Early intervention for Parkinson's disease motor fluctuations

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This content is for healthcare professionals only.

Learning objectives

After watching the touchJOURNAL CLUB activity, you should:

- ✓ Recognise the burden of motor fluctuations in Parkinson's Disease and the need to optimise treatment to ensure the best possible disease outcomes.
- ✓ Describe the key results from the post hoc analysis of the BIPARK studies including the efficacy of opicapone throughout the entire spectrum of motor fluctuations.
- ✓ Understand the implications of these results for clinical practice, including the potential for early intervention on motor fluctuations in PD.

Faculty disclosures

- **Prof. Dr Georg Ebersbach**
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- **Dr Mónica Kurtis**
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Unmet medical needs for patients with Parkinson's disease and motor fluctuations

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Long-term levodopa therapy and OFF-time

Limitations of levodopa therapy

- Levodopa is a front-line treatment for PD.[1]
- With the disease progression, after a few years of levodopa use, most patients can exhibit a shorter motor response to each levodopa dose ("wearing-off fluctuation").[2]
- Delaying levodopa initiation leads to reduced quality of motor control.[3,4]
- Levodopa dose is an independent risk factor for the development of MF and dyskinesias.[5]

Burden of MF

- OFF periods are associated with reduced HRQoL compared with patients without OFF periods.[6,7]
- Patients have an increased risk of falls, leading to injury and an associated further reduction in HRQoL.[8,9]
- Increased OFF time is associated with increased care partner burden.[10,11]

HRQoL, health-related quality of life; MF, motor fluctuations; PK, Parkinson's Disease.

1. Fackrell R, et al. Neurodegener Dis Manag. 2018;8(5):349-360; 2. Cenci MA. Front Neurol 2014;5:242; 3. National Institute for Health and Care Excellence (NICE). Parkinson's disease in adults: pharmacological management of motor symptoms. Available at: https://www.nice.org.uk/guidance/ng71/chapter/Recommendations#pharmacological-management-of-motor-symptoms (Accessed November 2021); 4. Verschuur CVM, et al. N Engl J Med. 2019;380(4):315-324; 5. Olanow CW, et al. Lancet Neurol. 2006;5(8):677-87; 6. Stocchi F, et al. Parkinsonism Relat Disord. 2014;20(2):204-211; 7. Chapuis S, et al. Mov Disord 2005; 20(2): 224-30; 8. Rascol O, et al. J Neural Transm (Vienna) 2015; 122(10): 1447-55; 9. Grimbergen YA, et al. J Parkinsons Dis 2013; 3(3): 409-13; 10. Mosley PE, et al. J Geriatr Psychiatry Neurol 2017; 30(5): 235-52; 11 Onozawa R, et al. J Neurol Sci 2016; 364: 1-5.

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Management of levodopa-induced MF

Levodopa dose modification

- Switch to smaller, more frequent levodopa doses, increase total levodopa dose or switch to controlled-release preparations.[1]

Dopamine agonists

- Co-administration of levodopa with dopamine agonists to prolong dopamine stimulation.[2]

COMT inhibitors

- Co-administration of levodopa with COMT inhibitors to extend levodopa bioavaliability.[3,4]

MAO-B inhibitors

- Co-administration of levodopa with MAO-B inhibitors to prevent dopamine degradation by MAO-B.[3]

COMT, catechol-O-methyltransferase; MAO-B, monoamine oxidase B.

1. Pahwa R, Lyons KE. Curr Med Res Opin. 2009;25(4):841-9; 2. Konta B, Frank W. GMS Health Technol Assess. 2008; 3. Finberg JPM. J Neural Transm (Vienna). 2019;126(4):433-448; 4. Tambasco N, et al. Curr Neuropharmacol. 2018;16(8):1239-1252.

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Opicapone in the treatment of MF

Opicapone

- Opicapone is a third generation, once-daily COMT inhibitor.[1,2]
- COMT inhibitors extend the half-life of levodopa.[3]
- Opicapone provides more pronounced and sustained COMT inhibition compared with entacapone.[2]

BIPARK-I and -II

- Two Phase III studies assessed the efficacy and safety of opicapone as adjunctive therapy to levodopa/DDCI in patients with MF.[4,5]
- Patients demonstrated significant decreases from baseline in OFF-time with opicapone 50 mg versus placebo, and non-inferior decreases versus entacapone (with opicapone demonstrating numerically greater results).[4,5]
- The most common AEs included dyskinesia, insomnia, constipation and dry mouth.[3,4]

AEs, adverse events; COMT, catechol-O-methyltransferase; DDCI, dopa decarboxylase inhibitors; MF, motor fluctuations.

1. EMA 2016. Available at: https://www.ema.europa.eu/en/documents/product-information/ongentys-epar-product-information_en.pdf (accessed September 2021);
2. Rocha JF, et al. Br J Clin Pharmacol 2013;76;763–75; 3. Gershanik OS. Mov Disord 2015;30:103–13; 4. Ferreira JJ, et al. Lancet Neurol. 2016;15(2):154-165;
5. Lees AJ, et al. JAMA Neurol. 2017;74(2):197-206.

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The impact of opicapone across the MF spectrum: BIPARK-I and –II post hoc analysis

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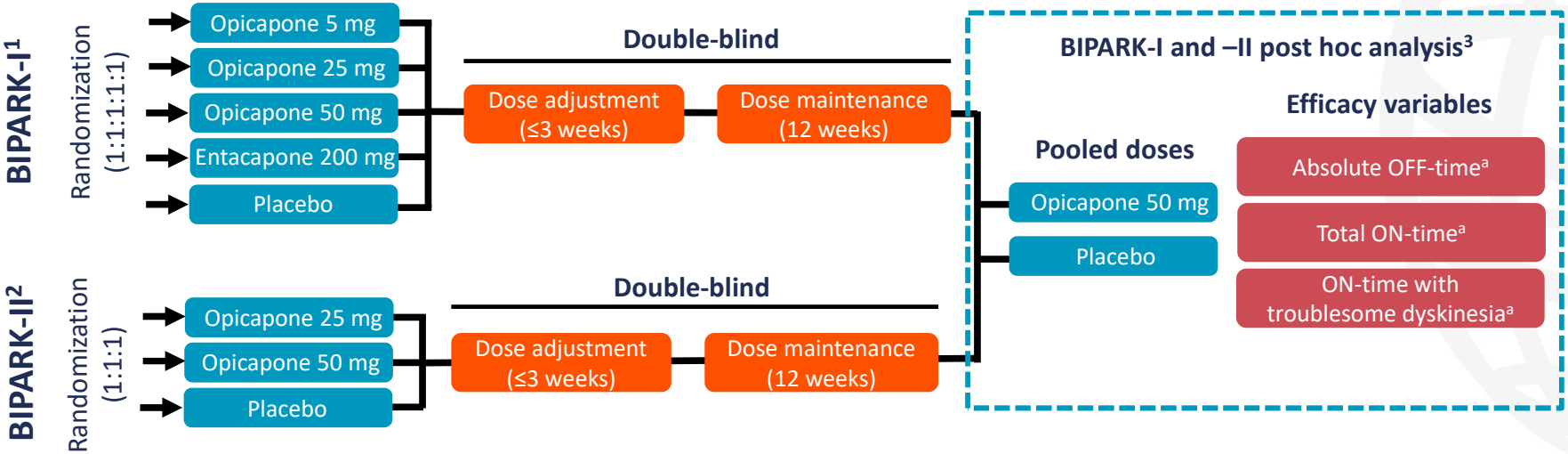
Objective and key methods

BIPARK I and II post-hoc analysis objective: to evaluate the efficacy and tolerability of opicapone versus placebo in patients with MF stratified by disease duration and levodopa treatment pathway



a, assessed by daily paper patient diaries. MF, motor fluctuations

1. Ferreira JJ et al. Lancet Neurol. 2016;15(2):154-165; 2. Lees AJ, et al. JAMA Neurol. 2017;74(2):197-206.
3. Rocha JF, et al. Front. Neurol. 2021;12:754016.

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Patients and post hoc subgroups

BIPARK I and II eligibility criteria: 30–83 years of age *(mean: 64.5)*, ≥3-year diagnosis of idiopathic PD *(mean 7.6)*, H&Y stage 1–3 at ON-state *(mean: 2.4)*, who were receiving levodopa for ≥1 year *(mean: 6.3 years; dose: 698 mg/day)* and experiencing end-of-dose MF *(mean OFF time: 6.2 hours/day)*.[1,2]

Post hoc analysis

Disease-related characteristics[3]

- Duration of PD: <6 vs ≥6 years; <7 vs ≥7 years; <8 vs ≥8 years; <9 vs ≥9 years
- H&Y staging: <2.5 vs ≥2.5
- Timing of onset of MF: ≤1 vs >1 years; ≤2 vs >2 years

Treatment-related characteristics[3]

- Levodopa intakes: <4 vs ≥4 daily; <5 vs ≥5 daily; <6 vs ≥6 daily
- Levodopa daily amount: <500 vs ≥500 mg; <600 vs ≥600 mg; <700 vs ≥700 mg; <800 vs ≥800 mg
- Levodopa duration: <4 vs ≥4 years; <5 vs ≥5 years; <6 vs ≥6 years; <7 vs ≥7 years; <8 vs ≥8 years
- Levodopa only: Yes vs no
- Levodopa + DA: Yes vs no
- Levodopa + MAO-B inhibitor: Yes vs no

DA, dopamine agonist; H&Y, Hoehn and Yahr; MF, motor fluctuations; MAO-B, monoamine oxidase B; PD, Parkinson's Disease.

1. Ferreira JJ et al. Lancet Neurol. 2016;15(2):154-165; 2. Lees AJ, et al. JAMA Neurol. 2017;74(2):197-206. 3. Rocha JF, et al. Front. Neurol. 2021;12:754016.

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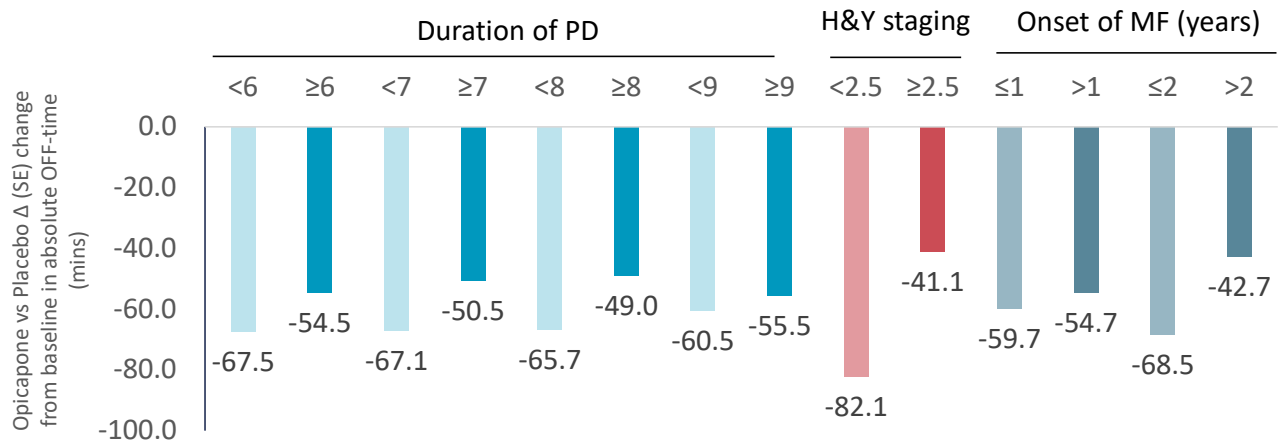
Impact of opicapone on OFF-time: disease-related subgroups

Opicapone was significantly more effective than placebo in reducing OFF-time (approximately -41 to -82 minutes; p<0.05) in all the subgroups analysed.



Reduction in OFF-time with opicapone was generally numerically greater than placebo in patients with earlier disease stages of the disease e.g. lower disease duration[1]

H&Y, Hoehn and Yahr; MF, motor fluctuations; PD, Parkinson's Disease.

1. Rocha JF, et al. Front. Neurol. 2021;12:754016.

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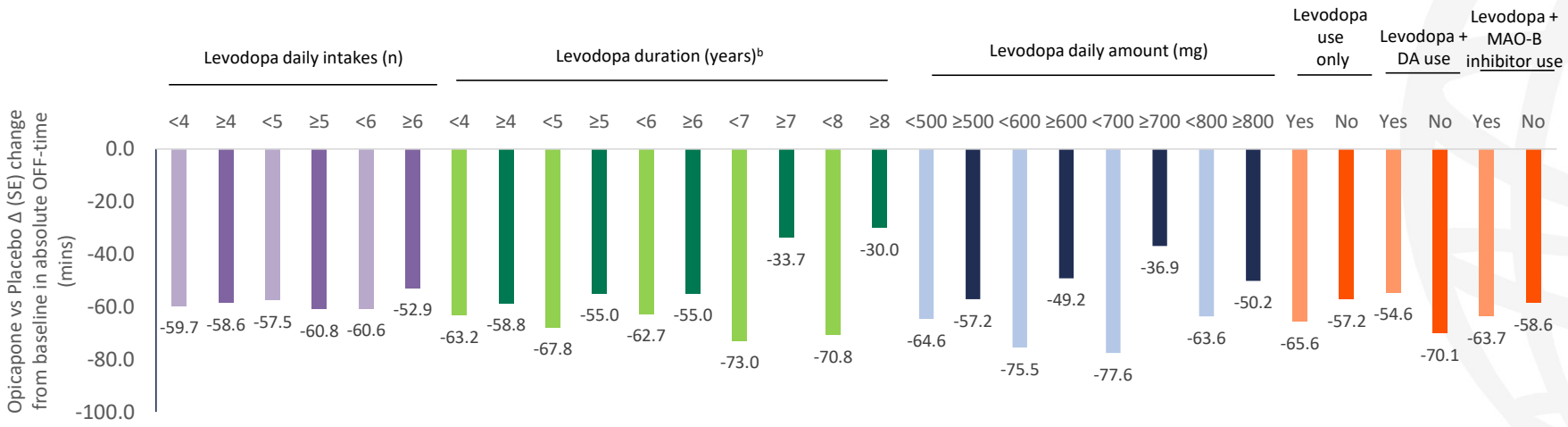
Impact of opicapone on OFF-time: treatment-related subgroups

Opicapone was significantly more effective than placebo in reducing OFF-time (approximately -49 to -76 minutes; p<0.05) in the majority[a] of subgroups analysed.



Decreases in OFF-time with opicapone were, in general, numerically greater than with placebo in patients at an earlier treatment pathway stage e.g. lower levodopa dose.[1]

[a]Exceptions included patients who received ≥6 levodopa intakes, treatment duration ≥7 and ≥8 years, and ≥700 mg/day levodopa, subgroups with a low sample size; DA, dopamine; MAO-B, monoamine oxidase B.

1. Rocha JF, et al. Front. Neurol. 2021;12:754016.

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Impact of opicapone on ON-time

Disease-related subgroups

- Opicapone was **significantly more effective than placebo (p<0.05) in increasing ON-time** in the majority of subgroups.[1]
- Exceptions included patients with disease duration ≥8 years and with onset of motor fluctuations >2 years previously.[1]

Treatment-related subgroups

- Opicapone was **significantly more effective than placebo (p<0.05) in increasing ON-time** in the majority of subgroups.[1]
- Exceptions included patients who received ≥6 levodopa intakes, with levodopa treatment duration ≥7 years and ≥8 years.[1]

Increases in ON-time with opicapone were, in general, numerically greater than placebo in patients with earlier stage disease or treatment pathway e.g. lower disease duration and lower levodopa dose.[1]

1. Rocha JF, et al. Front. Neurol. 2021;12:754016.

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Impact of opicapone on ON-time with troublesome dyskinesia

Disease-and treatment-related subgroups

- Opicapone vs placebo **did not significantly (p≥0.05) increase ON-time with troublesome dyskinesia** in the majority of subgroups.[1]
- Exceptions included patients receiving ≥5 levodopa intakes daily, levodopa treatment duration ≥4 and ≥6 years.[1]

Differences in ON-time with opicapone vs placebo were all <5 minutes and generally numerically lower in patients with earlier stage disease or treatment pathway e.g. lower disease duration and lower levodopa dose.[1]

1. Rocha JF, et al. Front. Neurol. 2021;12:754016.

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Implications of the BIPARK-I and II post hoc analysis

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Implications and considerations

Opicapone is efficacious throughout the spectrum of motor fluctuations and may be a useful early adjunct therapy for patients with motor fluctuations.

Considerations

- As with all DA-based treatments, healthcare practitioners should be aware that opicapone can cause hallucinations and insomnia.[1–3]
- Increased levels of levodopa are associated with increased risk of dyskinesia,[4] so levodopa dose adjustment may be required when using levodopa and opicapone.[2]

DA, dopamine.

1. Han JW, et al. J Korean Med Sci. 2018;33(47):e300; 2. EMA 2016. Available at: https://www.ema.europa.eu/en/documents/product-information/ongentys-epar-product-information_en.pdf (accessed September 2021); 3. Meder D, et al. Neuroimage. 2019;190:79-93; 4. Zhu K, et al. Parkinsonism Relat Disord. 2016;33:51-57.

Outstanding questions and unmet needs

Outstanding questions

- Opicapone effect in patients with less OFF-time at baseline (mean: 6.2 hours in BIPARK-I and -II).[1,2]
- Opicapone effect in patients with lower disease duration (mean: 7.6 years in BIPARK-I and -II).[1,2]
- Opicapone effect in patients with less time since levodopa initiation (mean: 6.3 years in BIPARK-I and -II).[1,2]
- Determination of effect on OFF-time using more objective measures e.g. wearable devices.[3]

Unmet needs in PD

- Improved understanding of the characteristics that determine levodopa and COMT responsiveness.
- Treatments that improve the non-motor fluctuations of Parkinson's Disease.[4]
- Treatments that improve axial motor symptoms including dysarthria, freezing and dysphasia.[5]

COMT, catechol-O-methyltransferase; PD, Parkinson's Disease.

1. Ferreira JJ et al. Lancet Neurol. 2016;15(2):154-165; 2. Lees AJ, et al. JAMA Neurol. 2017;74(2):197-206; 3. Osig C, et al. J Neural Transm (Vienna). 2016;123(1):57-64; 4. Rukavina K et al. Expert Rev Neurother. 2021;21(3):335-352; 5. Sharpe G, et al. Front Neurol. 2020;11:576569.

Take home messages

- With the disease progression, after a few years of levodopa use, most patients can exhibit a shorter motor response to each levodopa dose ("wearing-off fluctuation").

- The COMT inhibitor opicapone significantly decreases OFF-time versus placebo in patients throughout the spectrum of motor fluctuations, with larger numerical improvements in patients with early-stage disease.

- Opicapone may be a useful early adjunct therapy for patients with motor fluctuations.

COMT, catechol-O-methyltransferase.

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