The honeymoon's over: what next for people with Parkinson's?

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Meeting summary

The challenges of wearing-off in Parkinson's disease (PD) were highlighted in a Bial-sponsored satellite symposium at the International Congress of Parkinson's Disease and Movement Disorders (MDS) 2022. The symposium focused on both motor fluctuations and non-motor fluctuations (NMF), the latter often considered the hidden aspect of OFF-time. We discuss the role of the catechol-O-methyltransferase (COMT) inhibitor opicapone in the management of motor fluctuations, and also its emerging role in treating non-motor symptoms in patients with end-of-dose wearing-off. Particular consideration is given to pharmacokinetic and clinical data from the latest study on opicapone. These study results suggest that adding opicapone 50 mg to a stable levodopa regimen provides higher levodopa plasma bioavailability, while reducing levodopa plasma fluctuation levels, despite a concomitant 20% decrease in the total daily dose of levodopa. This is also associated with decreased OFF-time and increased ON-time, thus providing much-needed flexibility in tailoring treatment to the individual needs of patients with PD.

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

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Wearing-off – still a challenge

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The clinical diagnosis of PD is currently based on the presence of motor symptoms: bradykinesia, rigidity and rest tremor (UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria, 1988).[1] There are, however, a range of non-motor symptoms (NMS) and biomarkers – including depression, constipation, olfactory dysfunction, orthostatic hypotension, and rapid eye movement sleep behaviour disorder (RBD) – that may provide an opportunity for early identification and intervention for patients with PD.[2–5] These non-motor features appear many years before the motor symptoms of PD and progress throughout the disease course.[4]

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Opicapone prescribing information and adverse event reporting information can be found at the end of the article.

Box 1. Case study: 57-year-old female patient

PD disease duration of 6 years with no problems during this time

- Started to notice first signs of fluctuations with wearing-off: severe bilateral rest tremor, pronounced at the right hand; anxiety and depressive symptoms at wearing-off, with orthostatic hypotension

The patient's current medication:

- Levodopa/carbidopa 100/25 mg 4 x per day
- Levodopa/benserazide (soluble) 100/25 mg
- Ropinirole extended-release 6 mg
- Cardiac medications for atrial fibrillation

Diagnosis:

- Tremor predominant PD with wearing-off and bradykinesia
- Non-motor OFF with anxiety, orthostatic hypotension

Treatment goals:

- Reduce wearing-off by increasing dopaminergic medication, but without lowering blood pressure

With disease progression and fewer surviving dopaminergic neurons able to store levodopa, the majority of PD patients will start to experience motor complications including fluctuations, such as end-of-dose wearing-off and levodopa-induced involuntary movements or dyskinesias[6–8] within 10 years from diagnosis.[9,10] Akinesia and rigidity are hypodopaminergic motor behaviours associated with the OFF state,[11,12] and are often combined with NMS of feeling tired, weak, slow, and anxious.[11] Dyskinesia, a characteristic hyperdopaminergic feature,[8,11] may be accompanied by NMS features of euphoria and disinhibition.[11]

How troublesome this fluctuating response to medication (i.e. wearing-off and ON–OFF) is from a patient's perspective depends upon their disease stage and personal experience. Patients with PD who have experienced dyskinesia have a clear preference for spending time in the ON state and being capable of movement, even if this means a degree of dyskinesia, instead of being in the OFF state.[13]

While not all patients are started early on levodopa – the gold standard PD treatment[8] – levodopa is eventually needed as an additional treatment.[14–16] The milestone LEAP study, in which patients with early PD received levodopa treatment either immediately (early-start) or by 40 weeks (delayed-start) showed no evidence of a disease-modifying effect over the 80week study duration.[17] Moreover, Professor Trenkwalder emphasised that disease-related quality of life scores seemed to favour an early start of levodopa treatment,[17] and that a longer time period may have been needed for differences in dyskinesia between the early- and delayed-start groups to become evident. For patients who have been initiated with a dopamine agonist (DA), levodopa supplementation is required in over 50% of patients after 2 years,[15] and over 90% of patients at 6 years.[16]

In order to deep dive into the unmet needs and challenges surrounding wearing-off, a case study of a 57-year-old female patient with a disease duration of 6 years showing first signs of fluctuations with wearing-off was shown (see Box 1).

Professor Trenkwalder discussed treatment options and dosage adjustments to reduce wearing-off in this patient, through achieving a more continuous delivery of levodopa to the brain. Possible options that Professor Trenkwalder would consider include increasing the frequency of levodopa/carbidopa daily intakes, or adding a COMT inhibitor, such as opicapone 50 mg, with a reduction of levodopa dosage if needed.[18] In the long-term, advanced therapies are also a consideration. As the patient reported orthostatic hypotension, and this is a typical side effect of dopamine agonists,[19] the 6 mg ropinirole dose could either be maintained or reduced.

Managing motor fluctuations, including their early detection, close monitoring, and treatment adjustments during the disease course, remain a central goal to improving the quality of life of patients with PD.

Motor fluctuations: optimising levodopa through adjunctive therapies

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While levodopa is still the cornerstone therapy for patients with PD,[8] clinical challenges remain in terms of patients experiencing early morning OFF with motor and non-motor symptoms, end-of-dose wearing-off medication, delayed ON, and suboptimal or partial ON.[12] A recent survey of 409 healthcare professionals in Europe has highlighted that the first step taken to manage these motor fluctuations in the vast majority of patients (81%) was to change levodopa dosing (either increase total dose or fractionate it). In only 21% of patients an adjunctive therapy was added as a first step to manage motor fluctuations.[20]

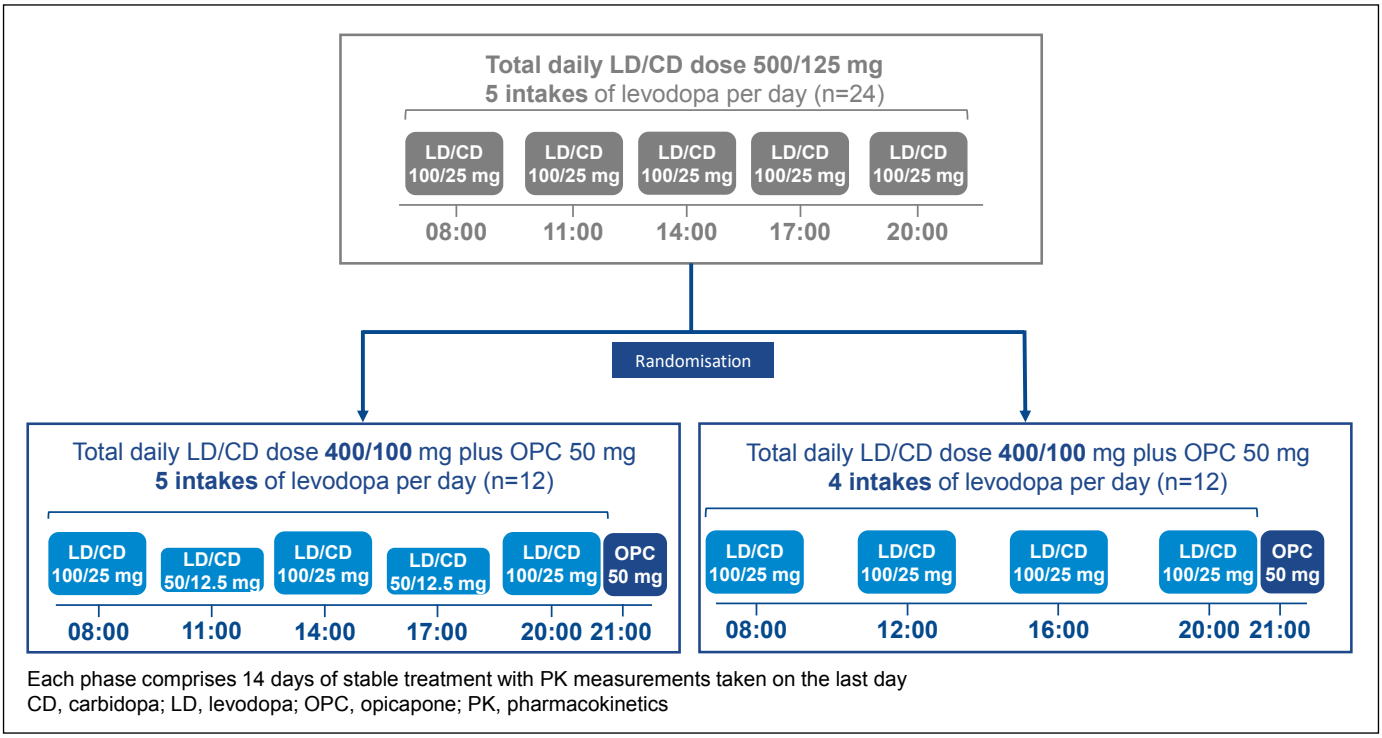
An adjunctive therapy to levodopa/dopa-decarboxylase inhibitor (DDCI) in the form of a COMT inhibitor enables dual inhibition of levodopa peripheral metabolism, thereby prolonging its presence in the plasma, increasing bioavailability and extending its elimination half-life.[21]

Effect of opicapone on levodopa pharmacokinetics in patients with PD and end-of-dose motor fluctuations

The aim of a recent Phase II European, open-label trial was to assess the effect of opicapone 50 mg once-daily on levodopa pharmacokinetics (PK) in two different levodopa/carbidopa treatment regimens in 24 patients with PD and end-of-dose motor fluctuations (EudraCT number: 2020–003139-12).[22] After an initial total daily dosing stable regimen of levodopa/carbidopa 500/125 mg (five intakes of 100/25 mg per day for 2 weeks), patients were changed to levodopa/carbidopa 400/100 mg plus opicapone 50 mg for an additional 2 weeks (Figure 1).[22] In two separate arms of 12 patients each, patients were randomised to receive either four or five daily intakes of levodopa/carbidopa: dosing for the four intake levodopa/carbidopa regimen occurred with 100/25 mg administered at 4-hour intervals and dosing for the five intake levodopa/carbidopa regimen occurred with alternating 100/25 mg and 50/12.5 mg at 3-hour intervals. Both arms received opicapone 50 mg administered 1 hour after the last daily intake of levodopa/carbidopa.[22]

The primary outcome was 12-hour levodopa pharmacokinetics (excluding the effect of the last (evening) daily levodopa/carbidopa intake); pharmacokinetics was assessed with

Figure 1. Phase II pharmacokinetic trial in patients with PD and end-of-dose motor fluctuations: study design[22]

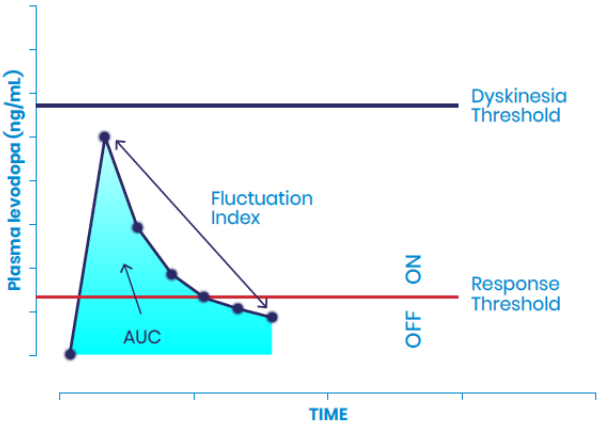


Each phase comprises 14 days of stable treatment with PK measurements taken on the last day
CD, carbidopa; LD, levodopa; OPC, opicapone; PK, pharmacokinetics

Box 2. Potential clinical impact of levodopa pharmacokinetics

Levodopa pharmacokinetics	Potential clinical impact
↓ Fluctuation index	↑ ON duration (↓ *time at OFF state*)
↑ AUC	
↑ C_{min}	↑ ON response (↓ *time to achieving or maintaining ON state*)
↑ C_{max}	↑ Risk for dyskinesia

Fluctuation index: calculated as: $[(C_{max} – C_{min})/C_{avg}]*100$
AUC: area under the curve – systemic exposure of levodopa
C_{min}: minimum observed plasma concentration
C_{max}: maximum observed plasma concentration



30-minute sampling. Secondary outcomes included clinical assessments of: timing of ON/OFF by investigators during the matching 12-hour PK evaluation, a 24-hour patient Hauser ON/OFF diary chart during the 3 days before each PK visit, Patient Global Impression of Change (PGI-C), and tolerability.[22]

Baseline demographics were similar between the arms: mean (standard deviation, SD) age was 62.2 (7.1) years, the mean duration of PD was 6.6 (3.2) years, with mean daily OFF time of 7.3 (1.6) hours. At baseline, about 30% of patients were on levodopa/carbidopa monotherapy.[22]

Pharmacokinetic data showed that, in comparison with the baseline levodopa/carbidopa 500/125 mg regimen, the levodopa/carbidopa 400/100 mg regimen of five intakes at 3 hour intervals plus opicapone 50 mg was characterised by a 2.5-fold increase in levodopa $C_{min,min}$ ($p<0.0001$), with a corresponding 29% increase in area under the curve (AUC_{total}) ($p<0.0001$). The stabilisation in C_{max}, in combination with an increase in C_{min}, resulted in a significant 40% decrease in the fluctuation index ($p<0.0001$) (see Box 2, Figure 2).[22] Despite the 100 mg lower total daily levodopa dose, adding opicapone 50 mg changed the clinical outcome for motor

Figure 2. Mean levodopa plasma profile versus time following 2-week, five daily intakes of levodopa/CD (total 500 mg/125 mg) compared with (A) 2-week five daily intake levodopa/CD (total 400 mg/100 mg) plus once-daily opicapone 50 mg, or compared with (B) 2-week four daily intake levodopa/CD (total 400 mg/100 mg) plus once-daily opicapone 50 mg[22]

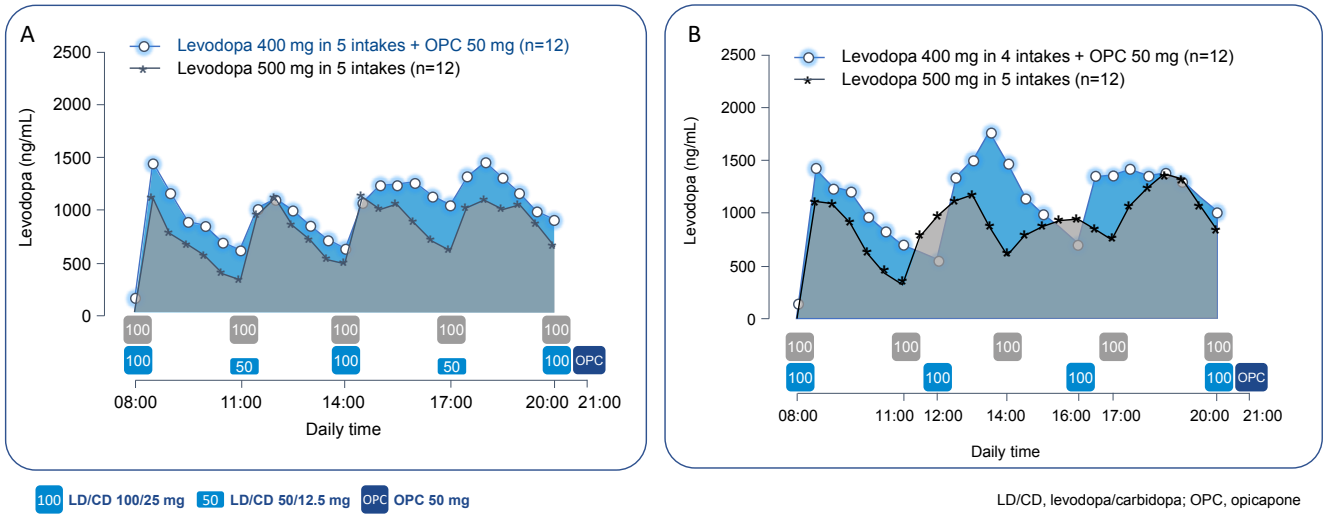


Table 1. 12-hour motor response following 2-week, five daily intakes of levodopa/CD (total daily dose of 500 mg/125 mg) compared with 2-week five daily intake levodopa/CD (total daily dose of 400 mg/100 mg) plus once-daily opicapone 50 mg and 2-week four daily intake levodopa/CD (total daily dose of 400 mg/100 mg) plus once-daily opicapone 50 mg[22]

	Geometric mean (90% CI)			
	Reference (five daily intakes, total dose levodopa/CD 500/125 mg)	**Test (four/five daily intakes, total dose levodopa/CD 500/125 mg)**	**Magnitude of change**	**p-value**
Five daily intakes, total daily dose of levodopa/CD 500/125 mg with opicapone vs *five* daily intakes, total daily dose levodopa/CD 400/100 mg plus opicapone 50 mg				
Time-to-ON (mins) (n=10)	41.84 (36.03, 48.59)	27.79 (18.64, 41.11)	–9.3 (–17.84, –0.74)	p=0.0420
ON-time (mins) (n=9)	333.1 (298.8, 371.2)	489.5 (441.1, 543.1)	158 (111.1, 205.6)	p=0.0002
OFF-time (mins) (n=9)	376.9 (349.9, 406.0)	208.7 (164.2, 265.3)	–157.2 (–203.9, –110.5)	p=0.0013
Five daily intakes, total daily dose of levodopa/CD 500/125 mg with opicapone vs *four* daily intakes, total daily dose of levodopa/CD 400/100 mg plus opicapone 50 mg				
Time-to-ON (mins) (n=12)	44.62 (38.75, 51.39)	39.48 (30.41, 51.26)	–1.6 (–13.37, 10.25)	p=0.3750
ON-time (mins) (n=10)	340.3 (292.0, 396.7)	394.3 (347.2, 447.6)	52.5 (–25.84, 130.8)	p=0.2394
OFF-time (mins) (n=10)	356.4 (313.2, 405.5)	299.3 (247.1, 362.5)	–51.5 (–129.4, 26.39)	p=0.2367

CD, *carbidopa;* CI, *confidence interval*

response (Table 1). There was a significant 34% reduction in time-to-clinical-effect (time-to-ON at 12 hours) with the five intakes of levodopa/carbidopa (total 400/100 mg) plus opicapone regimen versus baseline (mean difference –9.3 min (90% CI: –17.84, –0.74; p=0.0420) and a significant 20% increase in 24-hour total ON-time of 103.3 min (60.97, 145.7) (p=0.0007).[22]

When compared to the baseline levodopa/carbidopa 500/125 mg regimen, four intakes of total daily levodopa/carbidopa 400/100 mg (every 4 hours) plus opicapone 50 mg was also characterised by a two-fold increase in levodopa $C_{min,min}$ (p=0.0016), with a corresponding 27% increase in AUC_{total} (p=0.0003) (Figure 2). Despite the stabilisation in C_{max} in combination with a significant increase in C_{min}, the 10% decrease in fluctuation index was not statistically significant (p=0.1095) for this treatment arm. Adding opicapone 50 mg resulted in a 12% decrease in time-to-ON at 12 hours (although this was not significant) of –1.6 min (90% CI: –13.37, 10.25), p=0.3750, and a significant 11% increase in 24-hour total ON-time of 52.5 min (29.4, 75.6), p=0.0015.[22]

Improvement in patient outcomes was reported for both the four- and five-intake levodopa/carbidopa (total 400/100 mg) with opicapone 50 mg regimens versus baseline. For PGI-C, 92% of patients reported any improvement (minimally, much and very much improved) with the five-intake regimen (one patient had missing data), and 67% with the four-intake regimen.[22] Two treatment-emergent adverse events (TEAEs) were reported for two patients in the four-intake regimen only (one increased blood glucose, one increased gamma-glutamyltransferase); both events were mild and not related to either levodopa or opicapone. No dyskinesia was reported as an adverse event.[22]

Professor Isaacson emphasised that these PK and clinical outcome data complement what is already known about opicapone and could help to inform clinician decision-making in overcoming some of the challenges faced by patients presenting with motor fluctuations. Optimising levodopa therapy is key when managing motor fluctuations, and a once-daily evening dose of opicapone 50 mg may allow lowering total daily levodopa dose, providing added flexibility in tailoring treatment to the individual needs of patients with PD experiencing end-of-dose motor fluctuations.

The ADOPTION study: opicapone 50 mg as a first-line approach to treat wearing-off

The ongoing real-world ADOPTION study also aims to evaluate dosing flexibility with opicapone in patients with wearing-off, enrolling patients with motor fluctuations that occur earlier in the disease course. This ongoing study is a Phase IV, randomised, open-label exploratory trial in patients with PD (NCT04990284).[23] The aim of this study is to evaluate the potential of opicapone 50 mg to optimise levodopa/DDCI as a "first strategy" to treat wearing-off versus adding an additional dose of levodopa/carbidopa 100/25 mg. A total of 100 patients with symptoms of wearing-off for <2 years and treated with 3–4 daily oral levodopa doses up to 600 mg are to be recruited at 25 European sites. The primary endpoint is change from baseline in OFF-time at 4 weeks (using the Hauser diary). Secondary endpoints include tolerability, Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Movement Disorder Society Non-Motor Symptom Scale (MDS-NMSS), Parkinson's Disease Questionnaire-8 (PDQ-8), Clinician Global Impression of Change (CGI-C) and PGI-C.[23]

Non-motor fluctuations – the hidden side of OFF-time

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Levodopa-induced NMF remain one of the unmet needs in PD due to poor awareness by clinicians, a lack of unified guidelines for routine assessment, and subsequent under-management.[24] Currently, there is no strong evidence-base for the management of troublesome features of NMF, such as anxiety, fatigue, depression and RBD, which impact considerably on both patients and carers.[24] Overall, there is also a lack of adequate research in this area, as well as an unmet need to communicate the non-motor aspects of PD.[24]

In the 1970s, Marsden and Parkes first described autonomic and cognitive NMF in a patient who reverted to profound akinesia, sweating, fear, flushing and confusion after a period of dyskinetic ON.[25] A study carried out nearly 20 years later showed a 17% prevalence of NMF in 130 consecutive patients with PD.[26] It was only when a systematic study was performed more than 10 years later using the wearing-off questionnaire (WOQ-19) that prevalence of NMF was shown to be nearly as high as 50%.[27] In this study, fluctuations were categorised as either psychiatric (e.g. confusion, slowness of thought), autonomic (e.g. sweating, abdominal discomfort) or dysaesthesia (e.g. pain).[27] Further insights were gained from the international NMF study in 100 patients with advanced PD (NoMoFlu-PD).[28] In this landmark study, nine NMS such as dysphagia, anxiety, depression, inner restlessness, fatigue, concentration/attention, dizziness, bladder urgency and pain were worse during the OFF state compared to the ON state,[28] and therefore defined as NMS accompanying MF. The study also identified that NMS can be present in ON and worsen in OFF or appear solely during OFF. Two other phenomenon that can also occur are isolated NMF, which are behavioural changes during the ON state,[29] and metacognitions, where motor fluctuations induce anticipatory "thinking" which, in turn, can worsen the severity of the fluctuations.[29,30] In particular, anxiety – a specific feature of NMF – can be a negative driver of metacognition.[30] Dopaminergic stimulation has, however, the potential to improve neuropsychiatric signs and symptoms of anxiety, depression, and dopaminergic apathy that impact the quality of life in patients with PD.[31]

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

The 13-domain MDS-NMSS, and updated recent revision, is a useful tool that provides a comprehensive non-motor assessment in patients with PD.[32] This validated scale has a separate optional NMF subscale of eight items: depression, anxiety, thinking or cognitive abilities, bladder symptoms, restlessness, pain, fatigue, and excessive sweating. The NMF subscale of MDS-NMSS can be used to quantify the severity of NMF, even in patients with mild PD where NMF may be evident through to severe disease.[32,33]

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

The role of COMT inhibition as an adjunct in the treatment of NMF was initially investigated in two studies.[34,35] A single entacapone pill at bedtime with levodopa/carbidopa (n=39 patients) was found to have a significant therapeutic effect on sleep symptoms: mean (SD) PD Sleep Scale (PDSS) score at baseline, 92.2 (19.6) versus 3 months, 105.2 (20.9), p<0.001. There were improvements in overall sleep quality, distressing

dreams, sleep refreshment, insomnia (sleep onset and maintenance), fidgets in bed, numbness, nocturia and painful morning dystonia.[35] While tolcapone is not routinely used due to its hepatic side effects,[36] an open-label study (n=125) has demonstrated the ability of tolcapone (three times daily with levodopa/carbidopa) to significantly improve the NMS score by –15.72 (from a mean (SD) baseline of 55.77 (36.81)) (p<0.001) after 4 weeks of treatment. All domains (except perceptual problems/hallucinations, attention/memory and sexual function) improved with tolcapone adjunctive therapy versus pre-tolcapone, specifically mood/cognition by –3.19 points (from baseline mean (SD) 11.55 (12.65)) and sleep/fatigue by –3.74 points (from baseline mean (SD) 10.89 (7.92)). Significant improvements were also observed for the miscellaneous domain, which includes pain, of –1.63 points (baseline mean (SD) 6.78 (6.8)) (p<0.001).[34]

Two further real-world studies with the once-daily COMT inhibitor opicapone provide a consistent signal for an NMF effect with COMT inhibition. The Phase IV OPTIPARK study of opicapone assessed CGI-C as the primary endpoint. One of the secondary endpoints showed that, after 3 months (n=393), opicapone significantly improved NMSS total score by −6.8 (19.7) points (mean change (SD)) from 44.6 (30.3) (mean (SD)) (p<0.0001). This included NMSS domains for sleep/fatigue, mood/cognition and miscellaneous domains, with changes from baseline of –1.3 (6.3) (from 9.0 (7.53)), –1.5 (6.82) (from 6.7 (9.80)), and –1.6 (6.01) (from 8.2 (7.30)), respectively (p<0.0001 for all domains).[37]

The real-world single-centre OPEN-PD study (Opicapone Effectiveness on Non-motor symptoms in PD) validated the OPTIPARK findings.[38] This prospective, multicentre, observational, prospective, open-label, single-arm study showed a significant reduction in NMSS total score of 27.3% at 6 months (n=33): mean (SD) NMSS score at baseline 71.67 (37.12) versus 6 months 52.1 (34.76), p=0.002. After 6 months' treatment with opicapone, the same NMSS domains as OPTIPARK showed improvements versus baseline (mean (SD)): sleep/fatigue (–13.26 points from baseline 33.08 (19.02); p<0.0001), mood/apathy (–10.35 points from baseline 22.22 (22.58); p=0.001), and miscellaneous (–9.87 points from baseline 21.96 (18.56); p=0.021). Compared to baseline, opicapone also improved gastrointestinal symptoms by –4.03 points from a baseline of 19.44 (16.27); p=0.029).[38]

Improvements in the NMSS were associated with an 18.4% improvement in the 39-item PD Quality of Life Questionnaire Summary Index (PDQ-39SI) score at 6 months: mean (SD) baseline 26.67 (17.61), 6 months 21.75 (14.9) (p=0.001). This included significant improvements in domains for (mean (SD)) emotional wellbeing (–9.80 points vs baseline 36.74 (26.95); p=0.004), stigmatisation (–8.35 points vs baseline 22.72 (27.41); p=0.009) and pain/discomfort (–11.01 points vs baseline 34.34 (21.52); p=0.023).[38] Prof Chaudhuri highlighted that these data provide evidence that adding a COMT inhibitor to levodopa/carbidopa may help patients with many troublesome and often disabling NMF.

The safety and tolerability of opicapone in these studies was evaluated and opicapone was generally well tolerated.[37,38] OPTIPARK showed that 371 out of 495 patients (74.9%) experienced TEAEs. TEAEs that were at least possibly drug-related (reported in 45.1% of patients), such as dyskinesia (11.5%), dry mouth (6.5%) and dizziness (4.8%), generally arise early in the early treatment period (between 10–14 days).[37] Professor Chaudhuri highlighted that it is useful to let patients know that these are short-term, early side effects of treatment. In the OPEN-PD study, 13 adverse events occurred in 11 patients (33.3%), with dyskinesia and nausea the most frequent. Two patients discontinued due to an adverse event considered to be possibly related to opicapone (nausea and insomnia).[38]

A recent retrospective study that investigated the long-term non-motor effects of opicapone in PD (n=13) – using data collected from the Non-motor-International-Longitudinal study (NILS) and the OpiSleep study – supports these same findings.[39]

Ongoing trials with opicapone

Data are eagerly awaited from two ongoing opicapone trials which will help to consolidate the evidence base for opicapone in treating NMF associated with end-of-dose motor fluctuations. 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 patients with PD and end-of-dose motor fluctuations and associated pain. The primary endpoint is change from baseline in the King's PD Pain Scale (KPPS) Domain 3 (fluctuation-related pain) at 24 weeks, with KPPS Domain 4 (nocturnal pain) one of the

secondary endpoints. Recruitment is ongoing for 140 patients at 50 European sites (NCT04986982).[40] The OASIS study is a Phase IV, open-label, single-arm pilot trial that aims to evaluate the effect of opicapone 50 mg with levodopa/DDCI in patients with wearing-off and PD-associated sleep disorders. Sleep disorders, an integral part of NMF, will be assessed at baseline and 6 weeks using the PD Sleep Scale-2 (PDSS-2) total score. Recruitment is ongoing for 30 patients at 6 European sites (NCT04986982).[41]

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Opicapone prescribing information can be found here https://ema.europa.eu/en/medicines/human/EPAR/ongentys#product-information-section

For UK HCPs only, opicapone prescribing information and adverse event reporting can be found at: https://bialparkinsons.co.uk/prescribing-information/. **Adverse events should be reported. Reporting forms and information can be found at** https://yellowcard.mhra.gov.uk/ or in Ireland at www.hpra.ie. Adverse events should also be reported to BIAL on +44 (0)1628 531171 or bial@pharmalex.com

