statements such as 'fear of falling is always in the back of my mind', 'the sudden inability to move my legs, as if they were set in blocks of hardened concrete', and reports of symptoms that vary 'not only from day to day, but from hour to hour'.[12]

The quest, therefore, continues to develop adjunctive treatments that minimise the impact of motor fluctuations and OFF periods in patients with PD.

Role of COMT inhibition in the management of PD

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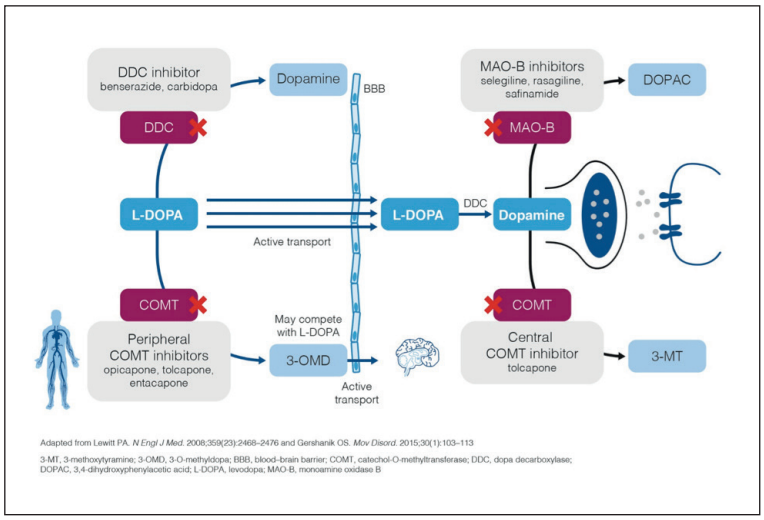
While physicians have individual preferences as to how and when to use adjunctive therapies, the choice of adjunctive treatment in patients with motor fluctuations should take into consideration a patient's symptoms, comorbidities, lifestyle and the potential benefit and risk of each class of agent. Although data indicate that starting levodopa treatment earlier in PD may be beneficial,[13–15] there is no clear definition as to when to initiate adjunctive therapy for patients experiencing OFF episodes. Initiation of adjunctive treatment to levodopa/DDCI can include a COMT inhibitor, a dopamine agonist, a monoamine oxidase-B (MAO-B) inhibitor and/or an adenosine A2A receptor antagonist. As the disease progresses, options include deep-brain stimulation, other levodopa/DDCI formulations/infusions and apomorphine preparations.

Figure 1. Adjunctive therapies help to reduce extensive metabolism of levodopa[16,17]



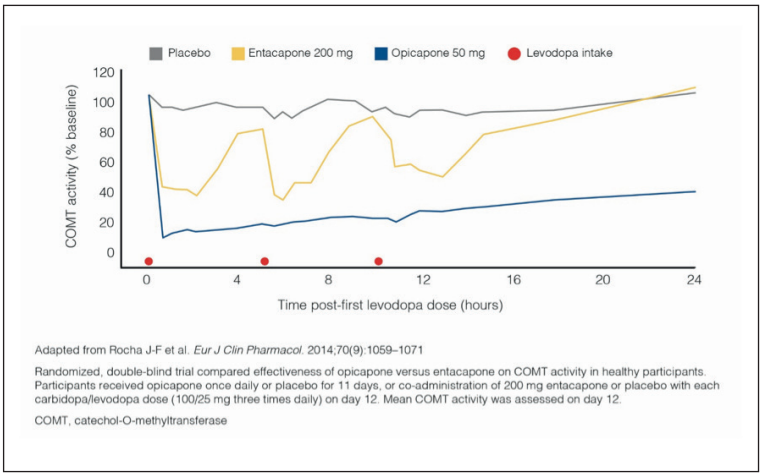
Levodopa can be considered as being 'wasted' in the peripheral circulation through conversion to dopamine via dopa decarboxylase (DDC), and to 3-O-methyldopa (3-OMD) via COMT, with only a small fraction of levodopa reaching the brain after active transport across the blood–brain barrier (Figure 1). Adjunctive therapies help to reduce this extensive metabolism of levodopa in the periphery; DCC inhibitors (benserazide and carbidopa) and peripheral COMT inhibitors (opicapone, tolcapone, entacapone) can prolong the effects of levodopa. Once levodopa crosses the blood–brain barrier, it is converted by DDC to dopamine; there is another opportunity here to impede the breakdown of dopamine with MAO-B inhibitors (selegiline, rasagiline, safinamide) and with the central COMT inhibitor tolcapone, thereby increasing the quantity of dopamine available in the central nervous system (Figure 1).[16,17]

By inhibiting the degradation of levodopa into 3-OMD (Figure 1), COMT inhibitors increase levodopa half-life and systemic exposure, thus smoothing the pharmacokinetic curve and increasing its duration of effect.[18] The aim of COMT inhibition is for a more continuous, rather than pulsatile, dopaminergic stimulation, thereby reducing motor fluctuations.[19]

The development of COMT inhibitors has a long history. The earlier generation COMT inhibitors tolcapone and entacapone became available in clinical practice in the late 1990s.[19] The most recent COMT inhibitor to be approved in the EU (2016) and US (2020) is opicapone.[20,21] Tolcapone recommended dosing is 100 mg three times daily (with an option to increase to 200 mg three times daily);[22,23] entacapone dosing is 200 mg with each levodopa/DDCI dose (maximum 10 times daily in the EU, and maximum 8 times daily in the US),[24,25] and opicapone dosing is 50 mg once daily at bedtime (at least 1 hour before or after levodopa combinations).[21,26]

Opicapone, a peripheral COMT inhibitor, is characterised by a high binding affinity for COMT, and a constant, slow dissociation rate of the enzyme–substrate complex leading to a long duration of action *in vivo*.[26–28] Administration of opicapone results in an increase in systemic, and thus central, levodopa levels, and a decrease in 3-OMD exposure (Figure 1). In a randomised, double-blind, parallel-group study comparing opicapone versus entacapone in healthy volunteers, opicapone 50 mg showed sustained COMT inhibition for >24 hours, while with entacapone COMT activity returned to baseline 5–7 hours post-dose (Figure 2).[28] Furthermore, opicapone demonstrated a significant increase in levodopa plasma exposure, but not peak concentration, versus entacapone.[28] Reductions in levodopa peak–trough fluctuations have also been demonstrated in a Phase I study in PD patients receiving opicapone 50 mg once-daily for 14 days, who were either on a carbidopa/levodopa (100/25 mg) regimen every 3 hours or every 4 hours. The addition of

Figure 2. COMT inhibition following administration of entacapone and opicapone[28]



opicapone 50 mg increased levodopa plasma trough levels and systemic exposure, reducing the peak–trough levodopa fluctuation index by 34–46%.[29]

In the US, opicapone is a recent addition to the therapeutic options available for patients with PD. Opicapone is indicated as adjunctive treatment to levodopa/carbidopa in patients with PD experiencing OFF episodes.[21] Its indication in Europe is adjunctive therapy to preparations of levodopa/DDCI in adult patients with PD and end-of-dose motor fluctuations who cannot be stabilised on those combinations.[26]

Clinical data and experience with opicapone

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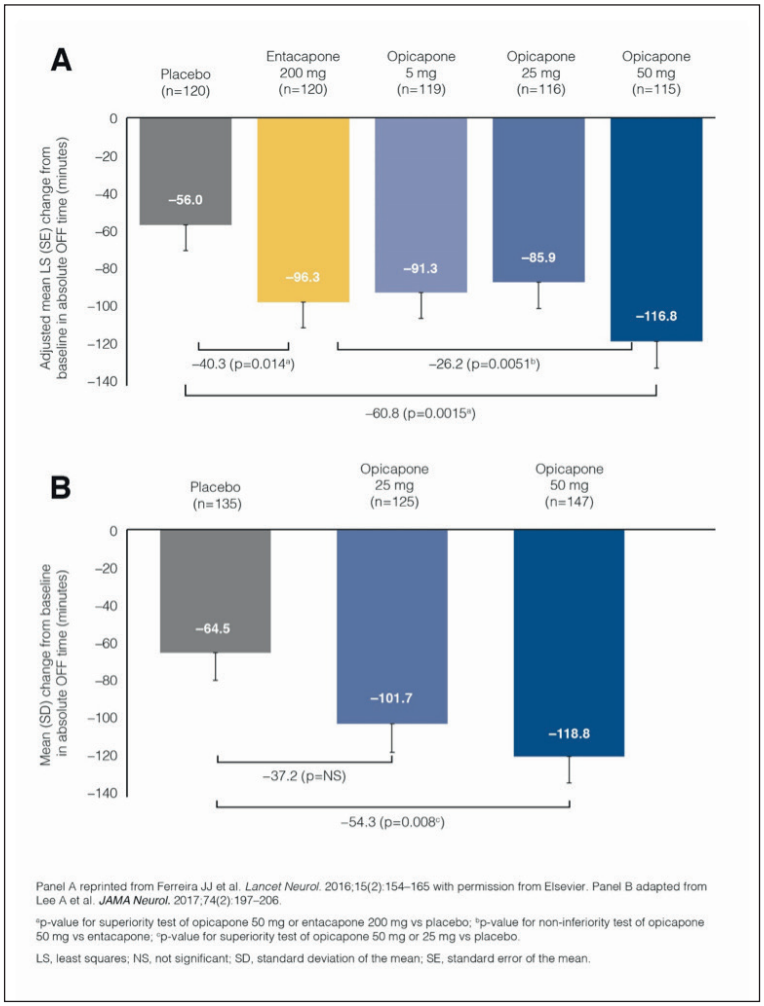
Phase III clinical data: BIPARK I and BIPARK II

Two large, Phase III, randomised, double-blind studies conducted in 30 countries have demonstrated the clinical efficacy and safety of opicapone as an adjunct therapy to levodopa/DDCI in >1000 adult patients with PD and end-of-dose motor fluctuations.[30–32]

BIPARK I was a placebo-controlled study (n=600) with an active-control group (entacapone),[30] and BIPARK II a placebo-controlled study (n=427), with double-blind periods lasting 14–15 weeks, and a 12-month open-label extension period.[31,32] The primary endpoint for both BIPARK I and II studies was change from baseline in absolute OFF time at the end of the study.[30,31] Treatment responders were defined as patients who achieved at least a 1-hour reduction in absolute OFF time. Rating scales were used to assess symptoms and global health condition.[30,31] Demographic and baseline characteristics were similar across treatment groups; in both studies, time since PD diagnosis was ~7–8 years, and mean duration of time in the OFF state was ~6 hours.[30,31]

In BIPARK I, opicapone 50 mg reduced absolute OFF time from baseline by 60.8 minutes vs placebo (p=0.0015), while entacapone 200 mg reduced absolute OFF time by 40.3 minutes vs placebo (p=0.014) (Figure 3a).[30] The change in absolute OFF time for entacapone was comparable to data from previous studies,[33] confirming the robustness of this trial design. Similarly, in BIPARK II, opicapone 50 mg reduced absolute OFF time from baseline by 54.3 minutes vs placebo (p=0.008) (Figure 3b).[31] Responder rates in BIPARK I showed that 70% of patients receiving opicapone 50 mg had a reduction in OFF time ≥1 hour vs 48% in the placebo group (p=0.001), and 65% had an increase in ON time ≥1 hour vs 46% in the placebo group (p=0.003). There were no significant differences in responder rates for entacapone versus placebo.[30] Global perception of benefit, relevant in both research and clinical practice settings, has been demonstrated for opicapone 50 mg in BIPARK I using the Clinician Global Impression of Change (CGI-C) and Patient Global Assessment of Change (PGI-C): significantly more patients in the opicapone 50 mg group improved on the

Figure 3. A. BIPARK I: change from baseline in absolute OFF time.[30] B. BIPARK II: change from baseline in absolute OFF time at 14/15 weeks[31]



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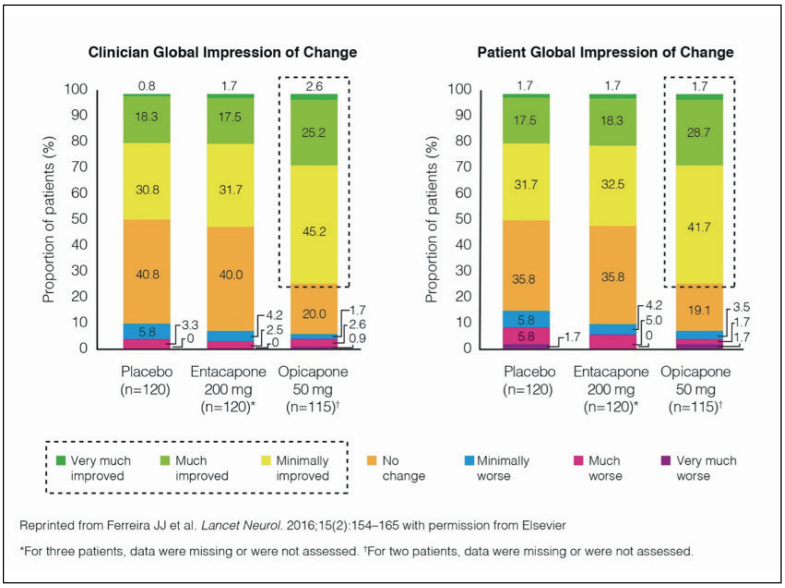
[a]p-value for superiority test of opicapone 50 mg or entacapone 200 mg vs placebo; [b]p-value for non-inferiority test of opicapone 50 mg vs entacapone; [c]p-value for superiority test of opicapone 50 mg or 25 mg vs placebo.

LS, least squares; NS, not significant; SD, standard deviation of the mean; SE, standard error of the mean.

Figure 4. Clinician and Patient Global Impression of Change for opicapone vs placebo and entacapone in BIPARK I (full analysis set)[30]



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*For three patients, data were missing or were not assessed. †For two patients, data were missing or were not assessed.

CGI-C (p=0.0070 vs entacapone; p=0.0005 vs placebo) and PGI-C (p=0.0091 vs entacapone; p=0.0008 vs placebo).[30] There were no significant differences in CGI-C or PGI-C for entacapone versus placebo (Figure 4) in BIPARK I,[30] nor between opicapone 50 mg and placebo in BIPARK II.[31]

Pooled safety data from BIPARK I and II confirm the long-term use of opicapone 50 mg once-daily was not associated with any unexpected safety concerns. Incidence of treatment-emergent adverse event (TEAEs), including serious TEAEs, deaths, and TEAEs leading to discontinuation were similar for opicapone 50 mg and placebo (Table 1).[34] For TEAEs with ≥2% difference for opicapone versus placebo, dopaminergic events and other PD symptoms were the most common AEs, and as expected, dyskinesia was the most frequently reported TEAE (opicapone 50 mg, 20.4%; placebo 6.2%).[34] The majority of dyskinesia events were reported during the first 3–4 weeks of treatment with opicapone 50 mg; these early events were mostly transient and the incidence of severe cases was low (opicapone 1.2% vs placebo 0.8%).[34] Therefore, monitoring of patients during the first few weeks after initiation on opicapone 50 mg is recommended.

Pooled patient diary data from BIPARK I and II open-label extension phases (12 months) showed that patients who switched from placebo to opicapone in the open-label phase (n=215) had an extra reduction in OFF time of 51.1 minutes.[35] In the open-label phase of BIPARK I, switching from entacapone to opicapone (n=100) also significantly reduced absolute OFF time from open-label baseline to study end (least-square mean improvement of −39.3 minutes in OFF time, p=0.006).[32] Efficacy was also maintained over the 1-year extension phase for patients who were originally treated with opicapone 50 mg during the double-blind phase of this study.[32]

Two post-hoc analyses of the BIPARK studies have further confirmed opicapone suitability as a prompt treatment option after onset of motor fluctuations. In the first, opicapone 50 mg used as the first adjunctive COMT inhibitor in patients recently diagnosed with motor fluctuations (≤ 1 year duration) demonstrated a decrease in absolute OFF

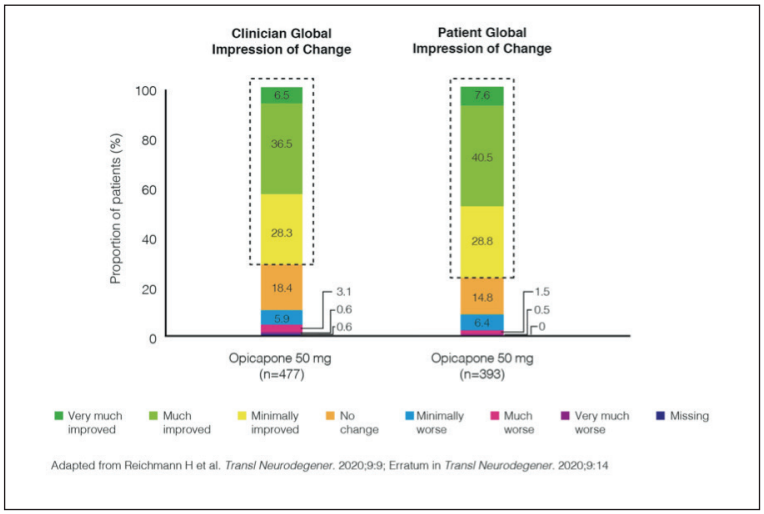
Table 1. BIPARK I and II pooled safety analysis: incidences of TEAEs[34]

Parameter	Placebo (n=257*)	Opicapone 50 mg (n=265)*
All TEAEs	147 (57.2)	170 (64.2)
Potentially related TEAEs	75 (29.2)	113 (42.6)
Serous TEAEs	11 (4.3)	13 (4.9)
Deaths	1 (0.4)	0
Patients with a TEAE leading to discontinuation	18 (7.0)	23 (8.7)

*Safety set. Potentially related: drug-event relationship reported as 'possible', 'probable', 'definite' by the investigator, or missing. TEAEs, treatment-emergent adverse events

time of 124 minutes from baseline vs 57 minutes with placebo.[36] In the second analysis, opicapone was evaluated as the first adjunctive therapy in patients with motor fluctuations treated only with levodopa/DDCI (i.e. patients who had not previously received dopamine agonists or MAO-B inhibitors), where it also reduced OFF time (–68.8 minutes vs placebo; p=0.0161) and increased ON time (79.8 minutes vs placebo; p=0.0049).[37]

Figure 5. Clinician Global Impression of Change and Patient Global Impression of Change at 3 months in OPTIPARK (full analysis set)[38,39]



Phase IV clinical practice experience: OPTIPARK

Real-world evidence highlighting the benefit of opicapone 50 mg in clinical practice is provided by OPTIPARK, a Phase IV, prospective, open-label, uncontrolled, single-group trial in adults with PD with motor fluctuations.[38] The aim of this study, conducted in 68 neurology centres in Germany and the UK, was to evaluate the change in patient's overall condition after 3 months of treatment with opicapone 50 mg in a clinical practice setting. Patients were in Stage I–IV of disease severity (modified Hoehn and Yahr staging) at ON and treated with 3–7 daily doses of levodopa/DDCI or levodopa/DDCI/entacapone. Total daily levodopa/DDCI dose could be adjusted according to the patient's condition throughout the trial (except on Day 1). Patients treated with entacapone before trial entry were to discontinue entacapone at the baseline visit; patients previously or currently treated with tolcapone and/or opicapone were excluded from the study.[38] The primary efficacy endpoint was CGI-C after 3 months of treatment with opicapone 50 mg once-daily. Secondary endpoints included PGI-C, Unified PD Rating Scale (UPDRS), 8-item Parkinson's Disease Questionnaire (PDQ-8), and Non-Motor Symptoms Scale (NMSS).[38]

A total of 495 patients were treated, and 393 patients completed 3 months of treatment. Mean (SD) age was 67.7 (9.0) years, disease duration was 8.5 (5.0) years, with duration of motor fluctuations 2.5 (3.2) years. Total levodopa daily dose was 580.1 (SD 289.1) mg.[38]

After 3 months of treatment with opicapone 50 mg, clinicians rated 71.3% of patients as improved (CGI-C), with 43.0% reported as much or very much improved,[38] and 76.9% of patients rated themselves as improved (PGI-C), with 48.1% of patients reporting they were much or very much improved (Figures 5).[38,39]

In summary, these real-world clinical data support what was observed in the two Phase III studies, and confirms the clinical utility of opicapone 50 mg as an effective and generally well-tolerated adjunct option in patients with PD and motor fluctuations.[38]

Symposium panel Q&A session

At the end of this live-streamed satellite symposium, delegates who participated in this event were able to ask questions to the panel. A selection of questions pertinent to the management of motor fluctuations and clinical use of COMT inhibitors, answered by the expert speaker panel, are presented here.

Initiating a patient on opicapone

In response to a question asking: 'How much of a dopamine dose reduction do we need once we start a patient on opicapone?', Professor Joaquim Ferreira replied that data from the pivotal clinical trials with opicapone show that there is no need for a pre-emptive levodopa dose reduction before initiating adjunct opicapone treatment.[30–32] The practical recommendation for clinical practice is not to reduce levodopa dose before starting adjunctive therapy with opicapone. Potential emerging adverse events, such as dyskinesia, are generally manageable by reducing levodopa dose, or frequency of levodopa administration, after the patient has started on opicapone treatment. According to the clinical condition of the patient, it is often necessary to adjust the daily dose of levodopa within the first few days to first weeks after initiating treatment with opicapone.[21,26]

Switching from one COMT inhibitor to another

In reply to the question: 'Are there scenarios where clinicians would switch from one COMT inhibitor to another?', Professor Cheryl Waters and the panel responded that this is a very pertinent question as there are now three COMT inhibitors available in clinical practice (tolcapone, entacapone and opicapone). With the limitation of hepatic monitoring required for tolcapone due to potential hepatic adverse events,[22] there are two first-line COMT inhibitor options (entacapone or opicapone). It may be necessary to switch from one COMT inhibitor to another due to lack of efficacy or side effects; for example, if a patient on entacapone experiences insufficient symptomatic control, or if diarrhoea or urine discolouration is a problem,[24,32] there is an option to switch to opicapone.

Starting a COMT inhibitor

One delegate asked, 'When should COMT inhibitors be started; should this be immediately after diagnosis of wearing off or should they be saved for more advanced stages of PD?' Professor Cheryl Waters replied that it is a physician's choice when COMT inhibitors should be started. Regarding opicapone, data from the pivotal clinical trials show that it can be used in patients with moderate motor fluctuations.[21,26,30–32] Building on these Phase III data, exploratory post hoc analyses evaluated the efficacy and safety of opicapone in patients with PD treated with levodopa/DDCI with ≤1 year duration of motor fluctuations (recent motor fluctuations [RMF]), as well as >1 year duration of motor fluctuations (long-standing motor fluctuations [LMF]).[40] Baseline characteristics in the groups were similar apart from mean daily levodopa dose being slightly higher for LMF (placebo: 742.3 mg; opicapone 50 mg: 739.3 mg) compared with RMF (placebo: 585.4 mg; opicapone 50 mg: 616.6 mg). Opicapone reduced absolute OFF time by approximately 1 hour for RMF and LMF versus placebo (least squares mean RMF: –65.2 min; least squares mean LMF: –60.5 min), while dyskinesia incidence was around half in the RMF (11.8% vs 23.5%).[40]

Hepatotoxicity

In a question by Professor Waters enquiring whether there are any signs of hepatotoxicity with opicapone, Professor Ferreira confirmed that in the preclinical data in human hepatocytes, clinical trials and pharmacovigilance data, there were no signals or alerts for hepatotoxicity.[34,41] There are also no recommendations in place for hepatic monitoring in patients with PD receiving opicapone.[21,26]

Conversion factor for levodopa and opicapone

In response to a question about the levodopa-equivalent dose (LED) for opicapone, the panel said that there was no consensual conversion factor proposed yet; however, based on a systematic review by Tomlinson and colleagues,[42] the LED for COMT inhibitors can be calculated based on conversion factors multiplied by the total daily levodopa dose. Entacapone and tolcapone conversion factors were defined as 0.33 and 0.5, respectively.[42]

Although there are no formal studies calculating the LED conversion factor of opicapone, different values have been proposed by different groups:

- Schade et al proposed a factor of 0.5 (same as tolcapone), based on literature search and clinical experience.[43]
- Martinez Castrillo et al proposed a factor of 0.4, based on literature search and analysis of randomised clinical trials.[44]
- Verber et al built a web app to calculate LED and assumed opicapone to have a factor of 0.7, based on literature search.[45]

Given the non-standardised methods to define the LED of a drug, a pragmatic conclusion may be to consider an opicapone LED conversion factor of approximately 0.4 to 0.5. However, this is subject to change with new studies and different calculation methods.

Concluding remarks

In summary, Professors Waters and Ferreira concluded that opicapone is an efficacious and well tolerated treatment – another option available for wearing off treatment. Professor Fernandez pointed out that while patients with PD may be experiencing wearing off, this is not always mentioned during visits, as patients may perceive this to be part of the disease course. Professor Fernandez concluded that as clinicians we need to remain vigilant and sensitive to what our patients with PD are experiencing.

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