How are we really optimising levodopa? The role of enzymatic inhibition

Proceedings from the Bial satellite symposium at the MDS Congress 2023

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Meeting summary

Optimising levodopa therapy as part of the challenge of treating 'wearing-off' in Parkinson's disease (PD) was the focus of a Bial-sponsored satellite symposium at the International Congress of Parkinson's Disease and Movement Disorders (MDS) 2023. The symposium profiled the rational use of adjunctive therapy to levodopa early in the disease, when motor fluctuations start to occur. This review of the symposium discusses the role of the catechol-O-methyltransferase (COMT) inhibitor opicapone in the management of motor fluctuations in the context of improving the plasma profile and bioavailability of levodopa and how, from a clinical perspective, dual enzymatic inhibition (dopa-decarboxylase (DDC) and COMT) may be one strategy for maximising the effectiveness of this cornerstone therapy. Particular consideration is given to the pharmacokinetic and clinical results from the latest trials of opicapone (203 pharmacokinetic trial and OGT_001 trial in South Korea). These findings, together with the soon-to-be-available results from the ADOPTION trial, may help to guide clinical decision-making in the early use of opicapone as part of a dual inhibition strategy in patients with PD experiencing end-of-dose motor fluctuations.

KEYWORDS: PARKINSON'S DISEASE, COMT INHIBITORS, OPICAPONE, DUAL INHIBITION

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The Challenge of OFF-time

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Our ageing population has played a major role in increasing the number of people with Parkinson's disease (PD), placing the global burden of this disease at 8.5 million people in 2019.[1]

Non-motor symptoms such as rapid eye movement (REM) sleep behaviour disorder, depression, constipation, anxiety and hyposmia are often present before the onset of the cardinal motor symptoms (bradykinesia, rigidity, tremor), which is typically when a clinical diagnosis of PD is made.[2] As the disease progresses, motor fluctuations and motor complications, such as dyskinesia, become more evident, accompanied by an

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increasing burden of non-motor symptoms such as fatigue and pain, urinary symptoms and cognitive impairment.[2]

Once levodopa therapy is initiated, about 10% of patients per year develop motor complications,[3] which might manifest as motor fluctuations or levodopa-induced dyskinesias.[3,4] The risk factors for developing levodopa-associated motor complications are disease progression and severity, increased levodopa dose, as well as genetic influencers, such as autosomal recessive PD (parkin, PINK1 and DJ-1).[3]

The onset of levodopa-associated motor fluctuations and their evolution can be elucidated by looking at how the therapeutic response to levodopa evolves with disease progression. At the start of treatment, there is an evident distinction between the short-duration response (SDR), which lasts a few hours after a single dose of levodopa, and the long-duration response (LDR), which can last up to 2 weeks after stopping therapy.[5] As the disease progresses, the sustained LDR gradually diminishes (losing the smooth drug effect), together with a change in the magnitude of the SDR – it is at this point that a patient becomes a 'fluctuator'.[5]

The challenge is thus to find effective strategies that enable the optimisation of levodopa's pharmacokinetic profile throughout the course of a patient's Parkinson's disease.[6]

Optimising levodopa: the rationale for dual inhibition

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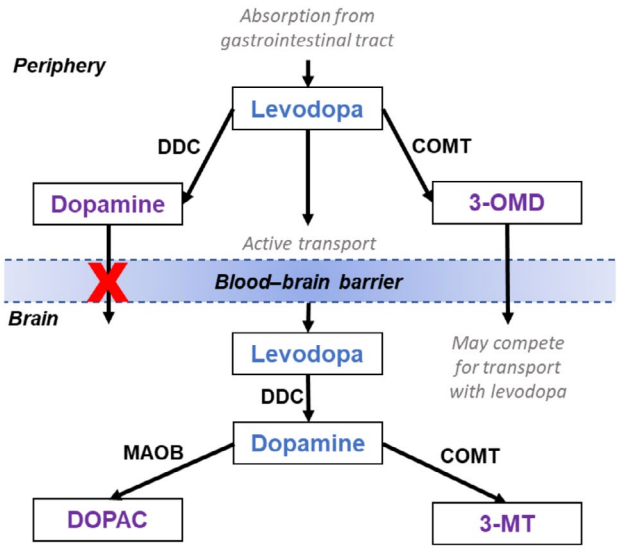
Despite levodopa being the cornerstone of PD therapy,[7] this prodrug of dopamine has a sub-optimal pharmacokinetic profile, with poor oral absorption from the gastrointestinal tract and poor penetration across the blood–brain barrier (BBB).[6,8,9] In the periphery, levodopa would normally be converted to dopamine by the enzyme dopa-decarboxylase (DDC) and to 3-O-methyldopa (3-OMD) by catechol-O-methyltransferase (COMT), with only a small fraction of each dose of levodopa reaching the brain after active transport across the BBB[10,11] (Figure 1).

The challenge physicians face is to overcome the extensive peripheral metabolism of levodopa, thereby improving its



COMT, catechol-O-methyl transferase; DDC, dopa-decarboxylase; MAOB, monoamine oxidase; DOPAC, dihydroxyphenylacetic acid; 3 OMD, 3-O-methyldopa; 3-MT, 3-methoxytyramine

Figure 1. Transport and metabolism of levodopa from the gastrointestinal tract to the brain for conversion to dopamine.

Adapted from: Lewitt et al, 2008 and Gershanik et al, 2015[10,11]

bioavailability to increase ON-time and decrease OFF-time.[9] The clinical necessity of using a DDC inhibitor (DDCI) to block the peripheral metabolism of levodopa is universally accepted and levodopa has invariably been administered with a DDCI since the mid-1970s.[12] While inhibiting peripheral DDC activity markedly improves levodopa bioavailability, it does not optimise the effectiveness of the drug because DDC inhibition diverts levodopa into the COMT pathway, thus increasing plasma and brain levels of 3-OMD and so reducing the potential availability of levodopa to the brain for conversion to dopamine[7,13] (Figure 1).

Professor Jenner argued that COMT inhibition represents an integral part of a dual inhibition strategy for minimising levodopa metabolism in the periphery and improving its symptomatic efficacy.[9,11] Currently, three COMT inhibitors are available. Tolcapone, one of the second-generation COMT inhibitors, inhibits both peripheral and central COMT activity and has a long duration of action with three times daily dosing.[11] However, its safety profile showed a relevant increase of liver enzymes,[11] requiring hepatic monitoring[14] and it is now rarely used in clinical practice. Entacapone, another

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second-generation COMT inhibitor, has a short half-life and its administration is required with every dose of levodopa.[11,15] In contrast, opicapone, as a third-generation COMT inhibitor, has a long duration of effect due to its high binding affinity to COMT that translates into a slow complex enzyme–substrate dissociation and prolonged enzyme inhibition.[16] In practical terms, a daily single 50 mg opicapone dose taken at bedtime as an adjunct to levodopa/DDCI provides effective blockade of COMT over the following 24 hours.[9,16] As opicapone dosing, and subsequent COMT inhibition, is not tied to levodopa administration, this allows the physician flexibility in optimising levodopa/DDCI treatment as required in individual patients.[17]

Professor Jenner noted that physicians use DDCIs on initiation of levodopa therapy but have tended to reserve COMT inhibition for use in later stages of the disease. However, when it comes to the use of enzyme inhibitors in PD treatment, it is important to recognise that the pharmacokinetic profile of levodopa does not change during the course of the disease, i.e. the challenge of improving the plasma profile of levodopa and maximising its availability to the brain is the same in early disease as it is in late disease.[18] Because of this, Professor Jenner pointed out that it would be plausible to consider the adjunctive use of COMT inhibitors in early PD – dual inhibition of DDC and COMT may be a strategy for maximising the effectiveness of levodopa as soon as end-of-dose motor fluctuations are seen (and if PD symptoms are poorly controlled).

How dose and regimen impact levodopa bioavailability

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As motor symptoms become evident, the patient's therapeutic regimen is adjusted accordingly by the treating physician.[9] One approach to treat recently diagnosed motor fluctuations might be to increase each oral dose of levodopa, but this may not eliminate the troughs in plasma levels and risks increasing the incidence and severity of dyskinesia. Another option would be to increase the frequency of levodopa dosing, but this may also lead to more peaks and troughs, and could translate into more OFF-time and dyskinesia experienced by patients.[17]

Adding opicapone may be an alternative strategy to adjusting levodopa dosing in patients with end-of-dose wearing-off.[17] This approach has been eloquently demonstrated in a recent exploratory Phase 2 trial which assessed the effect of opicapone 50 mg on levodopa pharmacokinetics (PK) in different levodopa/carbidopa regimens in 24 patients with end-of-dose motor fluctuations.[17] In this open-label, crossover study, after an initial stable regimen of levodopa/carbidopa 500/125 mg per day (five intakes of 100/25 mg per day for 2 weeks), PK parameters and clinical outcomes were evaluated over a 12-hour period (baseline). Patients were then randomised to two separate arms (n=12 patients each), both reducing the total levodopa/carbidopa daily dose to 400/100 mg whilst adding opicapone 50 mg. Patients were to receive levodopa/carbidopa in either four or five daily intakes: dosing for the four-intake regimen occurred as 100/25 mg administered at 4-hour intervals, and dosing for the five-intake regimen occurred as alternating 100/25 mg and 50/12.5 mg doses at 3-hour intervals. Both arms received opicapone 50 mg administered 1 hour after the last daily intake of levodopa/carbidopa.[17] At the end of 2 weeks treatment, a further evaluation of the PK parameters and clinical outcomes was carried out over a 12-hour period and compared to baseline.[17]

This small PK trial demonstrated that, despite a reduction of 100 mg in the total levodopa/carbidopa daily dose, adding opicapone 50 mg increased total exposure to levodopa (AUC_{total}) by 27% in the four-intake levodopa/carbidopa 400/100 mg + opicapone arm (p=0.0003) and by 29% (p<0.0001) in the five-intake levodopa/carbidopa 400/100 mg + opicapone arm compared to baseline AUC_{total} (geometric mean (90% confidence interval)) measures of 10,126 (8940, 11,469) h•ng/mL and 9097 (8111, 10,202) h•ng/mL, respectively.[17]

These changes to levodopa pharmacokinetics were also associated with decreased OFF-time and increased ON-time (both secondary endpoints) compared to baseline, as measured by investigators during the 12-hour pharmacokinetic evaluation days and by patients completing 24-hour patient Hauser diaries during the 3 days before each pharmacokinetic visit.[17]

Professor Ferreira highlighted that, in his clinical experience, once-daily opicapone 50 mg is a suitable treatment option in patients with end-of-dose wearing-off and not stabilised on

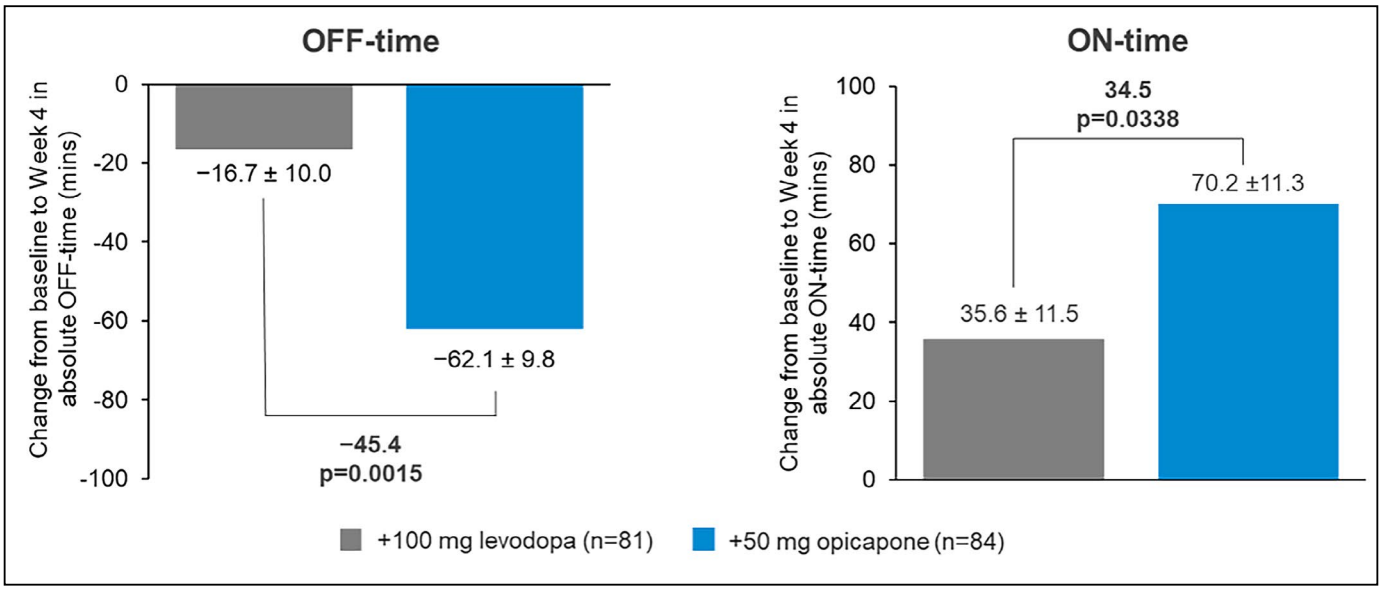

Figure 2. Opicapone 50 mg vs an additional 100 mg levodopa in patients with early motor fluctuations: impact on OFF- (primary endpoint) and ON-time (secondary endpoint)[19]

their current regimens.[17] The possibility of using opicapone 50 mg to optimise levodopa/DDCI as an early add-on approach to treat patients recently diagnosed with end-of-dose motor fluctuations is being explored in two Phase 4 e**A**rly L-**D**opa with **O**picapone in **P**arkinson's pa**T**ients w**I**th mot**O**r fluctuatio**N**s (ADOPTION) trials. Results from the European open-label exploratory trial across 25 sites in Europe are imminent, whilst the results from the South Korean (OGT_001) study have been recently released.[19] Both trial results may help to guide clinical decision-making in the early use of opicapone in patients with PD experiencing motor fluctuations[20] (NCT04990284[21]).

Emergence of motor fluctuations: evidence for initial adjunctive therapy

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Similar in design to the European ADOPTION study,[20] the aim of the recent South Korean OGT_001 study was to evaluate the effect of adding opicapone 50 mg versus additional levodopa 100 mg as a first-line strategy for the treatment of end-of-dose wearing-off in patients with Parkinson's disease.[19]

This exploratory Phase 4, randomised, multicentre, open-label trial included adult patients with a modified Hoehn & Yahr stage I–III score (at ON) and has a mirror design to the European ADOPTION study.[20] To be eligible, patients had to have been on a stable regimen of levodopa/DDCI (3–4 intakes per day,) up to a maximum daily dose of 600 mg levodopa, for at least 4 weeks before screening. They had to have signs of end-of-dose wearing-off for less than 2 years (but for at least 4 weeks), and an average total daily OFF-time of at least 1 hour (but less than 5 hours average total daily OFF-time while awake).[19]

A total of 193 patients enrolled in OGT_001 and the full analysis set included 165 patients. Baseline characteristics for both groups (randomised set, n=88 for opicapone 50 mg and n=81 for levodopa group) showed a similar mean age of 64 years, a similar disease duration (5.0 years for the opicapone arm; 5.7 years for levodopa arm), and a similar mean daily OFF-time of 3.4 hours in both groups. Over 90% of patients were receiving three intakes of levodopa doses per day with the average total daily dose just over 400 mg.[19] Key baseline characteristics that differed from the patient population in the pivotal Phase 3 trials for opicapone (BIPARK I and II) were that patients in OGT_001 had a shorter mean time since PD diagnosis (7.0 years, BIPARK I; 8.2 years, BIPARK II), less time in the OFF-state (6.2 hours, BIPARK I; 6.3 hours, BIPARK II), and were on a lower levodopa daily dose (695 mg/day, BIPARK I; 700 mg/day, BIPARK II).[19,22,23]

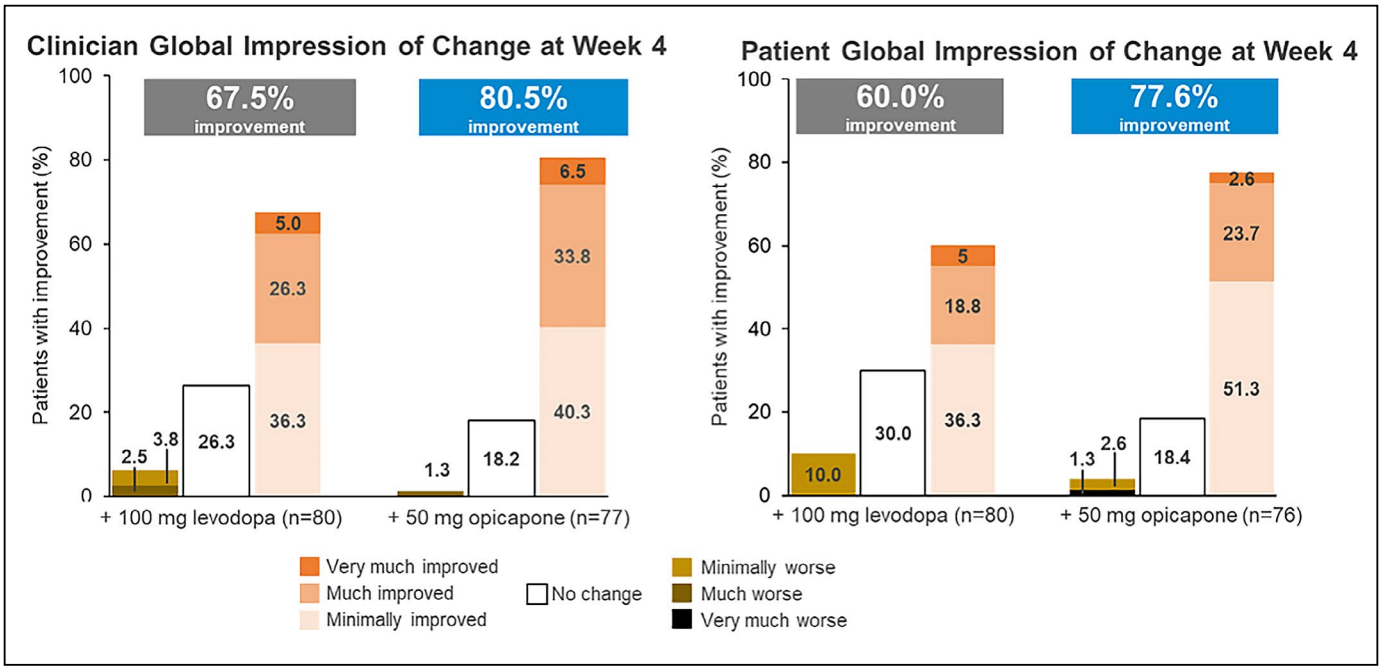

Figure 3. Opicapone 50 mg vs an additional 100 mg levodopa in patients with early motor fluctuations – clinician and patient Global Impression of Change (secondary endpoints; final analysis set)[19]

The primary endpoint was change from baseline in OFF-time at 4 weeks from baseline.[19]

In this trial, opicapone 50 mg (n=84) appeared to be more efficacious in improving OFF- and ON-time than an additional 100 mg levodopa (n=81), with an adjusted mean change (±SE) OFF-time of –62.1 (9.8) minutes versus –16.7 (10.0) minutes (p=0.0015), and ON-time (secondary endpoint) increased by 70.2 (11.3) minutes versus 35.6 (11.5) minutes (p=0.0338) at Week 4, respectively (Figure 2).[19]

Both groups showed a numerical improvement in motor symptoms scores (adjusted mean change (±SE)) from baseline to Week 4 on the Movement Disorder Society-Unified Parkinson's Disease Rating Scale Part III (secondary endpoint) but the differences between the opicapone (–3.4 (±0.7) from 22.0 (±10.0) at baseline) and levodopa (–2.5 (±0.7) from 23.7 (±11.5) at baseline) arms were not statistically significant (mean difference vs levodopa of –0.9, p=0.3591).[19]

From both a physician and patient perspective, beneficial effects of opicapone 50 mg were reported in 80.5% of patients (62/77 patients) judged to have an improvement in Global Impression of Change (minimally, much or very much improved) as measured by clinicians (CGI-C) versus 67.5% (54/80 patients) with additional levodopa 100 mg (no statistical analysis performed for this endpoint). Improvement in the patient-reported Clinical Global Impression of Change (PGI-C) was reported by 77.6% (59/76 patients) in the opicapone arm versus 60.0% (48/80 patients) in the levodopa arm (Figure 3) (no statistical analysis performed for this endpoint).[19]

Opicapone appeared to be generally well tolerated. The percentage of patients who reported any adverse events was higher for opicapone vs the levodopa group (38% vs 19%) (n=33 and n=15, respectively), with the most common adverse events (>4% of opicapone patients) being dizziness (9% vs 4%), dyskinesia (8% vs 1%) and constipation (5% vs 3%). However, the proportion of patients who discontinued due to an adverse event was low (<5%) and similar between the treatment groups (3.5% vs 2.5%, respectively).[19]

The exploratory OGT_001 trial results, together with the results of the PK trial,[17] suggest that opicapone 50 mg may represent an efficacious alternative and generally well-tolerated therapeutic option versus an additional 100 mg levodopa dose to treat PD patients recently diagnosed with end-of-dose wearing-off.[19]

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