touchROUNDTABLE

The clinical evidence for opicapone across the duration of PD

An expert panel discussion

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Online activity details

This resource has been downloaded from a touchROUNDTABLE.

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www.touchneurologytmc.com/parkinsons-disease/learning-zone/clinical_evidence_for_opicapone_across_duration_of_PD

This content is for healthcare professionals based in Europe only.

Learning objectives

After watching the touchROUNDTABLE activity, you should better be able to:

- ✓ Discuss the clinical trials examining the effects of opicapone in treating patients with PD and early motor fluctuations, their key results and implications.
- ✓ Describe the clinical studies investigating the early intervention with COMT inhibitors in patients with early motor fluctuations, and their results.
- ✓ Understand the potential of opicapone to treat non-motor symptoms, including the design of ongoing trials investigating these outcomes.

Expert panel

Prof. Olivier Rascol

University Hospital of Toulouse &
University of Toulouse,
Toulouse, France

Prof. Peter Jenner

King's College London,
London, UK

Prof. Joaquim Ferreira

Universidade De Lisboa,
Lisboa, Portugal &
CNS – Campus Neurológico,
Torres Vedras, Portugal

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Disclosures

- **Olivier Rascol**
  Has participated in clinical trials sponsored by Bial and have received honoraria for consultancy and advisory boards from Bial; has acted as a scientific advisor for drug companies developing antiparkinsonian medications (Abbott, Abbvie, Acorda, Adamas, Affiris, Biogen, Britannia, Cynapsus, Denali Pharmaceuticals, Impax, Lundbeck, Merck, Neuroderm, Novartis, Orian Pharma, Osmotica, Oxford-Biomedica, Prexton, Servier, Sunovion, TEVA, UCB, Zambon) and has received unrestricted scientific grants from academic non-profit entities (Toulouse University Hospital, French Health Ministry, MJFox Foundation, France-Parkinson, European Commission EU FP7, and Horizon 2020).

- **Peter Jenner**
  Has received honoraria for consultancy and advisory boards from AbbVie, Adamas, Bial, Britannia Pharmaceuticals, FP Pharmaceuticals, Kyowa Kirin, Roche, UCB, Worldwide Clinical Trials, Zambon, Chiesi Pharmaceuticals, and Profile Pharma.

- **Joaquim Ferreira**
  Has participated in clinical trials sponsored by Bial and have received honoraria for consultancy and advisory boards from Bial; has received grants from GlaxoSmithKline, Grunenthal, Fundação MSD (Portugal), TEVA, Allergan, Novartis, Medtronic and consultancy fees from GlaxoSmithKline, Novartis, TEVA, Lundbeck, Solvay, BIAL, Merck-Serono, Merz, Ipsen, Biogen, Acadia, Allergan, Abbvie, Sunovion Pharmaceuticals, Zambon, Neuroderm, and Affiris.

Agenda

	Discussion open and introduction	5 mins	Olivier Rascol (Chair)
1	**PRESENTATION:** The biology of levodopa and the role of COMT inhibitors in levodopa pharmacokinetics	15 mins	Peter Jenner
2	**PRESENTATION:** Differentiating COMT inhibitors and the clinical development of opicapone for fluctuating Parkinson's disease	10 mins	Joaquim Ferreira
3	**PANEL DISCUSSION:** The role of opicapone in the treatment of early motor fluctuations	10 mins	All faculty
4	**PANEL DISCUSSION:** The role of opicapone in the treatment of non-motor symptoms	10 mins	All faculty
	Conclusions and close	5 mins	All faculty

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Introduction to Parkinson's Disease

Prof. Olivier Rascol

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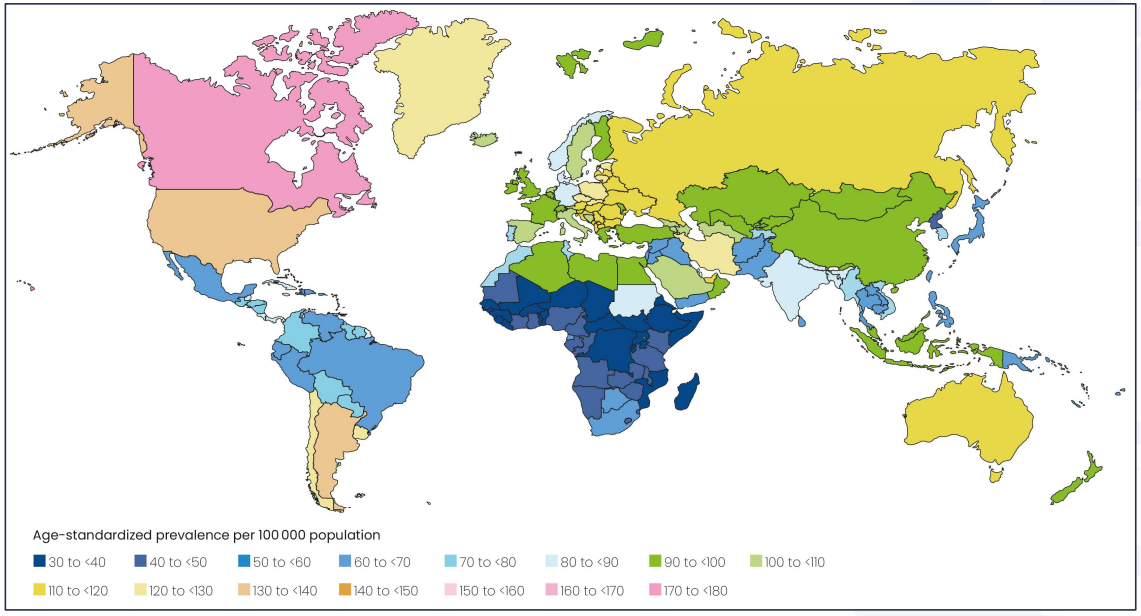
Epidemiology of Parkinson's disease

- Parkinson's disease is the 2nd most common neurodegenerative disease after Alzheimer's disease.[1–3]
- 6.1 million people diagnosed with Parkinson's disease globally (2016 data).[2]
  - Prevalence highest in North and South America and Europe.[2*]
  - Incidence: 10–18 cases/100 000 person-years.[1]
    - Incidence increases with age.
    - Peak incidence between 70 and 79 years of age.

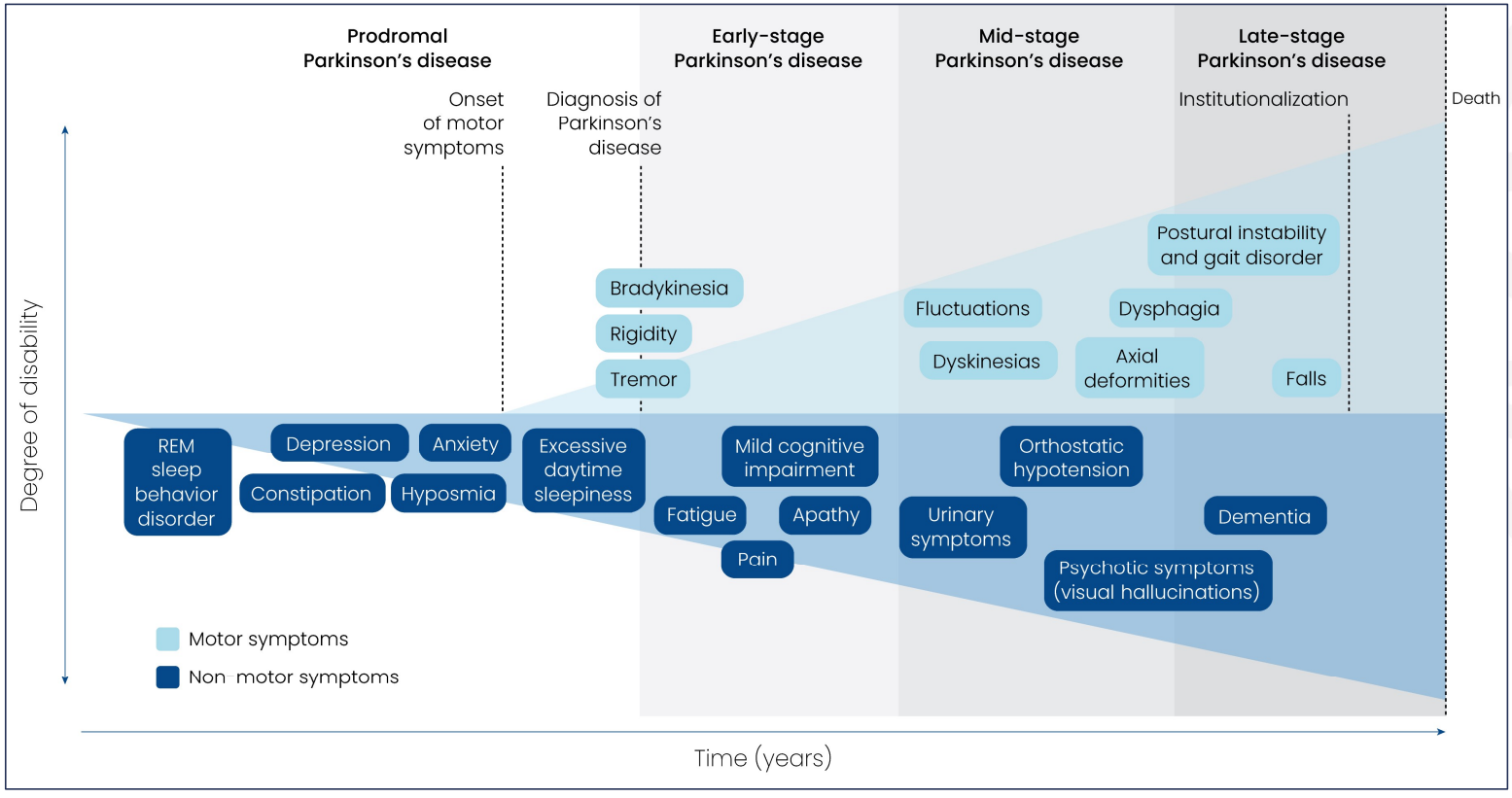


For both sexes; Adapted from Hirsch et al, 2016[3]

*Data do not reflect cases undiagnosed, unreported, or undisclosed.

1. Kalia LV, Lang AV. *Lancet.* 2015;386:896–912; 2. GBD 2016 Parkinson's Disease Collaborators. *Lancet Neurol.* 2018;17:939–53; 3. Hirsch L, et al. *Neuroepidemiology.* 2016;46:292–300.

Clinical symptoms associated with Parkinson's disease progression



REM, rapid eye movement.
Poewe W, et al. *Nat Rev Dis Primers*. 2017;3:17013.

Parkinson's disease guidelines

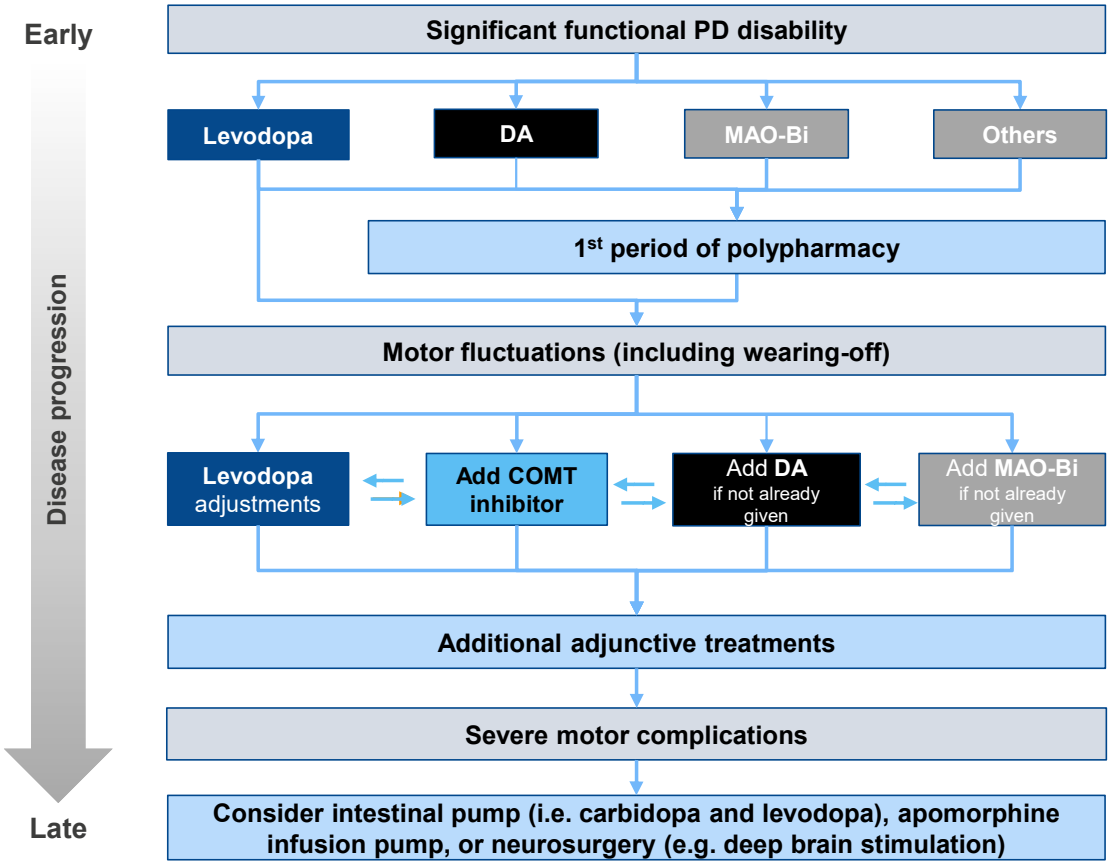


Figure based on information in published guidelines[1–4] and information from key opinion leaders and payer research conducted by roundtable sponsor

COMT, catechol-O-methyltransferase; CR, controlled release; DA, dopamine agonist; MAO-Bi, monoamine oxidase-B inhibitor; PD, Parkinson's disease.

1. Oertel WH, et al. Chapter 14: early (uncomplicated) Parkinson's disease. Chichester:Wiley-Blackwell, 2011; 217–236; 2. SIGN 113. 2010. Available at: https://www.parkinsons.org.uk/sites/default/files/2018-10/SIGN%20guideline%20Diagnosis%20and%20pharmacological%20management%20of%20Parkinson%27s.pdf (accessed Jan 2022); 3. National Institute for Health and Care Excellence. NG71. 2017; Available at: https://www.nice.org.uk/guidance/ng71/resources/parkinsons-disease-in-adults-pdf-1837629189061 (accessed Feb 2022); 4. Ferreira JJ, et al. *Eur J Neurol.* 2013;20:5–15.

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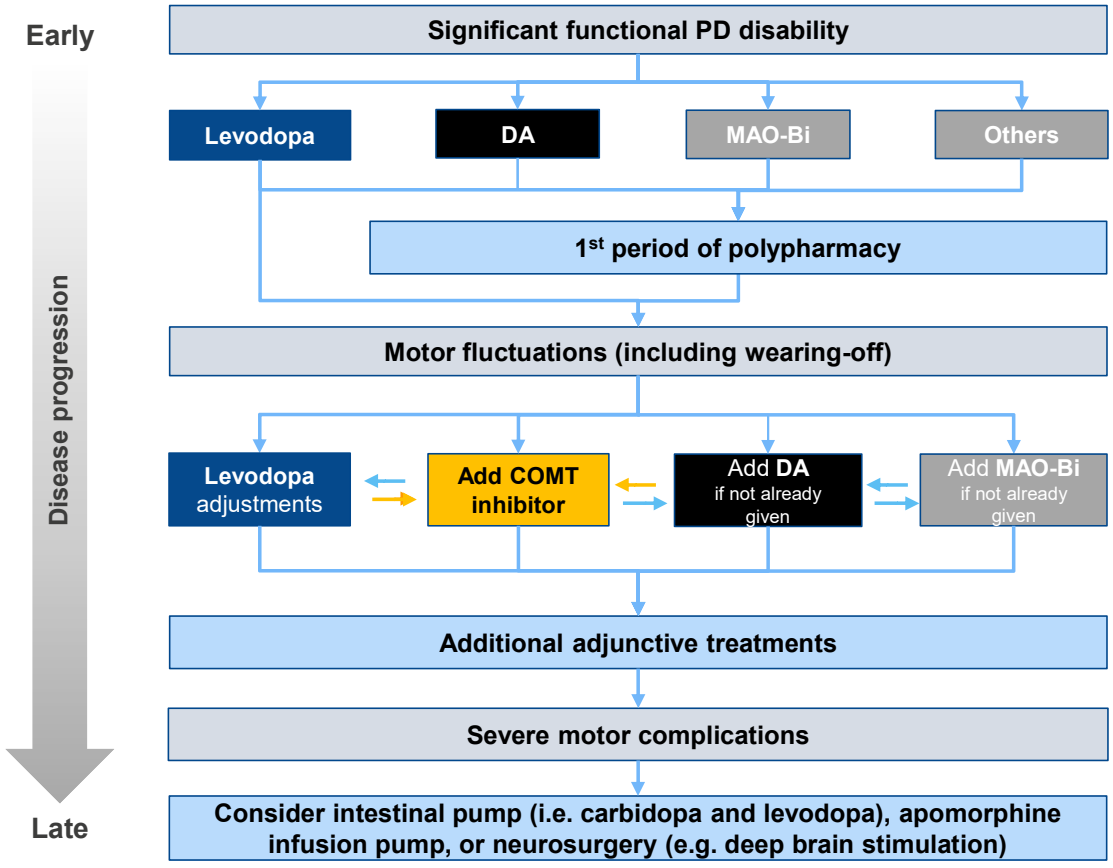
Parkinson's disease guidelines – current COMT inhibitor use



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1. Oertel WH, et al. Chapter 14: early (uncomplicated) Parkinson's disease. Chichester:Wiley-Blackwell, 2011; 217–236; 2. SIGN 113. 2010. Available at: https://www.parkinsons.org.uk/sites/default/files/2018-10/SIGN%20guideline%20Diagnosis%20and%20pharmacological%20management%20of%20Parkinson%27s.pdf (accessed Jan 2022); 3. National Institute for Health and Care Excellence. NG71. 2017; Available at: https://www.nice.org.uk/guidance/ng71/resources/parkinsons-disease-in-adults-pdf-1837629189061 (accessed Feb 2022); 4. Ferreira JJ, et al. *Eur J Neurol.* 2013;20:5–15.

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The biology of levodopa and the role of COMT inhibitors in levodopa pharmacokinetics

Prof. Peter Jenner

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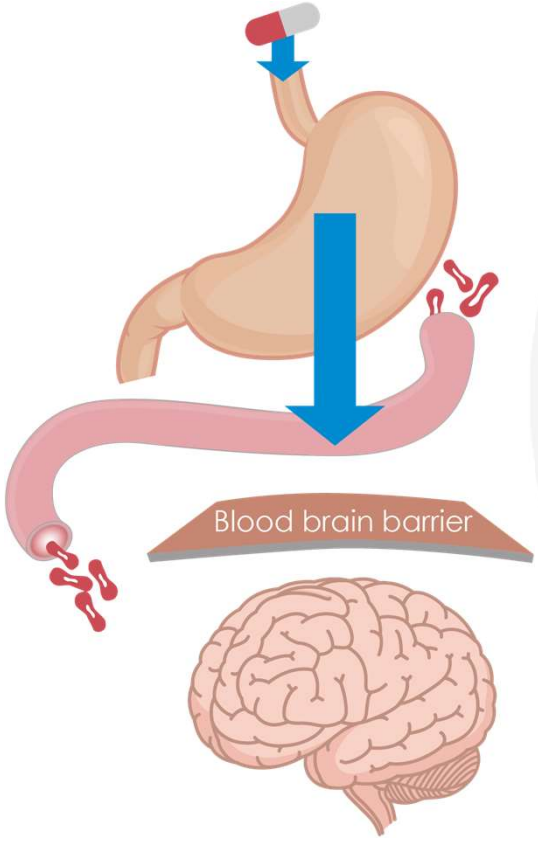
Challenges in delivering levodopa to the brain

- Absorption occurs only from the upper small intestine.
  - No absorption from lower sites.
  - Actively transported into blood stream.
  - Actively taken up into brain.
  - Amino acid competition occurs at the level of the blood-brain barrier.
- Short acting.
- Activity dependent on avoidance of peripheral metabolism and conversion to dopamine in brain.



Pinder RM, et al. *Drugs*.1976;11:329–377; Fahn S. *Mov Disord*. 2008;23:S497–S508; Fahn S, Poewe W. *Mov Disord*. 2015;30:1–3; Fahn S. *Mov Disord*. 2015;30:4–18; LeWitt P. *Mov Disord*. 2015;30:64–72; Kim HJ, et al. *Int J Neurobiol*. 2017;132:295–343.

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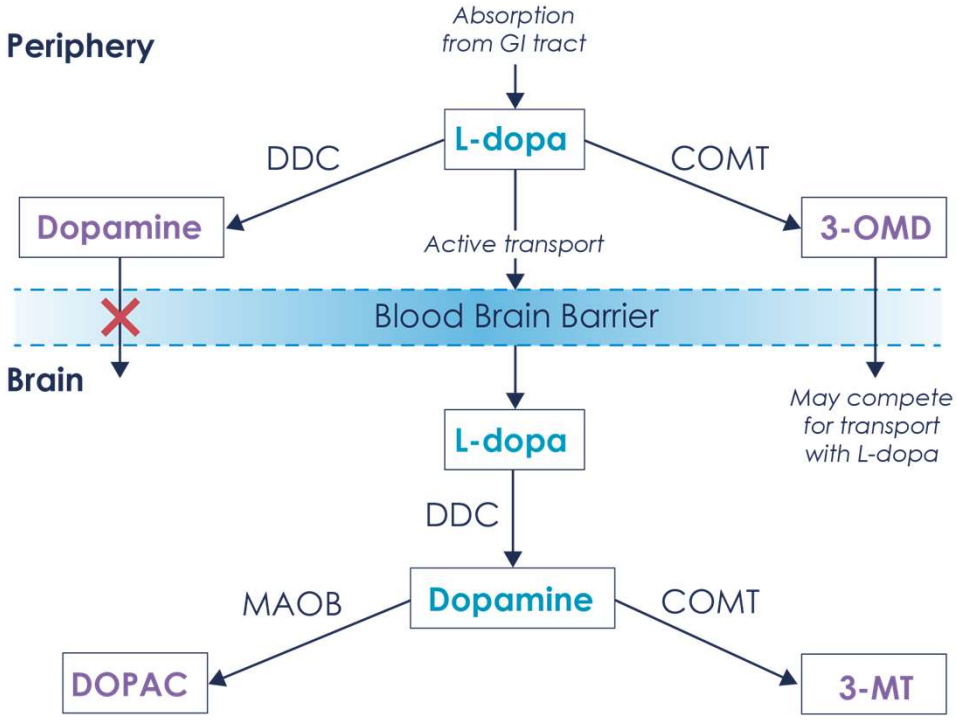
The journey of levodopa from the GI tract to brain



- Enzymatic activity in the periphery determines the amount of levodopa reaching the brain.
- Enzymatic conversion to dopamine in brain determines the extent of therapeutic effect.
- Enzymatic degradation of dopamine determines the duration of effect.
- **Enzyme inhibition is key to maximising the activity of levodopa.**

3-MT, 3-Methoxytyramine; 3-OMD, 3-O-Methyldopa; COMT, catechol-O-methyltransferase; DDC, dopa decarboxylase; DOPAC, 3,4-Dihydroxyphenylacetic acid; GI, gastrointestinal; L-dopa, levodopa; MAO-Bi, monoamine oxidase-B inhibitor;

Pinder RM, et al. *Drugs*.1976;11:329–377; Fahn S. *Mov Disord*. 2008;23:S497–S508; Fahn S, Poewe W. *Mov Disord*. 2015;30:1–3; Fahn S. *Mov Disord*. 2015;30:4–18; LeWitt P. *Mov Disord*. 2015;30:64–72; Kim HJ, et al. *Int J Neurobiol*. 2017;132:295–343. Lewitt PA, et al. *New Eng J Med*. 2008;359(23):2468–76; Gershanik OS, et al. *Mov Disord*. 2015;30:103–13.

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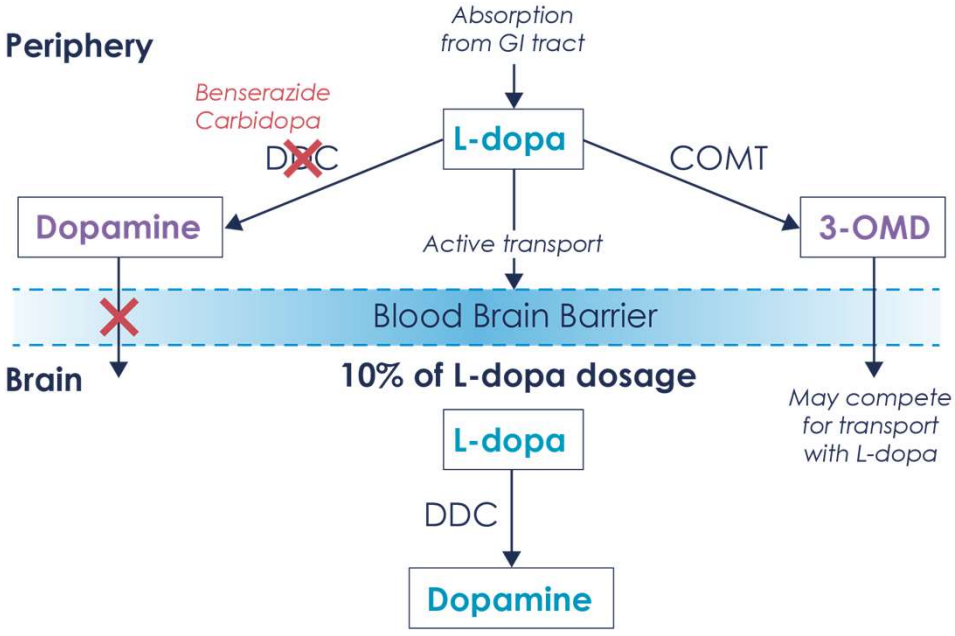
DDC-Is for Parkinson's disease



- Introduced into treatment more than 40 years ago.
- Selectively inhibit peripheral dopa decarboxylase activity.
- Only inhibit decarboxylation of exogenous levodopa.
- Act by scavenging pyridoxal phosphate.
- Reasonable oral bioavailability (50–75%).
- Plasma half-life 2–3h.
- Benserazide more potent than carbidopa.

3-MT, 3-Methoxytyramine; 3-OMD, 3-O-Methyldopa; COMT, catechol-O-methyltransferase; DDC, dopa decarboxylase; DDC-I, DDC inhibitor; DOPAC, 3,4-Dihydroxyphenylacetic acid; GI, gastrointestinal; L-dopa, levodopa; MAO-Bi, monoamine oxidase-B inhibitor;

Pinder, RM et al. *Drugs.* 1976;11:329–377; Fahn S. *Mov Disord.* 2008;23:S497–S508; Tayarani-Binazir KA. 2014 Available at: https://kclpure.kcl.ac.uk/portal/files/44453499/2014_Tayarani_Binazir_Kayhan_A_0104422_ethesis.pdf (accessed January 2022); Fahn S. *Mov Disord.* 2015;30:4–18; LeWitt P. *Mov Disord.* 2015;30:64–72; Kim HJ, et al. *Int J Neurobiol.* 2017;132:295–343; Lewitt PA, et al. *New Eng J Med.* 2008;359(23):2468–76; Gershanik OS, et al. *Mov Disord.* 2015;30:103–13.

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DDC-Is in daily use

- Revolutionised the treatment of Parkinson's disease.
- DDC-I used in fixed ratio to levodopa (1:4 and 1:10).
- Accepted clinical benefit at all stages of Parkinson's disease.

- Routinely used in combination with levodopa.
- Most commonly used adjunct treatment for Parkinson's disease.
- Marked reduction in daily levodopa dose.
- Increased delivery of levodopa to brain.
- Reduction in peripheral side-effects of levodopa (nausea, vomiting, gastrointestinal disturbance).
- Clinically equivalent effect of carbidopa and benserazide.

DDC, dopa decarboxylase.

Pinder, RM et al. *Drugs.* 1976;11:329–377; Fahn S. *Mov Disord.* 2008;23:S497–S508; Fahn S, Poewe W. *Mov Disord.* 2015;30:1–3; Fahn S. *Mov Disord.* 2015;30:4–18; LeWitt P. *Mov Disord.* 2015;30:64–72; Kim HJ, et al. *Int J Neurobiol.* 2017;132:295–343.

COMT inhibitors and Parkinson's disease

- Last of the enzyme inhibitors to be developed for Parkinson's disease.
- Essential component of the peripheral metabolism of levodopa.
- Difficult development due to toxicity with early candidates.
- Problems overcome by new chemical entities.

COMT, catechol-O-methyltransferase.

Enter the 'Capones'

Tolcapone

- Inhibits peripheral and central COMT activity.
- Long duration of action.
- 3 times daily dosing.
- Increased liver enzymes.

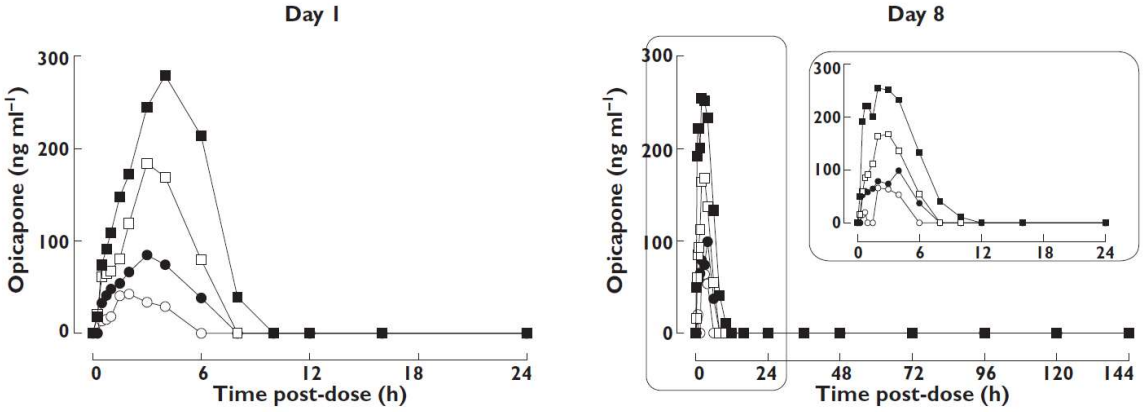
Entacapone

- Inhibits peripheral COMT activity.
- Short duration of effect.
- Up to 10 times daily dosing.
- No effect on liver enzymes.

COMT, catechol-O-methyltransferase.

Opicapone – a 3rd generation COMT inhibitor

- Long-acting COMT inhibitor.
- Short terminal plasma half-life.
- Exceptionally high binding affinity.
- Slow complex dissociation.
- Long duration of effect in vivo.



Rocha et al. 2013[1]

COMT, catechol-O-methyltransferase.

1. Rocha JF, et al. *Br J Clin Pharmacol*. 2013;76:763–7652; 2. Krauß J, Bracher F. *Sci Pharm*. 2018;86:E43.

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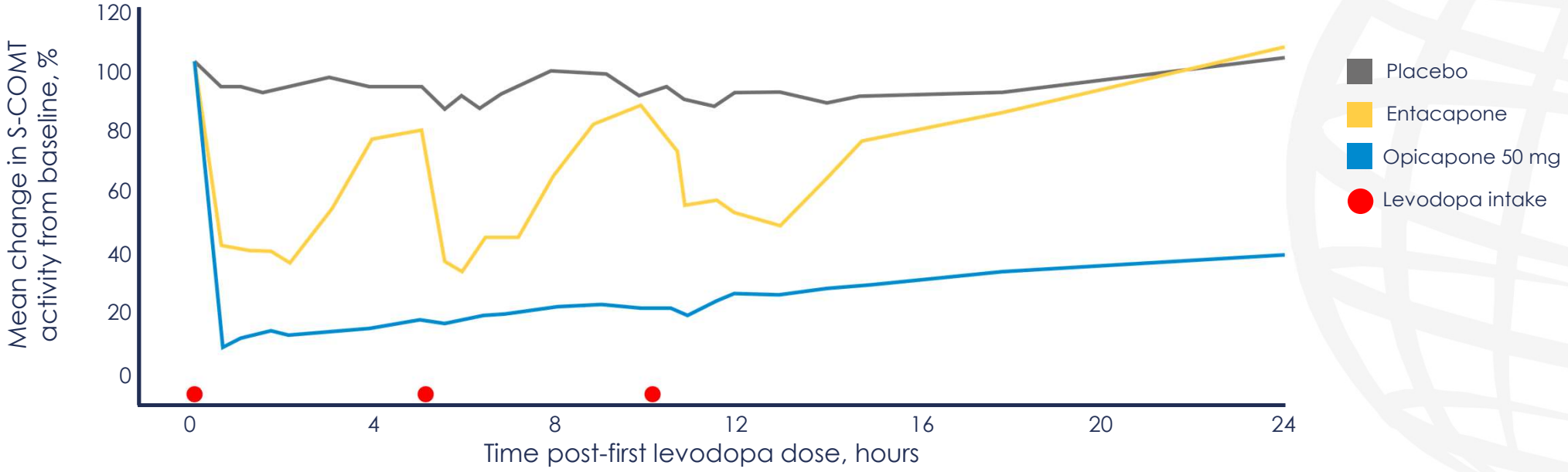
Comparison of COMT inhibition by opicapone and entacapone



COMT, catechol-O-methyltransferase.
Rocha J, et al. *Eur J Clin Pharmacol.* 2014;70:1059–1071.

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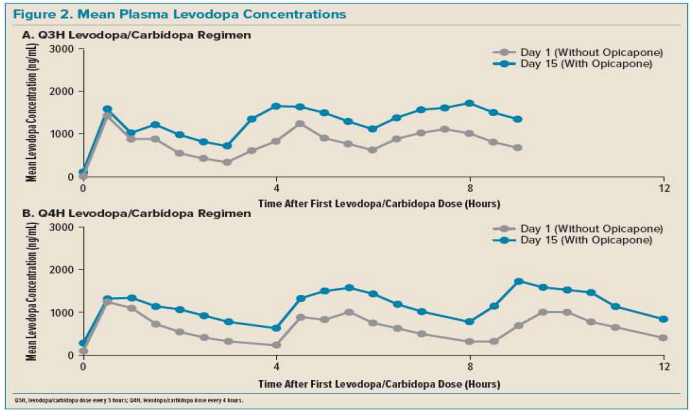
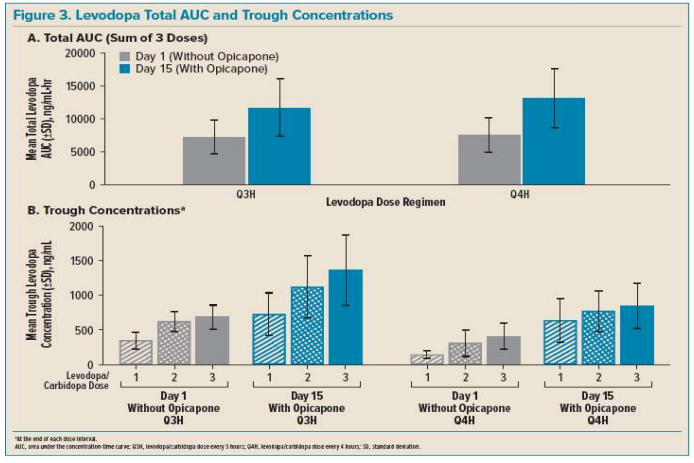
Opicapone reduces plasma levodopa fluctuations





- Once-daily opicapone resulted in substantial and prolonged S-COMT inhibition associated with increased overall systemic exposure to levodopa.
  - Opicapone increased the plasma AUC for levodopa.
  - Opicapone increased trough levodopa concentrations.
  - Opicapone increased trough levodopa concentrations and decreased peak-to-trough fluctuations.
  - Opicapone effects on levodopa concentrations may alleviate fluctuations associated with 'OFF' episodes.

AUC, area under the curve; COMT, catechol-O-methyltransferase.

Loewen G, et al. *Mov Disord.* 2019;34:Suppl.S2:A143; Loewen G, et al. Available at: https://www.neurocrinemedical.com/wp-content/uploads/2019/06/OPC_1706_PK_2019-PSG-Poster.pdf (accessed January 2022).

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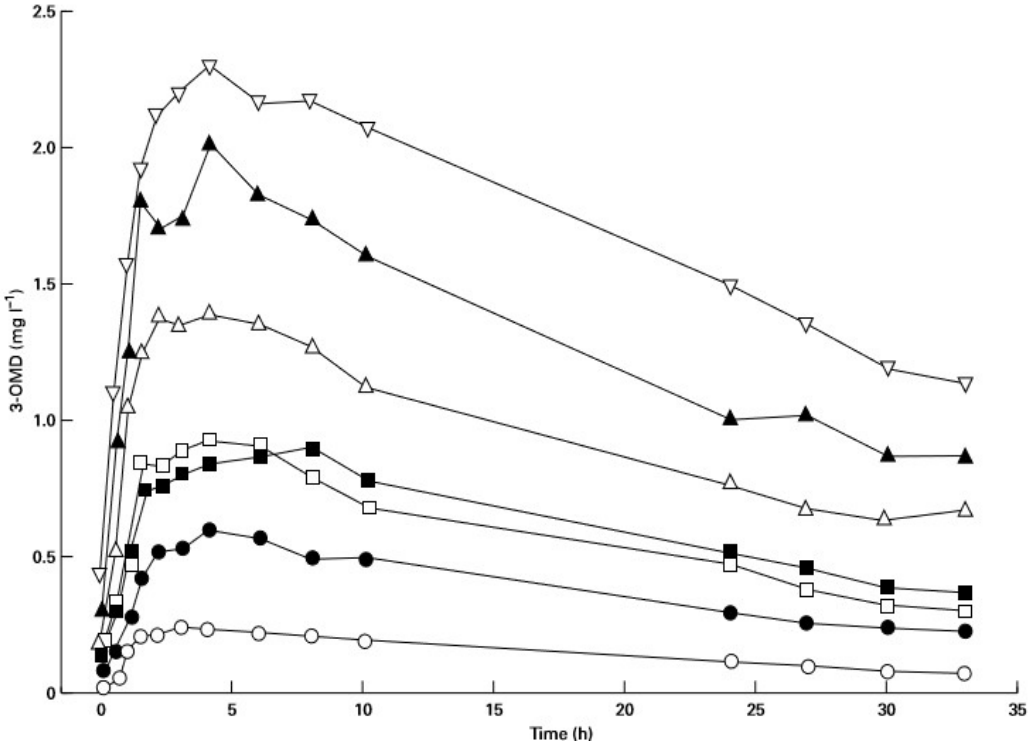
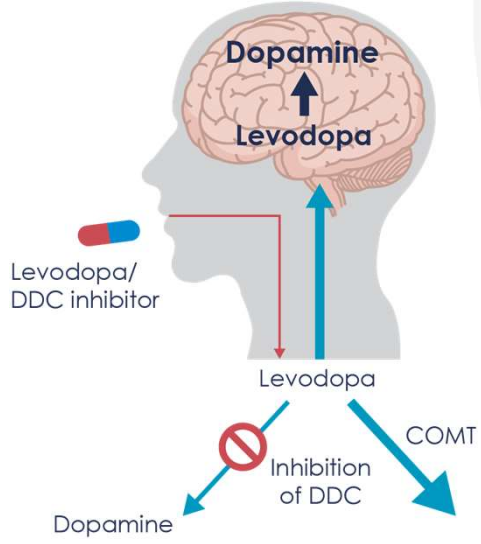
Peripheral DDC inhibition increases 3-OMD levels



- Inhibiting peripheral decarboxylase activity diverts levodopa in to the COMT pathway and elevates plasma levels of 3-OMD.
- Inhibiting both pathways maximises levodopa availability to brain.



3-OMD, 3-O-Methyldopa; COMT, catechol-O-methyltransferase; DDC, dopa decarboxylase.
Dingemanse J, et al. *Br J Clin Pharmacol*. 1997;44(1):41-8; Schapira AVH. Maryland Heights;Mosby. 2007:927–960.

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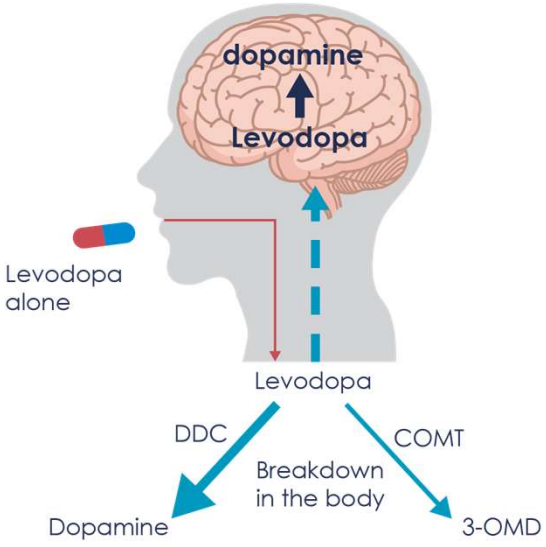
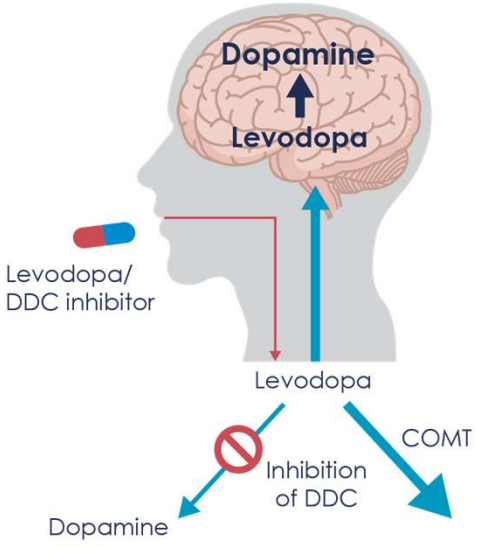
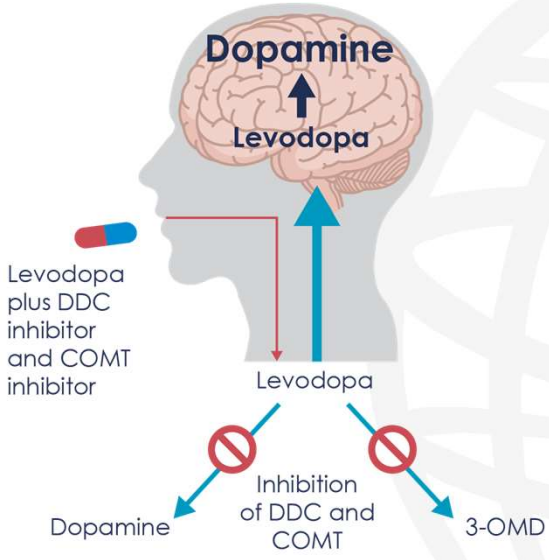
Effect of DDC and COMT inhibition







30–50% reduction in plasma variability with dual inhibition

COMT, catechol-O-methyltransferase; DDC, dopa decarboxylase.
Schapira AVH. Maryland Heights;Mosby. 2007:927–960.

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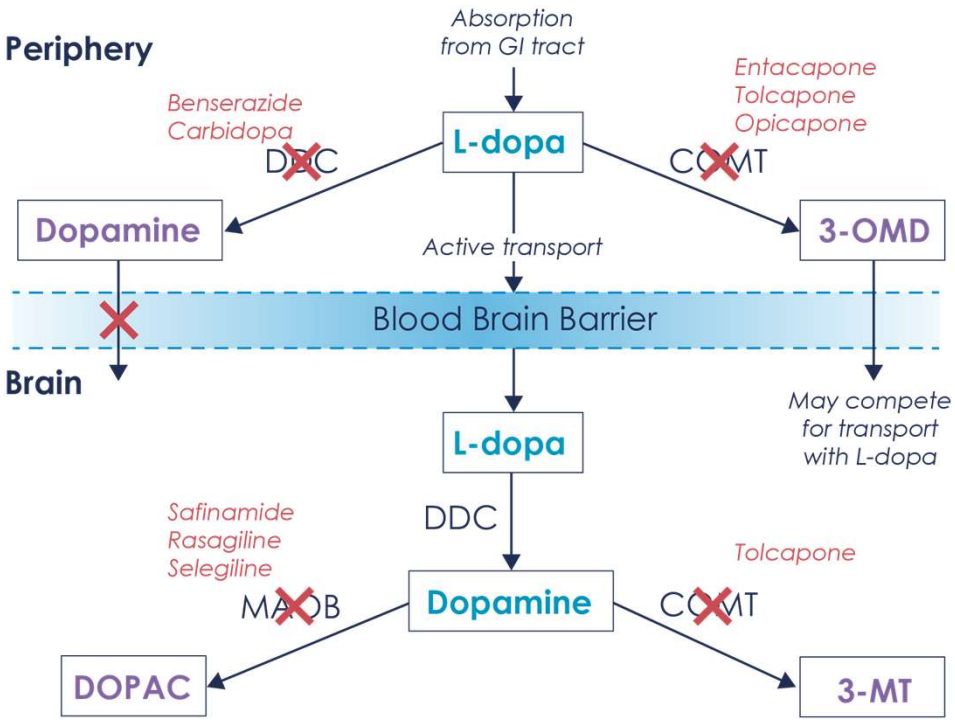
Using enzyme inhibitors in Parkinson's disease



- The plasma pharmacokinetic profile of levodopa does not change in Parkinson's disease.
- Peripheral decarboxylase inhibitors are used whenever levodopa therapy is introduced – early or late.
- COMT inhibitors are used later in the disease to overcome end of dose deterioration.
- Both improve the plasma profile levodopa and extend its duration of effect when treating 'wearing OFF'.

3-MT, 3-Methoxytyramine; 3-OMD, 3-O-Methyldopa; COMT, catechol-O-methyltransferase; DDC, dopa decarboxylase; DOPAC, 3,4-Dihydroxyphenylacetic acid; GI, gastrointestinal; L-dopa, levodopa; MAO-Bi, monoamine oxidase-B inhibitor.

1. Lewitt PA, et al. *New Eng J Med*. 2008;359(23):2468–76; 2. Gershanik OS, et al. *Mov Disord*. 2015;30:103–13; Kiss L, et al. *J Med Chem*. 2010;53:3396–3411.

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Conclusions

- Enzyme inhibitors are valuable adjuncts to treating ‘wearing OFF’ to levodopa in Parkinson’s disease.
- Peripheral DDC-I have become an essential component of levodopa treatment and are always used in combination.
- Nobody would employ levodopa without including a DDC-I.
- COMT inhibitors markedly increase the delivery of levodopa to brain but are usually used late in the treatment paradigm.
- What makes sense is to maximise the efficacy of levodopa and reduce fluctuations in plasma and brain levels of levodopa by employing both enzyme inhibitor classes in combination.
- Opicapone provides an effective choice for treating ‘wearing OFF’ through COMT inhibition.

COMT, catechol-O-methyltransferase; DDC-I, dopa decarboxylase inhibitor.

1. Lewitt PA, et al. New Eng J Med. 2008;359(23):2468–76; 2. Gershanik OS, et al. *Mov Disord*. 2015;30:103–13; Kiss L, et al. *J Med Chem*. 2010;53:3396–3411.

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Differentiating COMT inhibitors and the clinical development of opicapone for fluctuating Parkinson's disease

Prof. Joaquim Ferreira

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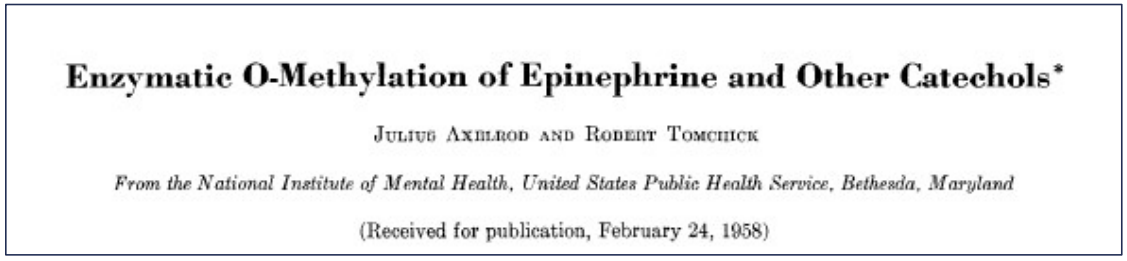
Discovery of COMT



Enzymatic O-Methylation of Epinephrine and Other Catechols*

JULIUS AXELROD AND ROBERT TOMCHICK

From the National Institute of Mental Health, United States Public Health Service, Bethesda, Maryland

(Received for publication, February 24, 1958)

Axelrod J, Tomchick, R. J Biol Chem 1958;223:702–5

- **Late 1980s: second-generation COMT inhibitors**
  - Entacapone and tolcapone marketed for the treatment of Parkinson's disease.

- **Late 1980s: second-generation COMT inhibitors**
  - Entacapone and tolcapone marketed for the treatment of Parkinson's disease.

COMT, catechol-O-methyltransferase; CR, controlled release; DA, dopamine agonist; MAO-Bi, monoamine oxidase-B inhibitor; PD, Parkinson's disease.
Bonifacio MJ, et al. *CNS Drug Reviews.* 2007;13:352–379.

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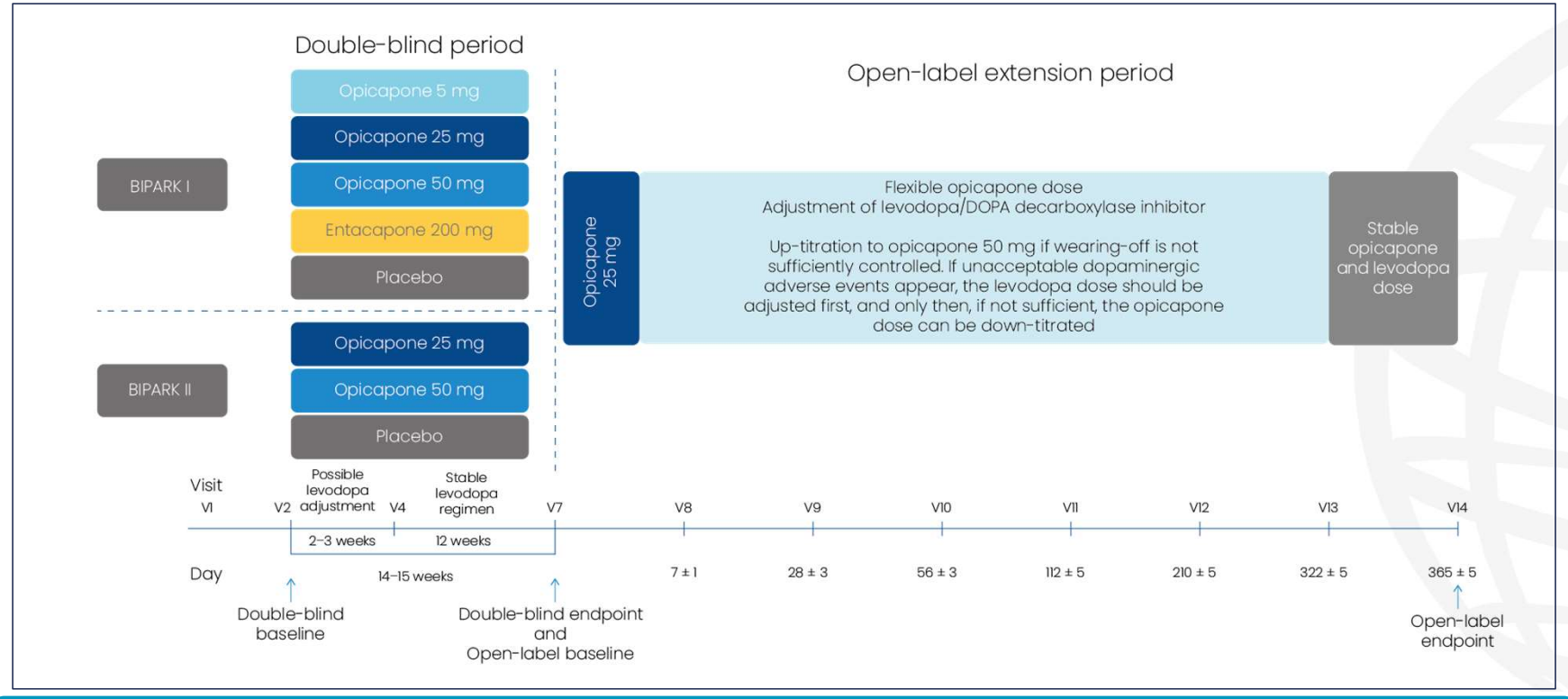
Phase III trials: BIPARK-I and BIPARK-II

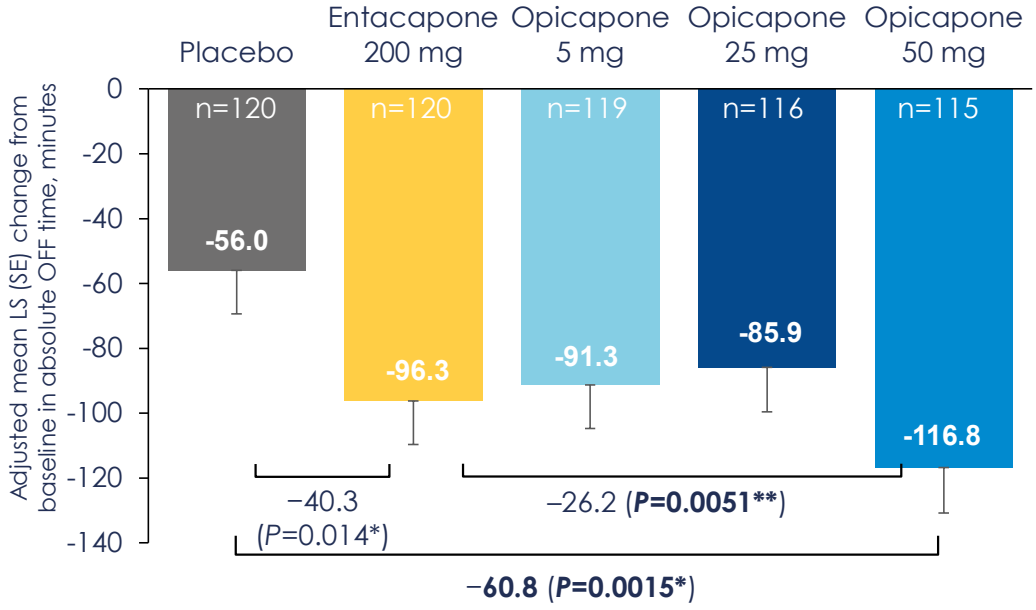


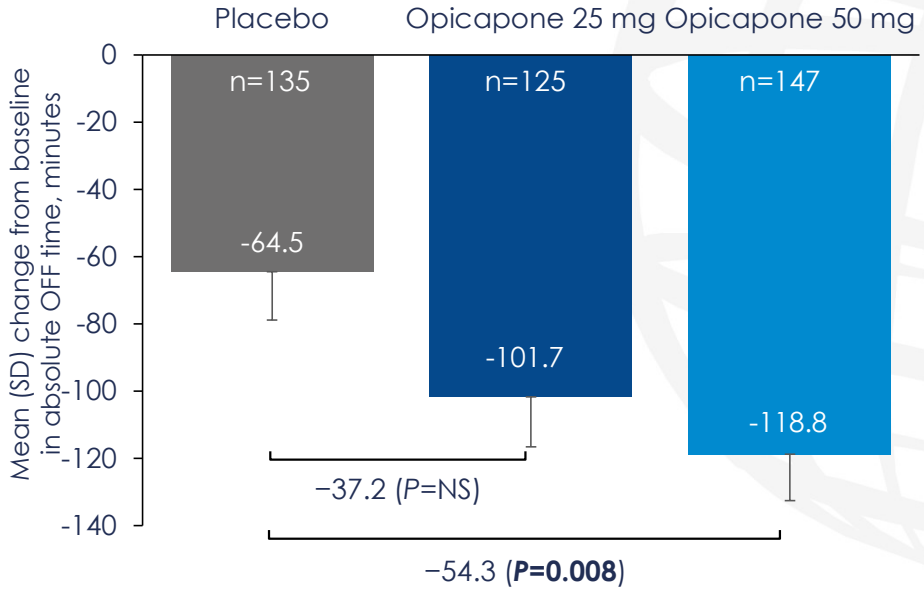
Primary endpoint: Change from baseline in absolute OFF-time to endpoint, assessed using patient 24-h paper diaries.[1,2]

COMT, catechol-O-methyltransferase.

1. Ferreira JJ, et al. *Lancet Neurol.* 2016;15(2):154–65. 2. Lees AJ, et al. *JAMA Neurol.* 2017;74(2):197–206; 3. Ferreira JJ, et al. *Neurology.* 2018;90(21):e1849–57.

Opicapone was associated with a significantly greater reduction from baseline in OFF-time than placebo in BIPARK-I and BIPARK-II (primary endpoint)





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

1. Ferreira JJ, et al. *Lancet Neurol.* 2016;15(2):154–65. 2. Lees AJ, et al. JAMA *Neurol.* 2017;74(2):197–206.

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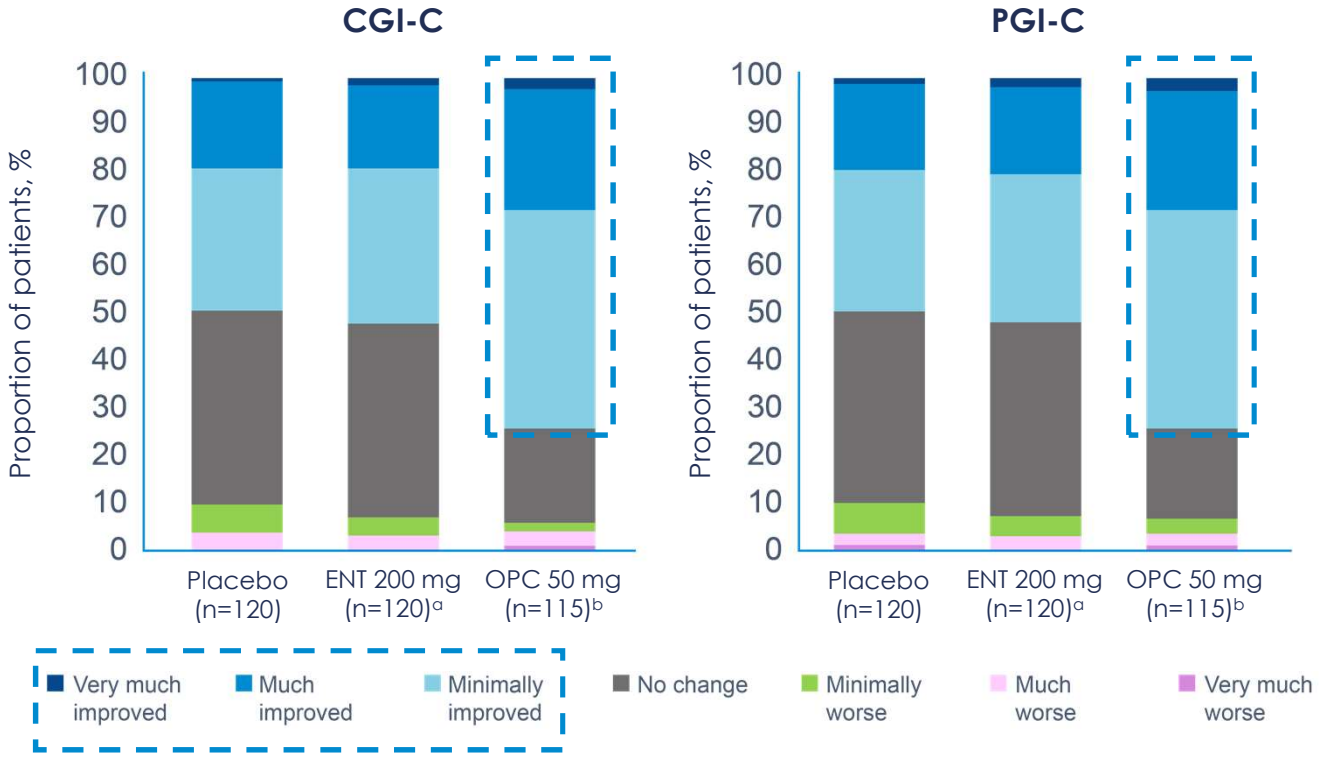
BIPARK-I: CGI-C and PGI-C for opicapone versus placebo and entacapone



- Significantly more patients in the opicapone 50 mg group improved on the CGI-C[c,d] and PGI-C[e,f] vs entacapone and placebo[g].
- No significant differences in CGI-C[h] or PGI-C[i] for entacapone vs placebo.

[a]Data were missing or were not assessed for three patients; [b]Data were missing or were not assessed for two patients; [c]P=0.0070 vs entacapone; [d]P=0.00051 vs placebo; [e]P=0.0091 vs entacapone; [f]P=0.0008 vs placebo; [g]Analyses conducted in the full analysis set. P values are for comparisons between improved scores and worsened scores only (excluding no-change scores); [h]P=0.61; [i]P=0.47.
CGI-C, Clinician's Global Impression of Change; ENT, entacapone; OPC, opicapone; PGI-C, Patient's Global Impression of Change.
1. Ferreira JJ, et al. *Lancet Neurol.* 2016;15(2):154–65. 2. Lees AJ, et al. *JAMA Neurol.* 2017;74(2):197–206.

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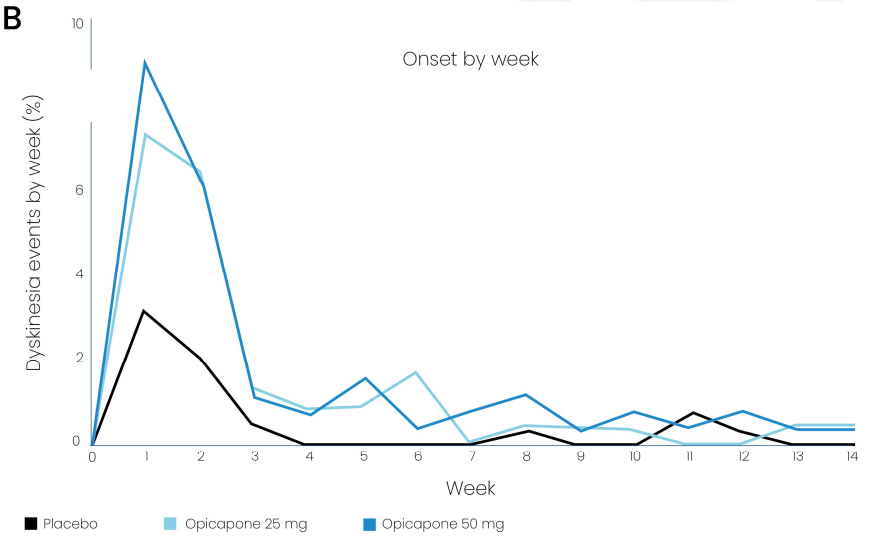
BIPARK-I and BIPARK-II: Safety

Pooled analysis (double-blind phase) of TEAS with ≥2% difference in any opicapone group versus placebo

Preferred term Decreasing frequency[3]	Placebo		Opicapone 25 mg		Opicapone 50 mg		Total Opicapone	
	n (%)	Severe n (%)	n (%)	Severe n (%)	n (%)	Severe n (%)	n (%)	Severe n (%)
Dyskinesia	16 (6.2)	2 (0.8)	39 (16.0)	3 (1.2)	54 (20.4)	3 (1.1)	93 (18.3)	6 (1.2)
Constipation	5 (1.9)	0	12 (4.9)	0	17 (6.4)	0	29 (5.7)	0
Insomnia	4 (1.6)	1 (0.4)	17 (7.0)	1 (0.4)	9 (3.4)	1 (0.4)	26 (5.1)	2 (0.4)
Dry mouth	3 (1.2)	1 (0.4)	16 (6.0)	1 (0.4)	8 (3.0)	0	24 (4.7)	1 (0.2)
Blood CPK increased	5 (1.9)	1 (0.4)	7 (2.9)	0	13 (4.9)	1 (0.4)	20 (3.9)	1 (0.2)
Dizziness	3 (1.2)	1 (0.4)	10 (4.1)	1 (0.4)	9 (3.4)	0	19 (3.7)	1 (0.2)
Somnolence	5 (1.9)	0	10 (4.1)	0	5 (1.9)	0	15 (2.9)	0
Urinary tract infection	2 (0.8)	0	4 (1.6)	0	10 (3.8)	0	14 (2.8)	0
Weight decreased	0	0	1 (0.4)	0	10 (3.8)	1 (0.4)	11 (2.2)	1 (0.2)
Hallucination	1 (0.4)	0	6 (2.5)	0	3 (1.1)	0	9 (1.8)	0



Adapted from Lees, *et al*[3].

CPK, creatinine phosphokinase; TRAE, treatment-emergent adverse events.

1. Ferreira JJ, et al. *Lancet Neurol.* 2016;15(2):154–65. 2. Lees AJ, et al. *JAMA Neurol.* 2017;74(2):197–206; 3. Ferreira JJ, et al. *Neurology.* 2018;90(21):e1849–57.

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BIPARK-I and BIPARK-II pooled safety analysis

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

Incidences of TEAEs, serious TEAEs, deaths, and TEAEs leading to discontinuation were similar across the opicapone and placebo groups

[a]Safety set. Potentially related: drug-event relationship reported as 'possible', 'probable', 'definite' by the investigator, or missing.
TEAE, treatment-emergent adverse events.
Lees A, et al. *J Parkinsons Dis*. 2019;9(4):733-740.

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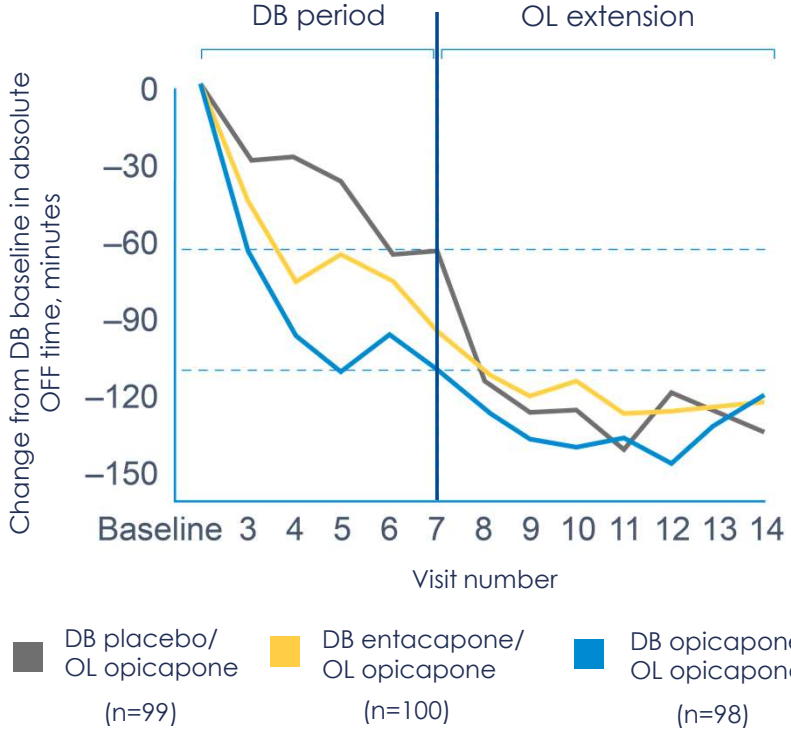
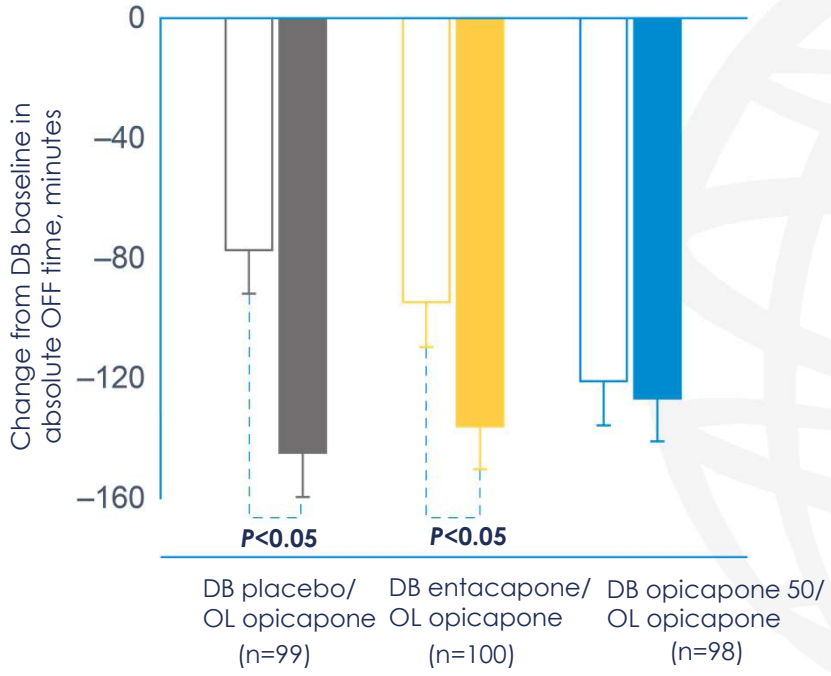
BIPARK-I OL extension: change in OFF time in patients switched from placebo or entacapone to opicapone





Patients switching from entacapone to opicapone had a LS mean improvement from baseline of -39.3 minutes in OFF time[a]

[a]Change in absolute OFF time from open-label baseline to Visit 14.
DB, double-blind; LS, least squares; OL, open-label.
Ferreira JJ, et al. *Neurology*. 2018;90(21):e1849–57.

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Opicapone versus entacapone

Summary of main differentiators

Once-daily administration.[1–3]

Higher inhibition of COMT activity and enhanced levodopa bioavailability.[3–5]

Greater clinician and patient **impression of improvement**.[6]

- Opicapone 50 mg versus entacapone in BIPARK-I double-blind phase: *P*=0.007 in PGI-C and *P*=0.0091 in CGI-C.

Significant **improvement** in **ON- and OFF-time** in entacapone-to-opicapone **switchers**.[7–9]

- Significant increases in **ON-time without dyskinesia** (45.7 min; *P*=0.015).
- Significant reductions in **OFF-time** (−39.3 min; *P*=0.006), even in **entacapone non-responders**[a] (−45.3 min; *P*=0.0399).
- Significant improvement in the UPDRS III score (−2.3; *P*=0.0016).

Opicapone does not cause **diarrhea**.[1,2]

Opicapone causes **less urine discoloration** than entacapone.[1,2,4,10]

[a]Non-responders according to PGI-C.

CGI-C, Clinician's Global Impression of Change; COMT, catechol-O-methyltransferase; PGI-C, Patient's Global Impression of Change; UPDRS, Unified Parkinson's Disease Rating Scale.

1. EMA. Ongentys summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/ongentys-epar-product-information_en.pdf. (Accessed July 2020); 2. European Medicines Agency. Comtan Summary of product characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/comtan-epar-product-information_en.pdf (Accessed July 2020); 3. Rocha JF, et al. *Br J Clin Pharmacol.* 2013;76;763–75; 4. Almeida L, et al. *Clin Pharmacokinet.* 2013;52(2):139–51; 5. Rocha JF, et al. *Eur J Clin Pharmacol.* 2014;70:1059–71; 6. Ferreira JJ, et al. *Lancet Neurol.* 2016;15(2):154–65; 7. Ferreira JJ, et al. *Neurology.* 2018;90(21):e1849–57; 8. Ferreira J, et al. *Eur J Neurol.* 2019;26(Suppl 1):112–346 (abstract EPR2061); 9. Ehret R, et al. *Mov Disord.* 2018;33(Suppl 2):S1-S929(abstract 232); 10. Ferreira JJ, et al. *Eur J Neurol.* 2015;22:815–25.

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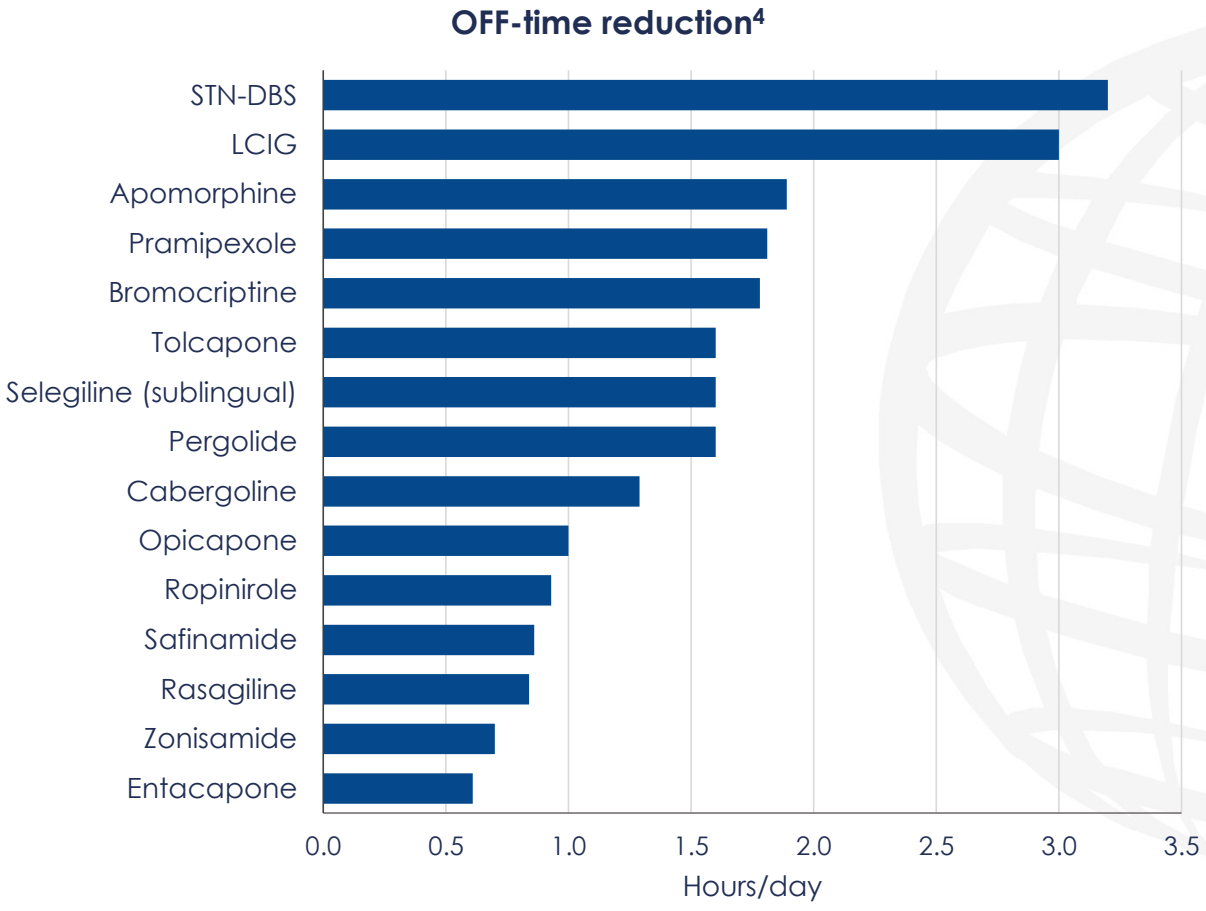
OFF-time reductions

- Average treatment effect at reducing OFF-time over placebo:
  - Opicapone: -60 minutes.[1,2]
  - Entacapone: -40 minutes.[3]
  - Tolcapone 100 mg: -90 minutes.[3]



LCIG, levodopa-carbidopa intestinal gel; STN-DBS, subthalamic nucleus deep brain stimulation

1. Fabbri M, et al. Mov Disord. 2018;33:1528–39; 2. Ferreira J, et al. *Lancet Neurol.* 2016;15 154–65; 3. Deane KH, et al. *Cochrane Database Syst Rev.* 2004;(4):CD004554; 4. Fabbri M, et al. *Drugs Aging.* 2018;35:1041–54.

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COMT inhibitor practical issues

Tolcapone[1]

100 mg
three-times daily

Entacapone[2]

200 mg
with each levodopa/DDC-I dose[a]

Opicapone[3]

50 mg
once-daily
at bedtime[b]

[a]Max 10 per day (EU); [b]At least 1 hour before or after levodopa combinations.
COMT, catechol-O-methyltransferase; DDC-I, dopa-decarboxylase inhibitor.
1. EMA. Tasmar Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/tasmar-epar-product-information_mt.pdf (Accessed January 2022); 2. EMA. Comtess Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/comtess-epar-product-information_en.pdf (Accessed January 2022); 3. EMA. Ongentys Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/ongentys-epar-product-information_en.pdf (Accessed January 2022).

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The role of opicapone in the treatment of early motor fluctuations

Panel discussion

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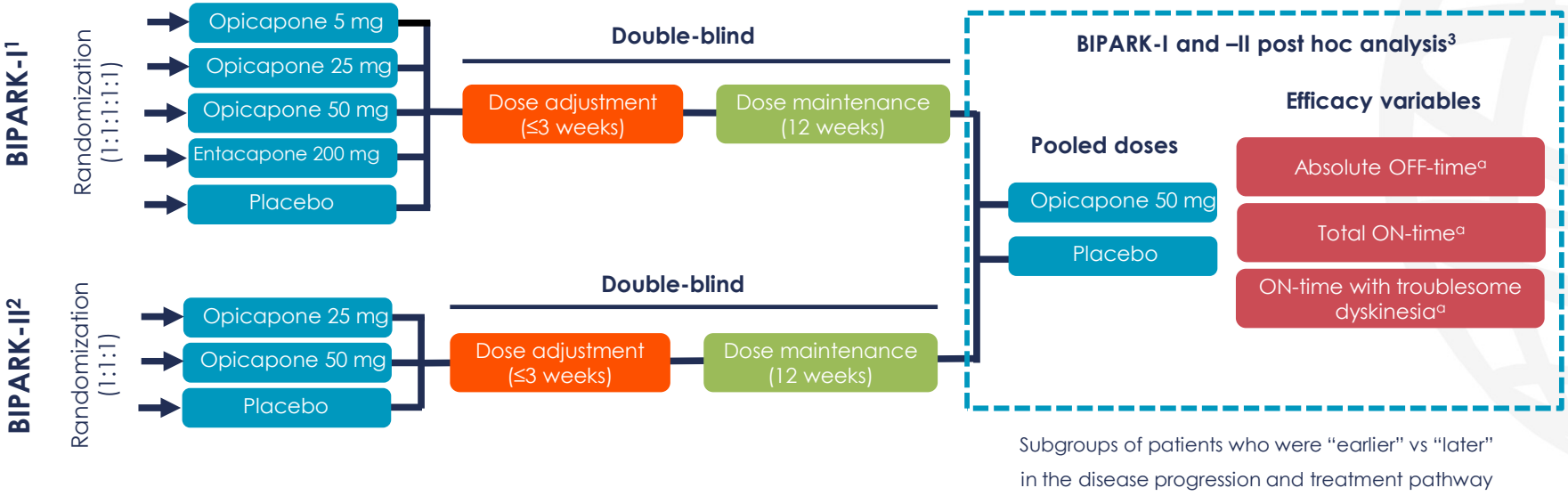
Early use in patients with MF: A post-hoc analysis of BIPARK-I and -II

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



Subgroups of patients who were "earlier" vs "later" in the disease progression and 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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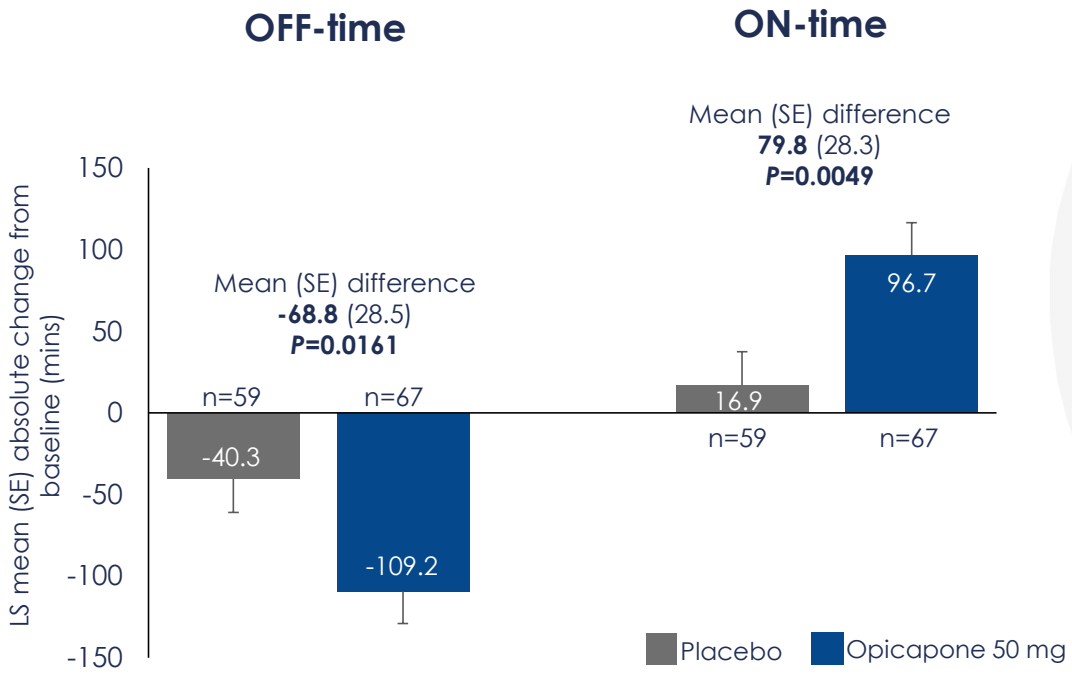
Efficacy of opicapone in patients with treated with levodopa/DDC-I alone[a] (BIPARK-I/II post-hoc analysis)

Opicapone was efficacious as a **first-line adjunctive therapy** in levodopa-treated patients with Parkinson's disease and end-of-dose motor fluctuations



[a]without dopamine agonists or monoamine oxidase-B inhibitors.
DDC-I, dopa-decarboxylase inhibitor; LS, least squares; mins, minutes; SE, standard error; TEAE, treatment-emergent adverse event.
Ferreira J, et al. *Mov Disord*. 2020;35(suppl 1):S1-S70(abstract 999).

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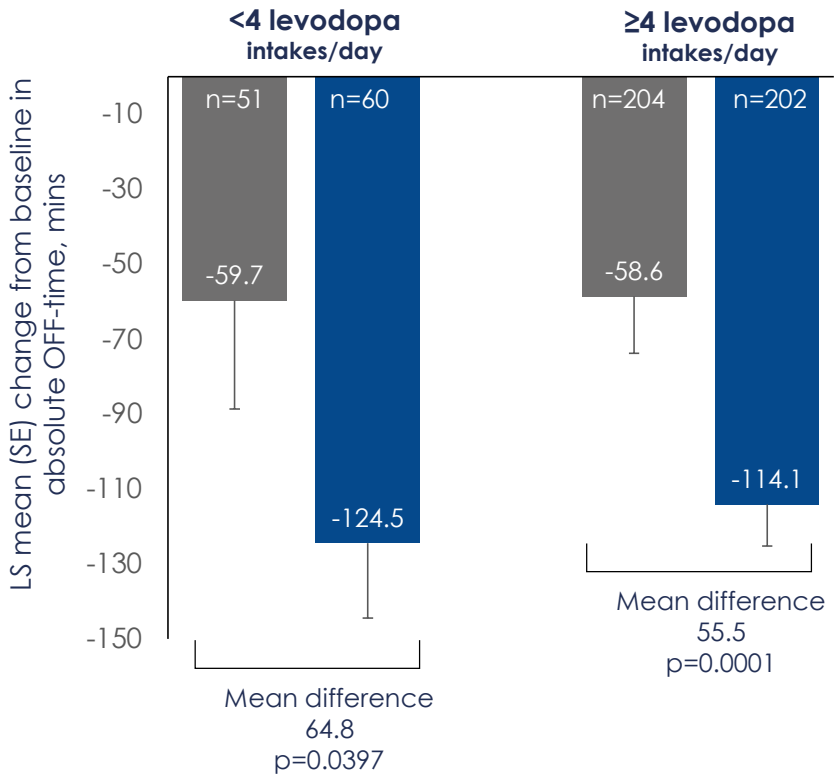
Efficacy of opicapone in patients with <4 levodopa intakes (BIPARK-I/II post-hoc analysis)

There was a trend towards a lower incidence of dopaminergic-related TEAEs in patients who were less advanced in their disease course (as measured by number of levodopa intakes)[2]



SE, standard error.

1. LeWitt P, et al. *Ann Neurol.* 2020;88(suppl 25):S1-S280(abstract 490); 2. Ebersbach G, et al. *Mov Disord.* 2021;36(suppl 1):S1-S599(abstract 380).

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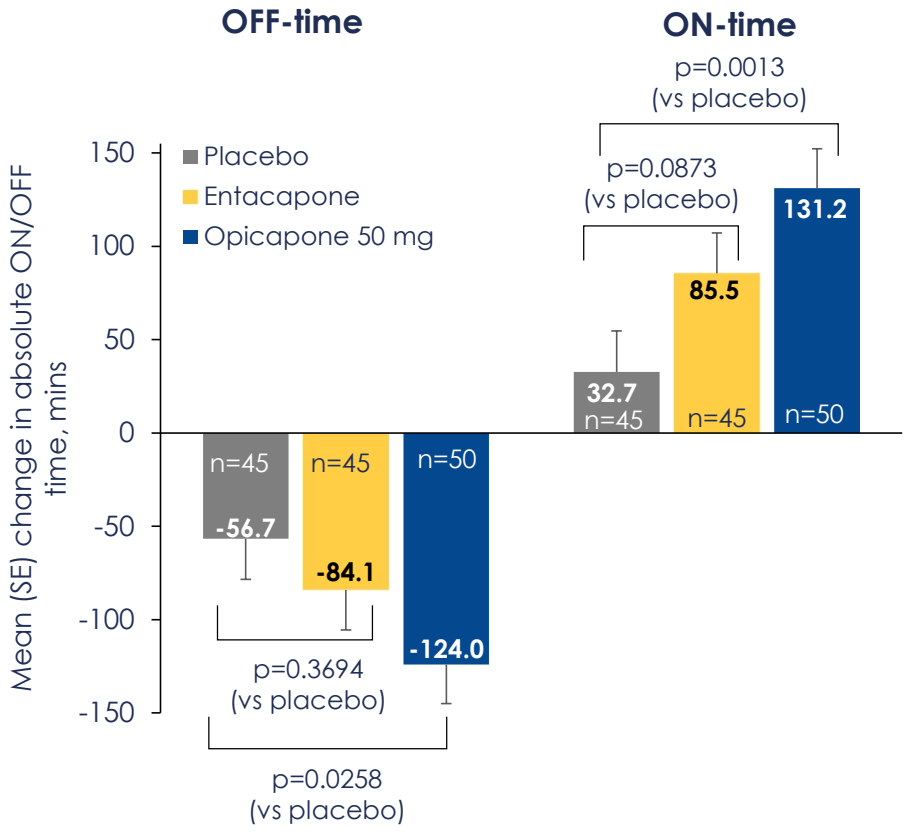
Efficacy of opicapone in patients ≤1-year duration of motor fluctuations (BIPARK-I post-hoc analysis)[a]

Opicapone demonstrated overall added benefit as a first adjunctive COMT inhibitor, in comparison with placebo and entacapone in levodopa-treated patients with <1 years of motor fluctuations



SE, standard error.
COMT, catechol-O-methyltransferase; SD, standard deviation; SE, standard error.
Lees A, et al. *Mov Disord.* 2020;35(suppl 1):S1-S70(abstract 1028).

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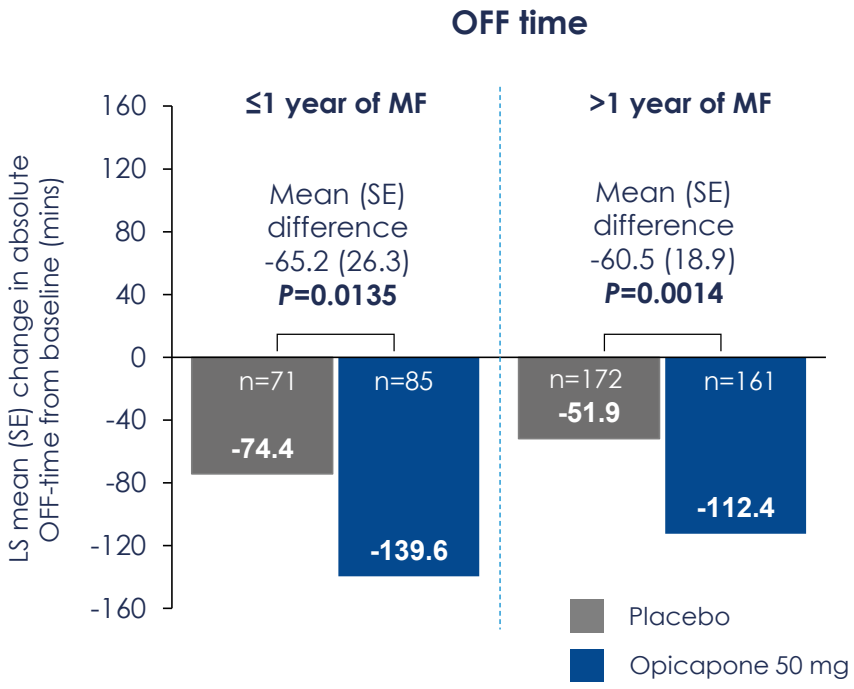
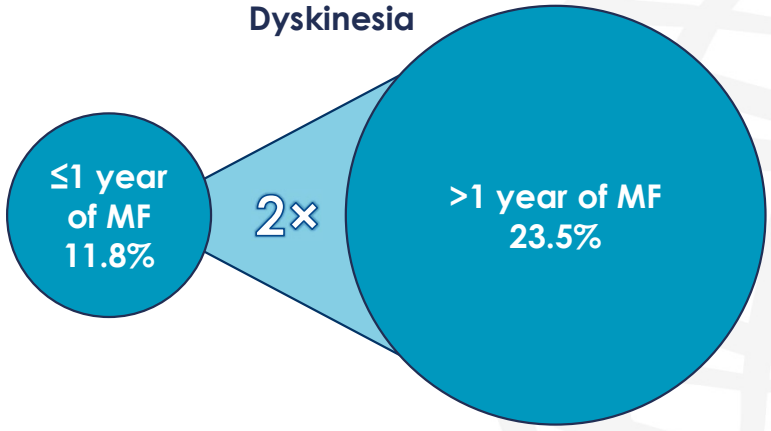
Efficacy opicapone in patients with ≤1 year of motor fluctuations (BIPARK-I/II post-hoc analysis)





Changes in absolute OFF time were significantly greater for opicapone versus placebo in both patients with ≤1 vs >1 year duration of motor fluctuation

Lower incidence of dyskinesia opicapone in patients with ≤1 vs >1 year of motor fluctuations

LS, least squares; SE, standard error; MF, motor fluctuations; SD, standard deviation.
Ebersbach G, et al. *Mov Disord.* 2020;35(suppl 1)S444(abstract 993) and presented poster.

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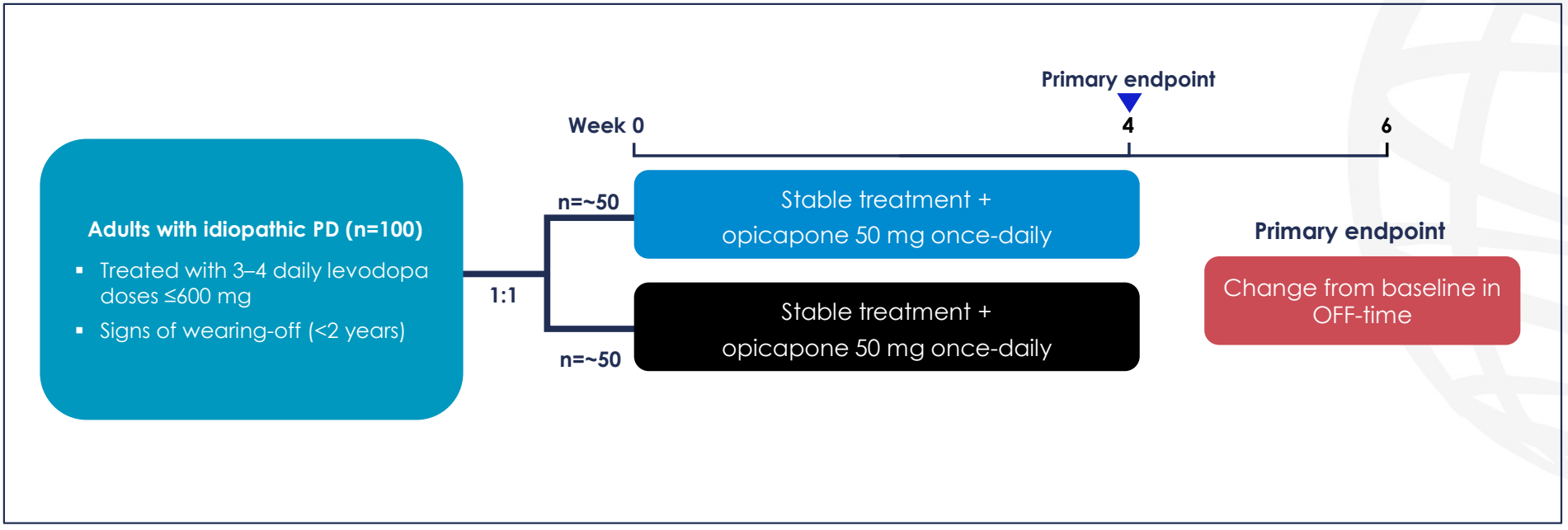
Discussion questions part 1

Q1 What is your usual approach to treat recently diagnosed fluctuations?

Q2 Will these data change the traditional positioning of COMT inhibitors in the treatment pathway? Would you need additional data to support an earlier use?

Opicapone as early add-on to levodopa/DDC-I in patients with motor fluctuations: the ADOPTION trial

Phase IV, parallel, randomised, open-label exploratory trial



ADOPTION: eArly levoDopa with Opicapone in Parkinson's paTients wIth motOr fluctuatioNs; CGI-C, Clinician Global Impression of Change; DDC-I, dopa-decarboxylase; MDS-NMS, Movement Disorder Society Non-Motor Rating Scale; PD, Parkinson's disease; PDQ-8, Parkinson's disease Questionnaire-8; PGI-C, Patient Global Impression of Change; UPDRS, Unified Parkinson's Disease Rating Scale.

Ferreira J, et al. *Eur J Neurol*. 2021;28(Suppl 1):753–921(EPO-444).

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Discussion questions part 2

Q3 If positive results derive from this study, would this change the traditional positioning of COMT inhibitors in the treatment pathway and support the use of opicapone as primary option to treat motor fluctuations?

The role of opicapone in the treatment of non-motor symptoms

Panel discussion

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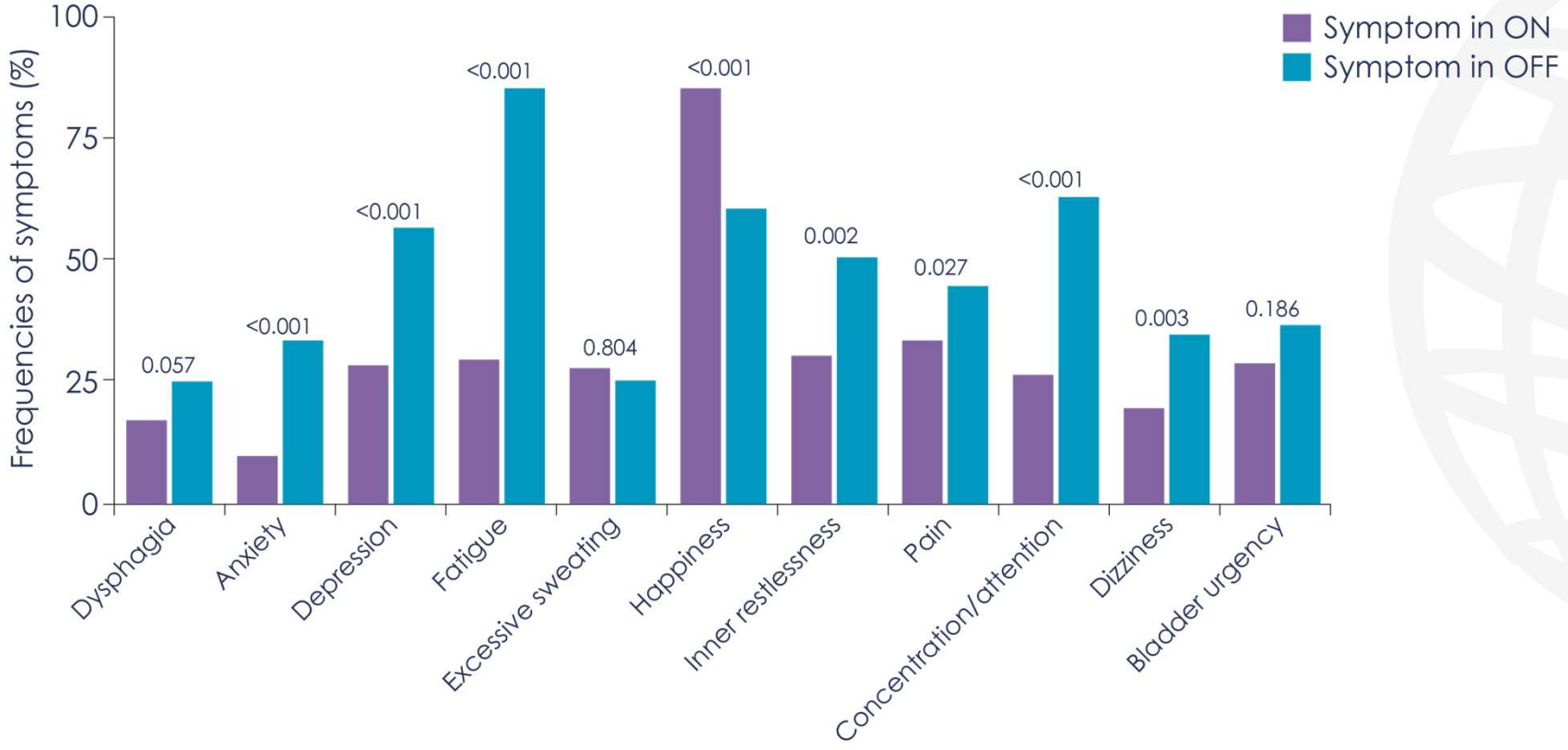
Frequency of non-motor fluctuations in patients with Parkinson's disease



Storch A, et al. *Neurology*. 2013;80:800–9.

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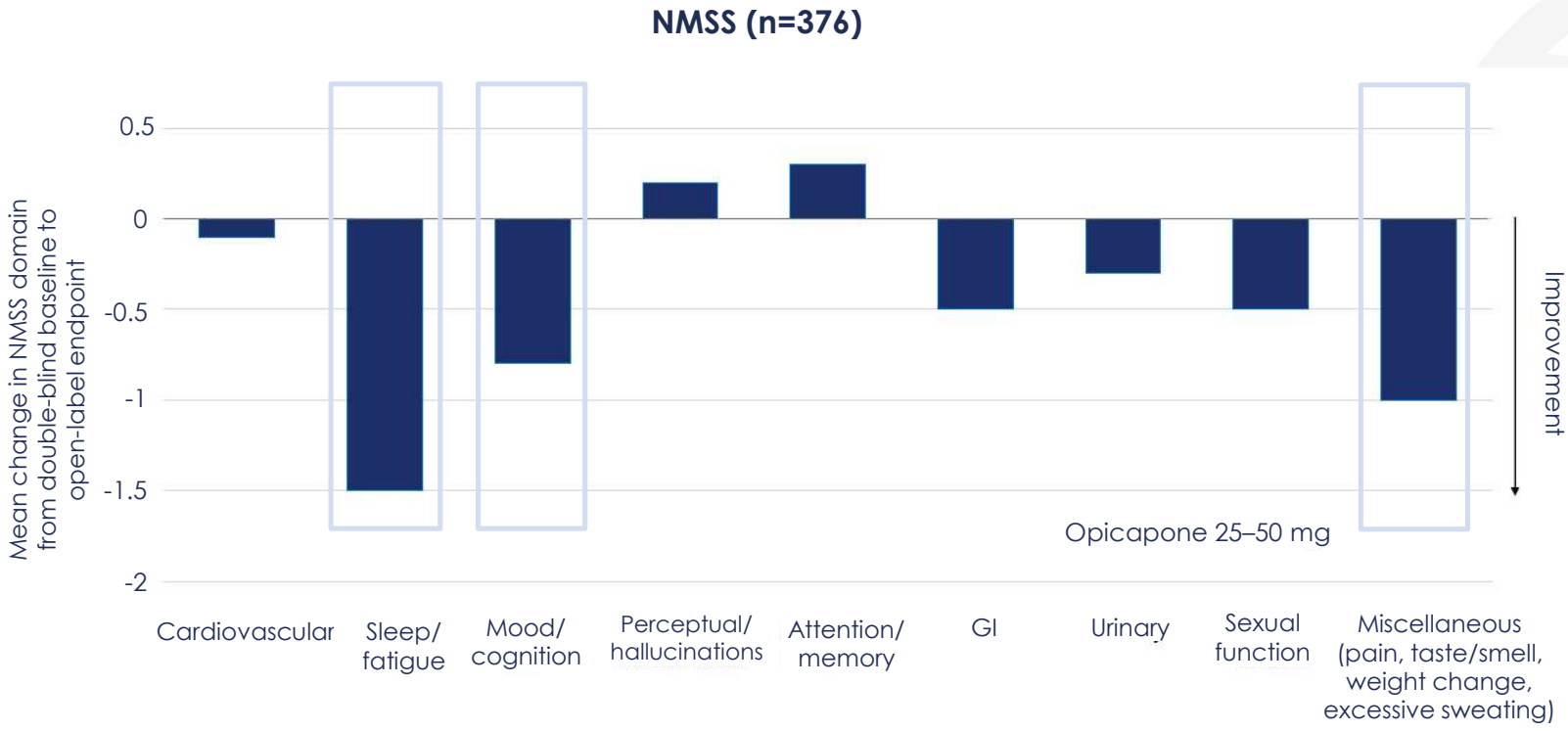
Change from baseline in NMSS domains in BIPARK-II[a]



GI, gastrointestinal; NMSS, Non-Motor Symptoms Scale.
[a]Phase III trial double-blind placebo-controlled trial with a 14–15 weeks doble-blind phase, and a 1 year open-label phase; full analysis set (n=376 patients).
Oliveira C, et al. *Eur J Neurol*. 2015;22(Suppl 1):120-482(abstract P1236).

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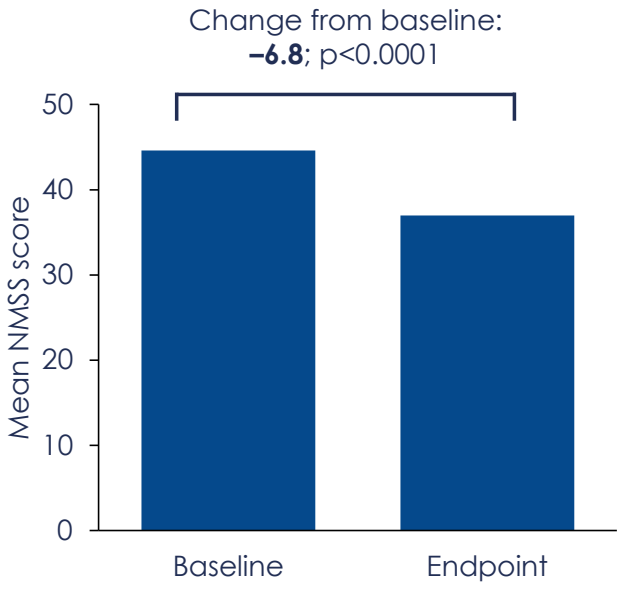
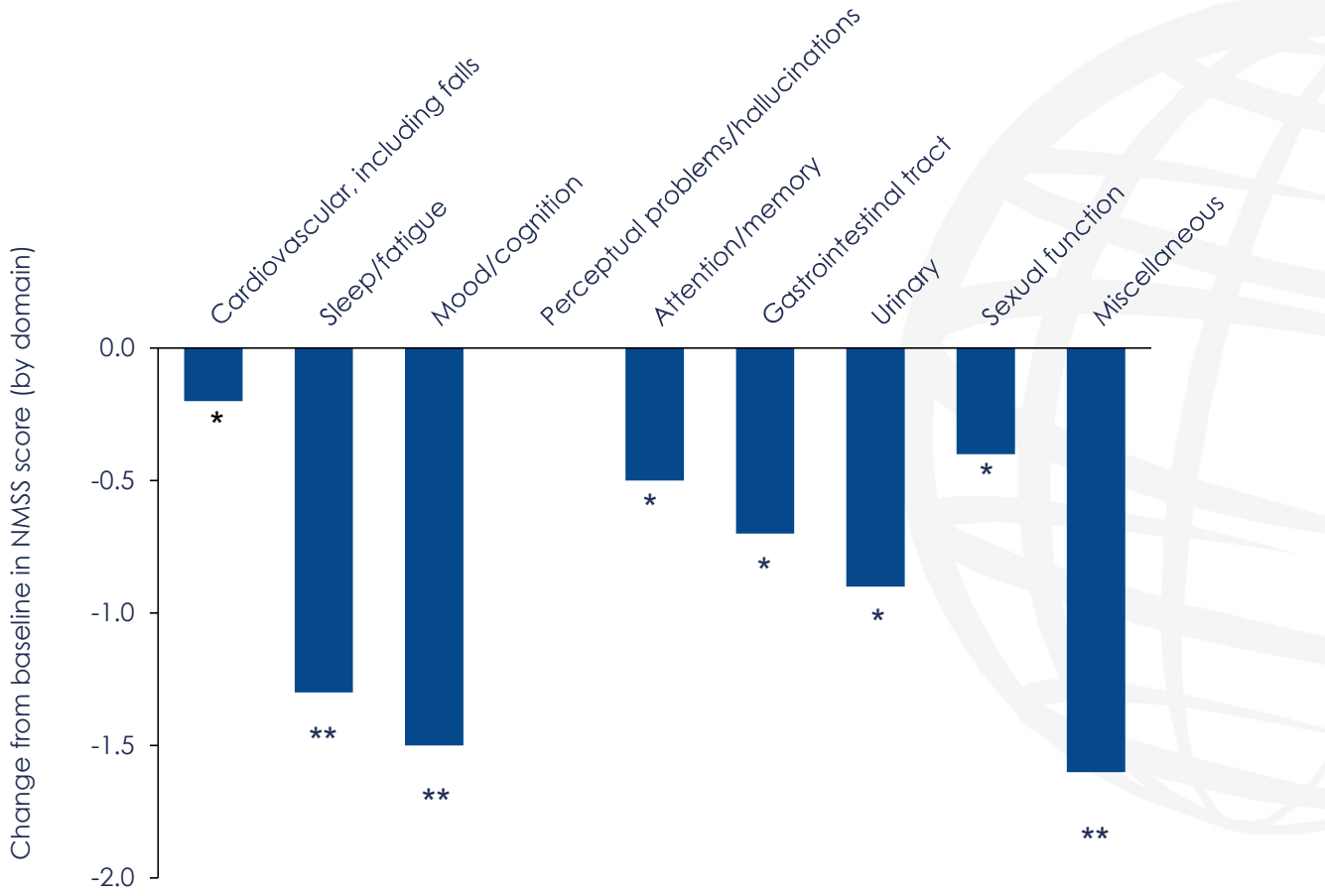
Change from baseline NMSS in OPTIPARK[a]





*p<0.05 vs baseline; **p<0.0001 vs baseline; [a]Phase IV, open-label trial of 3 months duration (n=477).
NMSS, Non-Motor Symptoms Scale.
Reichmann H, et al. *Transl Neurodegener.* 2020;9:1–9.

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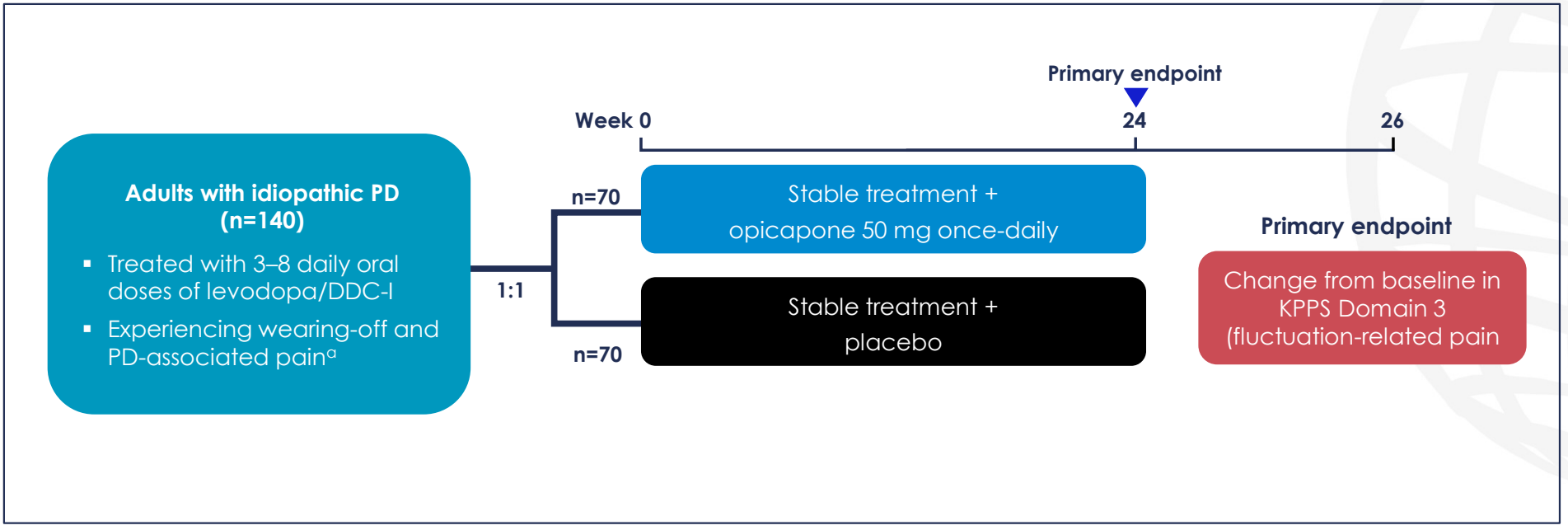
Discussion questions part 1

Q1 What is your perspective in terms of the impact of non-motor symptoms in patients with Parkinson's disease?

Q2 Do you think that COMT inhibitors may play an important role in the management of these symptoms?

Opicapone in patients with end-of-dose motor fluctuation-related pain: the OCEAN trial

Phase IV, randomised, double-blind, placebo-controlled trial



[a]score ≥12 in domain 3 (fluctuation-related pain) of KPSS at baseline.
OCEAN: OpiCapone Effect on motor fluctuations and associated pAiN; CGI-C, Clinician Global Impression of Change; DDC-I, dopa-decarboxylase; KPPS, King's-Parkinson's disease Pain Scale; MDS-NMS, Movement Disorder Society Non-Motor Rating Scale; OPC, opicapone; PD, Parkinson's disease; PDQ-8, Parkinson's disease Questionnaire-8; PGI-C, Patient Global Impression of Change; UPDRS, Unified Parkinson's disease Rating Scale.
Chaudhuri KR, et al. *Eur J Neurol*. 2021;28:753–921(EPO-744).

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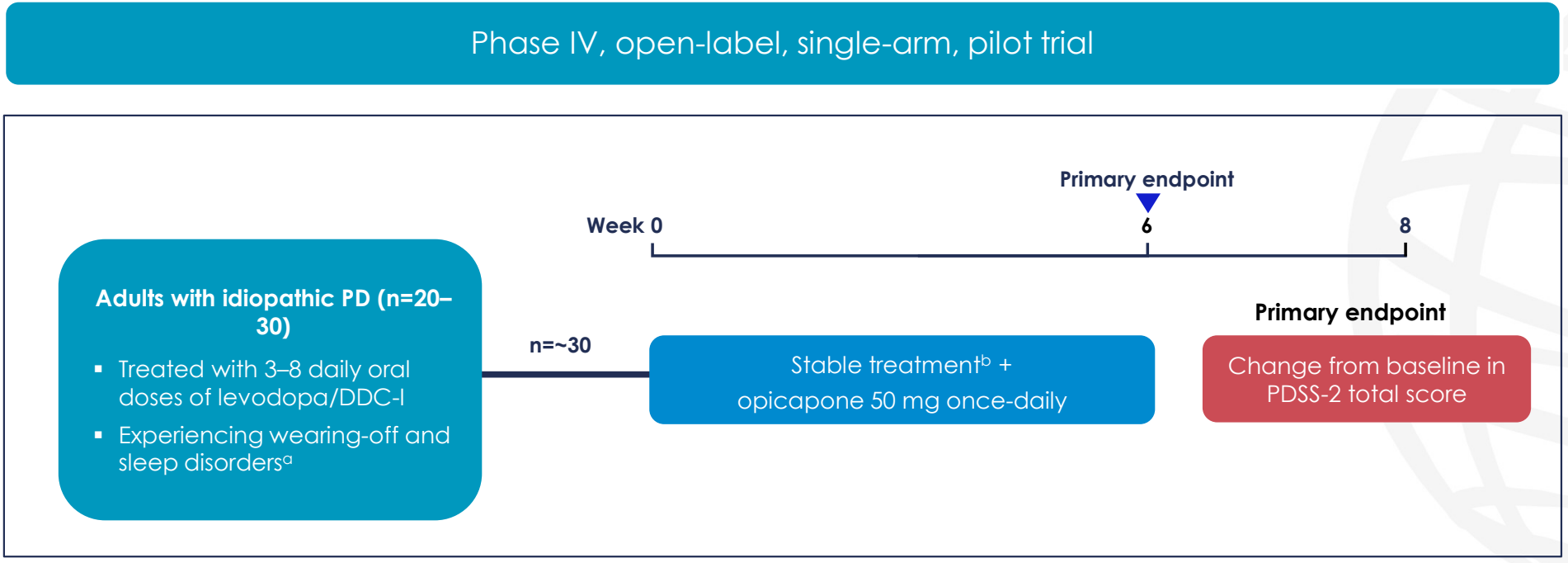
Opicapone in patients with end-of-dose fluctuations and associated sleep disorders: the OASIS trial



[a]score ≥18 in PDSS-2 total score at baseline; [b]levodopa/DDC-I daily dose, but not number of intakes, can be adjusted according to response in the first 2 weeks, but thereafter kept unchanged

OASIS: OpicApone in Sleep dISorder) study in Parkinson's disease; CGI-C, Clinician Global Impression of Change; DDC-I, dopa-decarboxylase; MDS-NMS, Movement Disorder Society Non-Motor Rating Scale; OPC, opicapone; PDQ-8, Parkinson's disease Questionnaire-8; PD, PD, Parkinson's disease; PDSS, Parkinson's disease Sleep Scale; PGI-C, Patient Global Impression of Change.

Costa R, et al. *Eur J Neurol.* 2021;28:753–921(EPO-300).

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Discussion questions part 2

Q3 If positive results are obtained, will they leverage the use of opicapone in the treatment of fluctuations?

Conclusions

- **Opicapone 50 mg, an oral once-daily COMT inhibitor[1–3]:**
  - has demonstrated efficacy (decreasing OFF time and increasing ON time) across the entire spectrum of motor fluctuations.
  - is **generally well tolerated**:
    - most AEs being an extension of levodopa-related dopaminergic adverse reactions and occurring early in the treatment.
  - recent post-hoc analysis associated opicapone's efficacy with **parameters of early disease**, suggesting its use upon motor fluctuations diagnosis.[4]
  - there may be an added benefit from using opicapone in the **treatment of non-motor fluctuations.**[5]

AE, adverse events;

1. Lees AJ, et al. *JAMA Neurol*. 2017;74:197–206; 2. Ferreira JJ, et al. *Neurology*. 2018;90:e1849–57; 3. Ferreira JJ, et al. *Lancet Neurol*. 2016;15:154–65; 4. Ebersbach G, et al. *Mov Disord*. 2020;35(Suppl S1):S445(Abstract 994); 5. Oliveira C, et al. *Eur J Neurol*. 2015;22(Suppl 1):120-482(abstract P1236).

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