Project ECHO®

Personalizing Treatment for PARKINSON'S DISEASE:

What Can You Do to Manage OFF EPISODES *in Your Patients?*

This activity is provided by Med Learning Group.
This activity is co-provided by Ultimate Medical Academy/Complete Conference Management (CCM).
This activity is supported by an educational grant from Sunovion.

Personalizing Treatment for Parkinson's Disease: What Can You Do to Manage Off Episodes in Your Patients?

FACULTY

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PROGRAM OVERVIEW

This live virtual TeleECHO program will explore the management of off episodes in patients with Parkinson's disease. Interactive case studies presented by expert faculty will evaluate pharmacologic approaches to reduce daily off time, including the efficacy and safety of on-demand therapies. Engaging whiteboard animation will review the pathophysiology of off episodes and the mechanism of action of treatment options.

TARGET AUDIENCE

This educational activity is intended for U.S.-based neurologists and movement disorder specialists involved in the management of patients with PD.

LEARNING OBJECTIVES

Upon the completion of this program, attendees should be able to:

- Discriminate between the various motor and non-motor "off" phenomena and their underlying developmental mechanisms
- Contrast the distinct mechanisms of action and clinical profiles of therapeutic strategies for treating "off" states
- Develop communication skills that can reveal the presence of "off" episodes

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Purpose: This program would be beneficial for nurses involved in the long-term treatment and management of patients with PD.
CNE Credits: 1.0 ANCC Contact Hour.

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CME Content Review

The content of this activity was independently peer reviewed.
The reviewer of this activity has nothing to disclose.

CNE Content Review

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2. Participate in the activity.
3. Complete pre-and-post surveys and evaluation.

You will receive your certificate as a downloadable file.

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AGENDA

1. **Off Episodes in Parkinson's Disease: An Overview**
    a. Incidence of off episodes in Parkinson's disease
    b. Motor and non-motor symptoms
    c. Types of off episodes
    d. Impact of off episodes on patient quality of life
    e. Timing of off episodes

2. **Management of Off Episodes**
    a. Factors affecting PD management
    b. Oral therapies
        i. Adjusting levodopa dose or administration frequency
        ii. Switching to an extended-release formulation
    c. Adjunctive therapies
        i. Efficacy and safety of available options
        ii. Selecting an appropriate agent
        iii. Common adverse events with adjunctive therapies
    d. On-demand therapies
        i. Inhaled levodopa
        ii. Subcutaneous apomorphine
        iii. Sublingual apomorphine film
    e. Surgical options for advanced disease

3. **Personalizing Treatment**
    a. Selecting treatment options based on type of off episode
    b. Considering patient-specific factors
    c. Goals of therapy
    d. Multidisciplinary care of Parkinson's disease

4. **Interactive Case Studies**

5. **Questions and Answers**

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Disclosures

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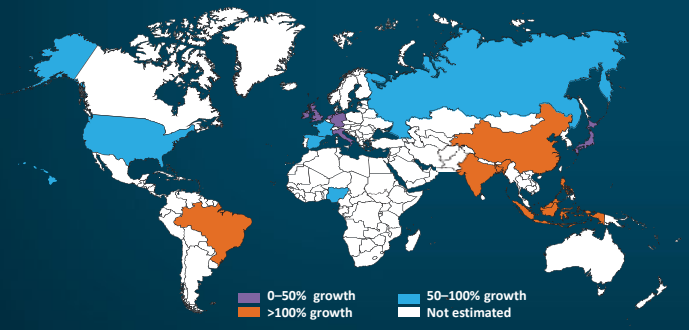
Learning Objectives

- Discriminate between the various motor and non-motor "off" phenomena and their underlying developmental mechanisms
- Contrast the distinct mechanisms of action and clinical profiles of therapeutic strategies for treating "off" states
- Develop communication skills that can reveal the presence of "off" episodes

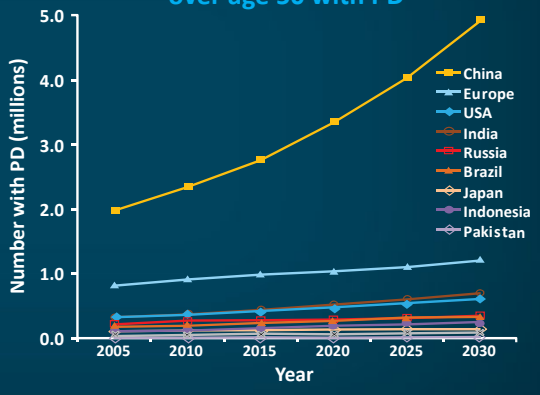
Current and Future Prevalence of Parkinson's Disease

- Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease
- Affects 1% of population over 60 years of age
- Enormous public health challenge

Projected number of individuals over 50 years of age with PD: 2005 through 2030



Projected number of people over age 50 with PD



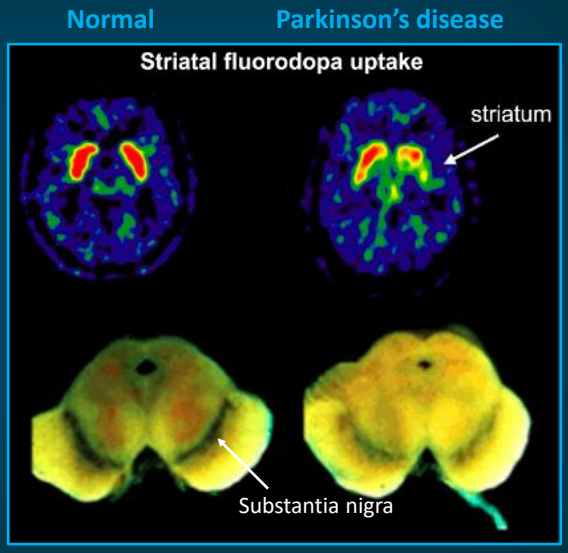
Dorsey ER, et al. *Neurology*. 2007;68:384-386. National Institute of Neurological Disorders and Stroke (NINDS). Parkinson's disease (www.ninds.nih.gov/Disorders/All-Disorders/Parkinsons-Disease-Challenges-Progress-and-Promise). Parkinson's disease statistics (https://parkinsonsdisease.net/basics/statistics). URLs accessed 8/15/2021.

Motor Symptoms Reflect Dopamine Loss

Classic symptom triad in PD

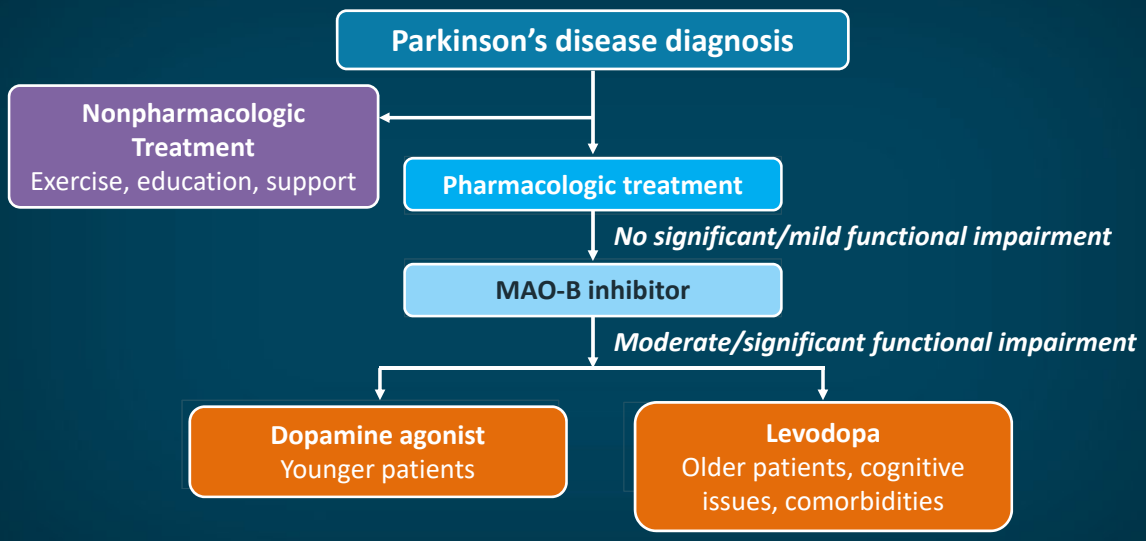
- Tremor
- Bradykinesia
- Rigidity

Loss of postural reflexes



Brooks DP, DePalma D. *Pharmacology.* 1993;47:43-49. Marsden CD. *Clin Neuropharmacol.* 1994;17(suppl 2): S32-S44. Lang AE, Lozano AM. *N Engl J Med.* 1998;339:1044-1053. Nyholm D, Lennernäs H. *Expert Opin Drug Metab Toxicol.* 2008;4:193-203.

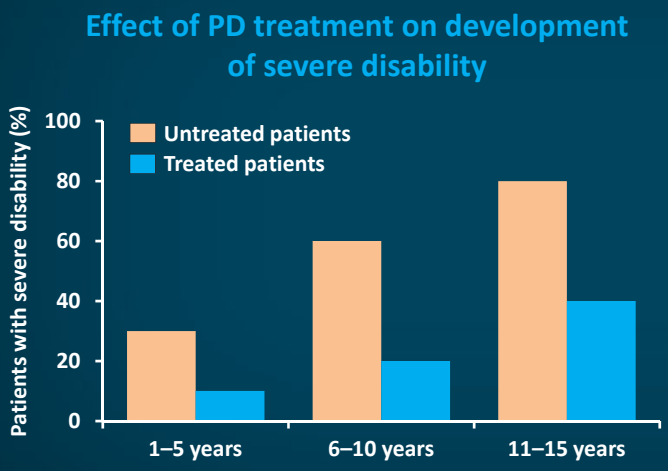
Early Treatment Algorithm



MAO-B = monoamine oxidase-B.

Modified from Lyons KE, Pahwa R. *Int J Neurosci.* 2011;121:27-36.

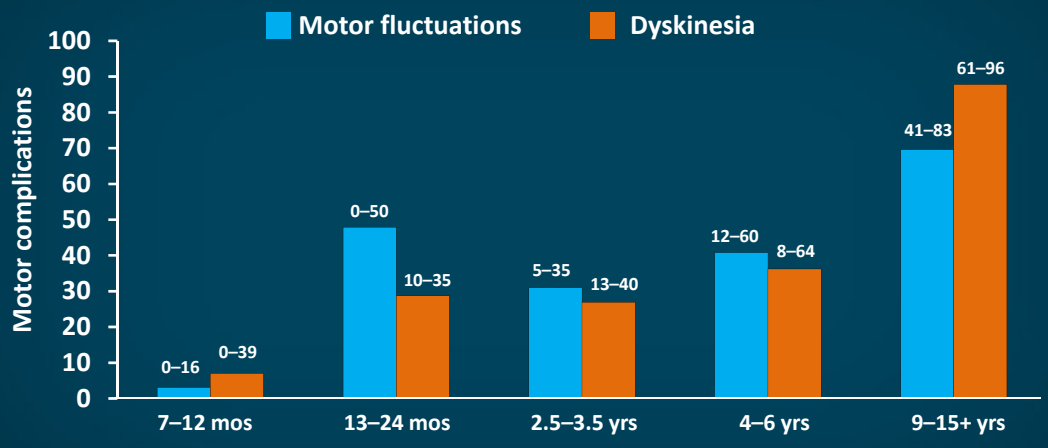
Levodopa Therapy Is Effective Treatment for Parkinson's Disease Throughout Its Course



- Rapid symptomatic relief
- Reduces morbidity
- Prolongs survival

Poewe WH, Wenning GK. *Neurology*. 1996;47(suppl 3):S146-S152.

Incidence of Levodopa-Induced Motor Complications



mo(s) = month(s); yr(s) = year(s).

Ahlskog JE, Muenter MD. *Mov Disord*. 2001;16:448-458.

How Do Patients With PD View Their OFF episodes?

Ranking of 10 most troubling symptoms in 173 patients with >6 years disease duration

Rank	Symptom/condition	Total score
1	Fluctuating response to medication	115
2	Mood	96
3	Drooling	85
4	Sleep	83
5	Tremor	67
6	Pain	60
7	Bowel problems	46
8	Urinary problems	40
9	Falls	39
10	Appetite/weight	36

"Voice of the Patient" project (FDA patient meeting, 2016)

"Participants expressed frustration with periods of 'off-time', which was described as **unpredictable exacerbation of symptoms** during which medications were less effective. A few described the unpredictability that off-time brought into their lives on a daily basis."

FDA = US Food and Drug Administration.

Politis M, et al. *Mov Disord.* 2010;25:1646-1651. FDA. The voice of the patient (www.fda.gov/media/124392/download). Accessed 8/12/2021

Impact of Different Types of OFF Episodes on Quality of Life

Impact of motor complications, especially levodopa-induced dyskinesias, on QoL was studied in 143 patients with PD

- Mobility, ADL, stigma, and communication most strongly affected
- Significant PDQ-39 Summary Index worsened in all 143 patients with PD

Dimensions of PDQ-39 Significantly Related to Motor Fluctuations					
PDQ-39 dimension	End-of-dose fluctuations	Nocturnal akinesia	Early morning akinesia	Unpredictable OFF episodes	Paradoxical Fluctuations
Mobility	✓	✓	✓	✓	✓
ADL	✓	✓	✓	✓	✓
Emotional well-being		✓			
Stigma	✓	✓	✓	✓	✓
Social support		✓			
Cognition		✓			
Communication	✓	✓	✓	✓	✓
Bodily discomfort		✓		✓	
Total score	✓	✓	✓	✓	✓

✓ = Statistically significant; QoL = quality of life; PDQ = Parkinson's Disease Questionnaire; ADL = activities of daily living.

Chapuis S, et al. *Mov Disord.* 2005;20:224-230.

Please click here for whiteboard animation

How Patients Experience the 4 Types of Off Episodes

Motor Fluctuations Reflect Different Types of OFF Episodes

- Types of motor fluctuations[1,2]
  - "End-of-dose wearing off"—predictable
  - "Delayed time to ON"
    - Delayed-ON (postprandial akinesia)
    - Suboptimal-ON
    - No ON (dose failure)
  - "ON–OFF" phenomena—unpredictable
  - Nocturnal akinesia
  - Early morning akinesia
- Dyskinesias[1] and nonmotor fluctuations[2,3] may also occur

Relative incidence of different motor fluctuations and dyskinesias[1]

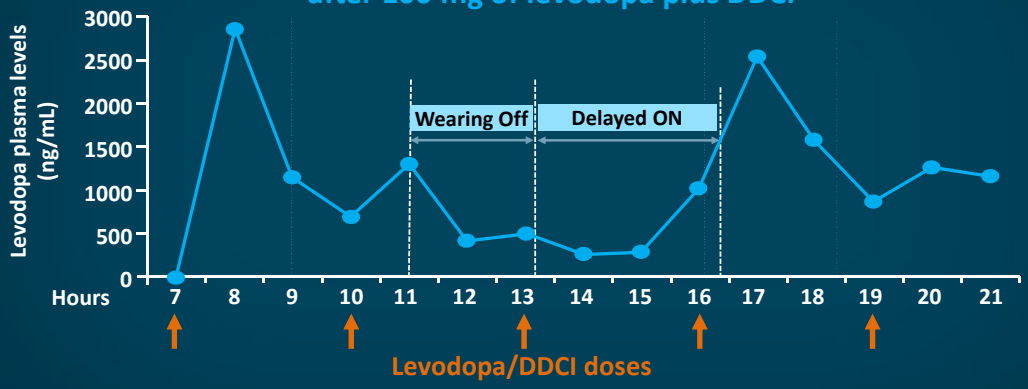
	Patients (n)	%
Fluctuations	94	66.0
Early morning akinesia	55	58.5
Nocturnal akinesia	54	57.5
End-of-dose fluctuations	74	78.7
Paradoxical fluctuations	47	50.0
"Unpredictable OFFS"	34	36.2
LID	81	57.0
Peak dose	59	72.8
Diphasic	14	17.3
OFF	10	12.4
Morning dystonia	27	33.3

LID = levodopa-induced dyskinesia; MF = motor fluctuation.

1. Chapuis S, et al. *Mov Disord.* 2005;20:224-230. 2. Stocchi F. *Parkinsonism Relat Disord.* 2009;15(suppl 1):S9-15. 3. Martinez-Martin P, et al. *Mov Disord.* 2007;22:1623-1629

OFF Episodes Can Be Predictable or Unexpected: Each Day May Have A Different Pattern

Delayed ON or no ON response: levodopa plasma level after 100 mg of levodopa plus DDCI



Lack of absorption is evident after the dose at 13 hours

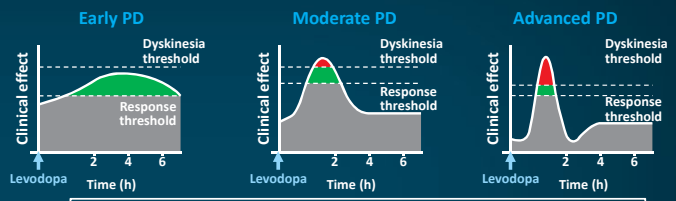
DDCI = dopa decarboxylase inhibitor; WO = wearing off.

Adapted from: Stocchi F. *Parkinsonism Relat Disord.* 2009;15(suppl 1):S9-15.

What Causes OFF Episodes?

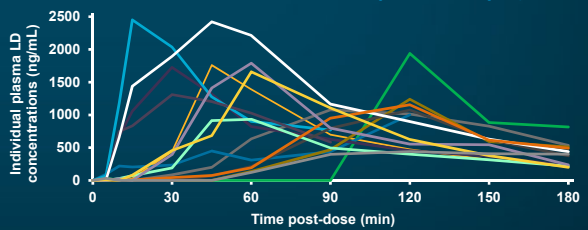
- Central mechanisms[1,2]
  - Progressive neurodegeneration causes striatal denervation leading to reduced presynaptic dopamine storage capacity
  - Long-term "*pulsatile*" delivery results in postsynaptic changes in striatal pathways
- Peripheral mechanisms[3]
  - Variability in GI absorption due to:
    - GI dysmotility and delayed gastric emptying secondary to PD and medications
    - Impaired absorption of levodopa transport across the gut-blood barrier
  - Short plasma half-life
  - Variability in blood-brain barrier transport

Change in LD response over time[4]



- Smooth extended duration of target clinical response
- Low incidence of dyskinesia
- Diminished duration of target clinical response
- Increased incidence of dyskinesia
- Short duration of target clinical response
- ON time is associated with dyskinesia

Plasma concentrations after oral levodopa/carbidopa (25/100)[5]

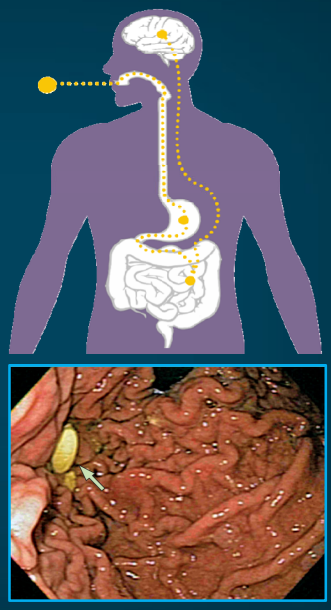


GI = gastrointestinal; LD = levodopa; 25/100 = 25 mg/100 mg.

1. Calabresi P, et al. *Nat Neurosci.* 2014;17:1022-1030. 2. Olanow CW, et al. *Lancet Neurol.* 2006;5:677-687. 3. Nyholm D, Lennernäs H. *Expert Opin Drug Metab Toxicol.* 2008;4:193-203. 4. Schapira AH, et al. *Eur J Neurol.* 2009;16:982-989. 5. Lipp MM, et al. *Sci Transl Med.* 2016;8:360ra136.

Absorption of Oral Levodopa Is Often Variable

- PD is associated with delayed gastric emptying
- Food can interfere with levodopa absorption
  - High-fat meals can slow gastric emptying
  - Amino acids from food proteins compete with levodopa for absorption
- Helicobacter pylori gastric infection can affect levodopa absorption
- Gut bacterial tyrosine decarboxylase can reduce levodopa absorption



Pfeiffer RF, et al *Parkinsonism Relat Disord.* 2020;76:63-71. Stacher G, et al. *Dig Dis Sci.* 1991;36:1259-1265. van Kessel SP, et al. *Nat Commun.* 2019;10:310.

Once OFF Episodes Emerge, Shared Clinical Decision-Making Can Help Guide Adjustment to Levodopa Regimen and/or Addition of Adjunctive Therapy

Early Oral/Non-GI			Advanced (surgical)
Oral levodopa dose adjustments	Adjunctive therapies	On-demand therapies	Surgical therapies
Increase IR levodopa dosing and/or frequency	Dopamine agonists	Sublingual apomorphine	LCIG infusion
Switch to extended-release levodopa	COMT/MAO-B inhibitors	Subcutaneous apomorphine	Deep-brain stimulation
	Non-dopaminergic agents	Inhaled levodopa	

COMT = catechol-O-methyltransferase; LCIG = levodopa-carbidopa intestinal gel; IR = immediate release.

Vijiaratnam N, Foltynie T. *Drugs.* 2020;80:775-796. Tanner CM. *Am J Manag Care.* 2020;26(12 suppl):S255-S264.

Medication Approaches to Reduce Daily OFF Time

- Carbidopa/levodopa
  - Increase levodopa during day or increase dosing frequency
  - Switch to sustained-release levodopa
  - Switch to ER capsules
  - Levodopa infusion
- Add dopamine agonists
  - Pramipexole
  - Pramipexole ER
  - Ropinirole
  - Ropinirole ER
  - Rotigotine transdermal
- Add MAO-B inhibitors
  - Rasagiline
  - Selegiline
  - Selegiline ODT (Zydis)
  - Safinamide
- Add COMT inhibitors
  - Entacapone
  - Opicapone
  - Tolcapone
- Add amantadine ER capsules at bedtime
- Add adenosine A2A antagonist
  - Istradefylline

ER = extended release; ODT = oral disintegrating tablet; A2A = adenosine A(2A) receptor.

Fox SH, et al. *Mov Disord*. 2018;33:1248-1266. Vijiaratnam N, Foltynie T. *Drugs*. 2020;80:775-796. Tanner CM. *Am J Manag Care*. 2020;26(12 suppl):S255-S264.

Factors Affecting PD Management

- Symptoms and symptom severity
- Occupational status and lifestyle
- Age
- Non-motor symptoms
  - Cognitive, behavioral, and psychiatric status
  - Sleep disorders (RBD, sleep apnea)
  - Orthostatic hypotension
  - Constipation
- Comorbidities and concomitant medications

RBD = REM (rapid eye movement) sleep behavior disorder.

Treatment Options

Available levodopa/ carbidopa formulations

CD/LD IR

- 25/100 IR
- 25/100 ODT
- 25/250 IR
- 10/100 IR

CD/LD ER

- 25/100 CR
- 50/200 CR
- 95 ER
- 145 ER
- 195 ER
- 245 ER

COMT inhibitors can also prolong plasma levodopa

COMT inhibitors

- Tolcapone
- Entacapone
- Opicapone

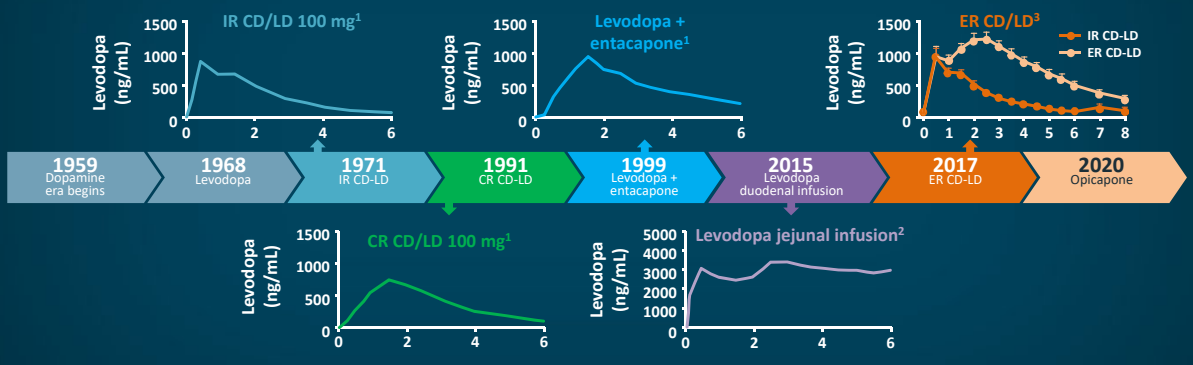
Combination

- CD/LD/EC

Additional therapies in development include longer ER formulations, continuous subcutaneous infusions, and gene therapies

CD = carbidopa; EC = entacapone.

Strategies to Increase Plasma Levodopa Include Higher Dose, More Frequent Timing, ER Formulations, and Inhibition of COMT



CR = controlled/sustained release.

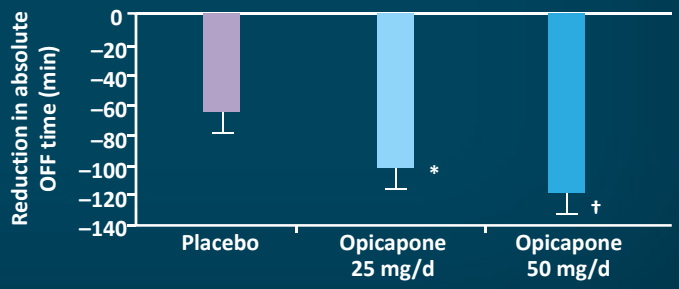
1. Hsu A, et al. *J Clin Pharmacol.* 2015;55:995-1003. 2. Nyholm D, et al. *AAPS J.* 2013;15:316-323. 3. Hauser RA, et al. *Neuropsychiatr Dis Treat.* 2018;14:839-842.

COMT Inhibitors

- Prevent peripheral degradation of levodopa by inhibiting COMT
- Prolong duration of levodopa benefit
- Potentially reduce levodopa dose necessary for a clinical benefit

Available options include:

- Tolcapone
- Entacapone
- Opicapone



*Not significant. †*P*< .01.

d = day.

Rinne UK, et al. *Neurology*. 1998;51:1309-1314. Parkinson study group. *Ann Neurol*. 1997;42:747-755. Brooks DJ, et al. *J Neurol Neurosurg Psychiatry*. 2003;74:1071-1079. Poewe WH, et al. *Acta Neurol Scand*. 2002;105:245-255. Lees AJ, et al. *JAMA Neurol*. 2017;74:197-206 and supplement.

Additional Treatment Options

Striatal dopaminergic tone can be increased by MAO inhibitor or dopamine agonist

- MAO-B inhibitors
  - Selegiline
  - Selegiline ODT
  - Rasagiline
  - Safinamide
- Dopamine agonists
  - Pramipexole
  - Pramipexole ER
  - Ropinirole
  - Ropinirole ER
  - Rotigotine

Nondopaminergic adenosine and glutamate antagonists can also modulate striatal pathways

- NMDA antagonists
  - Amantadine IR
  - Amantadine ER
  - Amantadine ER hs
- Adenosine A2A antagonist
  - Istradefylline

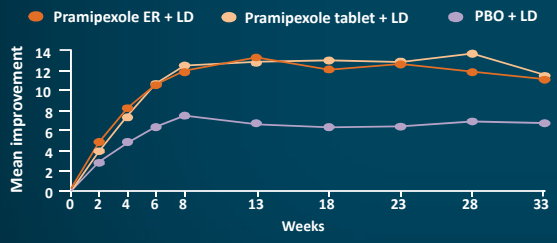
NMDA = N-methyl-D-aspartate; hs = at bedtime.

Controlled-Release Dopamine Agonists

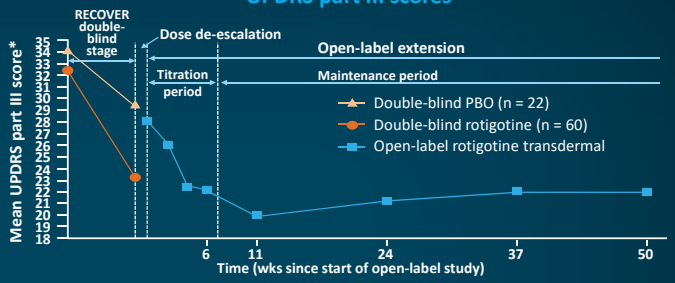
Available options include:

- Ropinirole
- Pramipexole
- Rotigotine

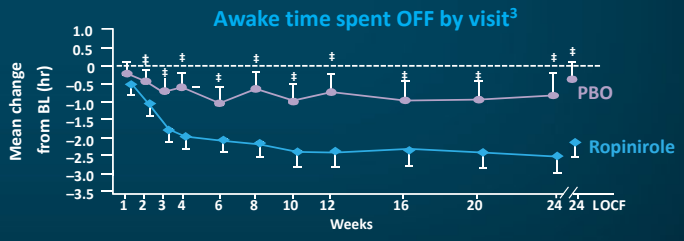
UPDRS parts II and III scores[1†]



UPDRS part III scores[2]



Awake time spent OFF by visit[3]



*Measured in early morning in RECOVERY but at any time of day during open-label extension; †P= .0135 (pramipexole ER vs PBO at week 33); ‡P< .005.

M = month; EoM = end of month; LOCF = last observation carried forward; SE = standard error; UPDRS = Unified Parkinson's Disease Rating Scale; XL = extended release; BL = baseline; PBO = placebo; hr(s) = hour(s).

1. Poewe W, et al. *Neurology.* 2011;77:758-766. 2. Trenkwalder C, et al. *Basal Ganglia*. 2012;2:79-85. 3. Pahwa R, et al. *Neurology.* 2007;68:1108-1115.

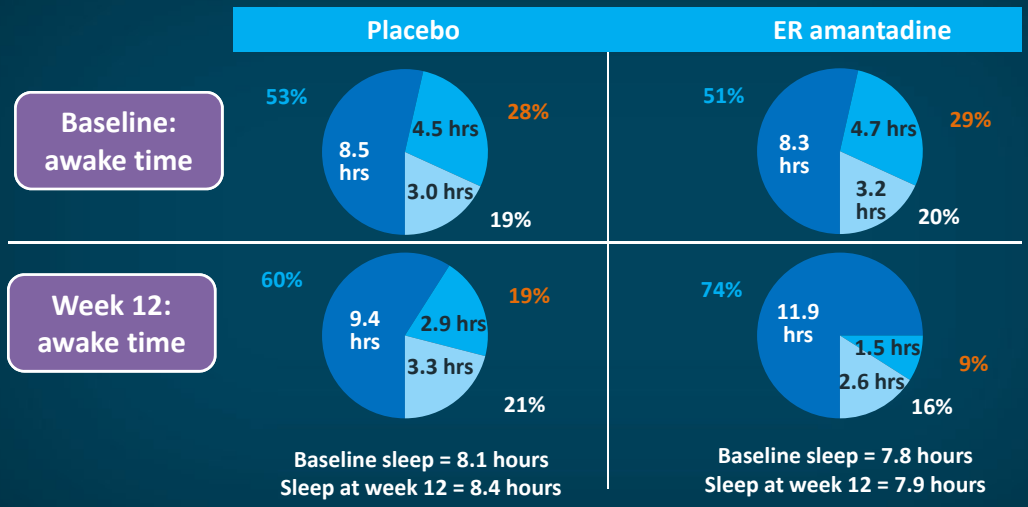
Safinamide

- Safinamide is an α-aminoamide
- Mechanism of action
  - Both dopaminergic and nondopaminergic
  - Inhibition of MAO-B
  - Na+ channel blockade
  - Modulation of stimulated release of glutamate
- Oral: 50 or 100 mg once in 1 day

Müller T. *Clin Pharmacol.* 2018;10:31-41.

Extended-Release Amantadine

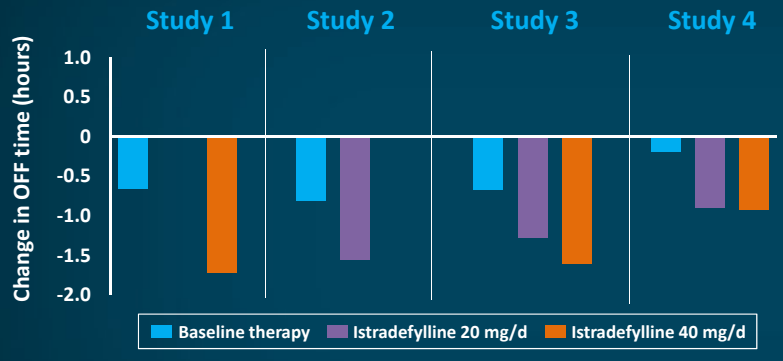
Diary summaries from patients with PD



Pahwa R, et al. *JAMA Neurol.* 2017;74:941-949.

Istradefylline—Once Daily

OFF time reduction ~1 hour



Decreased OFF time and increased ON time without troublesome dyskinesia at 12 weeks

Adenosine A2a receptors

- Enriched in basal ganglia
- Regulate indirect pathways
- Activation reduces motor activity
  - In contrast, dopamine increases motor activity

Increase in ON time without troublesome dyskinesia with istradefylline: 0.55-0.96 hrs/d across 4 clinical trials

*Nominal *P*-values: *P*= .026 in study 1 (40 mg); *P*= .135 in study 2 (20 mg); *P*= .085 (20 mg) and *P*= .048 (40 mg) in study 3; *P*= .008 for both 20 mg and 40 mg in study 4.

Istradefylline (Nourianz®) prescribing information (PI), 2020 (www.nourianz.com/assets/pdf/nourianz-full-prescribing-information.pdf)package insert]. Accessed 8/12/2021. Kalia LV, et al. *Mov Disord.* 2013;28:131-144. Mishina M, et al. *PLoS One*. 2011;6:e17338. Saki M, et al. *Naunuyn Schmiedebergs Arch Pharmacol*. 2013;386:963-972. Varani K, et al. *FASEB J*. 2010;24:587-598.

Reduction in OFF Time With Adjunctive Therapies

Medication	OFF-time reduction	Doses per day, no.
Dopamine agonists		
Pramipexole/ropinirole	1.5–2 hours/day	3
Pramipexole ER/ropinirole XL/rotigotine	0.7–1.5 hours/day	1
MAO-B inhibitors		
Rasagiline/safinamide/selegiline ODT	0.9–1.6 hours/day	1
COMT inhibitors		
Entacapone/opicapone	0.7–1.2 hours/day	0 (combination) –1
A2A antagonists		
Istradefylline	1 hour/day	1
NMDA antagonist		
Amantadine ER	1 hour/day	1

Pahwa R, et al. *Neurology.* 2006;66:983-995. Schapira AH, et al *Neurology.* 2011;77:767-764. Pahwa R, et al. *Neurology.* 2007;68:1108-1115. LeWitt PA, et al. *Neurology.* 2007;68:1262-1267. Pramipexole (Mirapex®) PI, 2021 (https://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Mirapex/Mirapex.pdf). Ropinirole PI, 2020. Pramipexole ER (Mirapex® ER) PI, 2018 (www.accessdata.fda.gov/drugsatfda_docs/label/2018/022421s017lbl.pdf). Ropinirole extended release (Requip® XL) PI, 2017 (www.accessdata.fda.gov/drugsatfda_docs/label/2017/022008s009lbl.pdf). Rotigotine transdermal system (Neupro®). Rasagiline (Azilect®) PI, 2020 (www.azilect.com/azilect.pdf). Selegiline orally disintegrating (Zelapar®) PI, 2021 (www.bauschhealth.com/Portals/25/Pdf/PI/Zelapar-PI.pdf). Entacapone PI, 2015 (www.ajantapharmausa.com/pdf/Entacapone_Tablets_Single_Package_Insert.pdf). Opicapone (Ongentys®) PI, 2020 (www.neurocrine.com/assets/ONGENTYS-PI.pdf). Istradefylline (Nourianz®) PI, 2020 (www.nourianz.com/assets/pdf/nourianz-full-prescribing-information.pdf). Amantadine (Gocovri) PI, 2021 (www.gocovrihcp.com/pdf/Gocovri_Prescribing_Information.pdf). URLs accessed 8/13/2021.

Common Dopaminergic Adverse Events in Advanced PD

	Dizziness	Hallucinations	Nausea	Orthostatic Hypotension	Somnolence	Dyskinesia
Carbidopa/levodopa	2–3%	3–5%	4–6%	1%	NR	13–16%
MAO-B inhibitors	2–14%	<3–6%	6–20%	2–9%	2–6%	18–21%
Dopamine agonists	2–26%	7–17%	11–30%	1–53%	7–32%	13–47%
Apomorphine SC	20%	10%	30%	20%	35%	35%
Entacapone	8%	4%	14%	4%	2%	25%
Istradefylline	6%	6%	6%	NR	NR	17%
Amantadine ER	16%	21%	8%	13%	<3%	NR

PI does not list frequency of AEs; taken from ELLDOPA, CALM-PD, and 056.

SC = subcutaneous.

Apomorphine injection (Apokyn®) PI, 2020 (www.apokyn.com/sites/all/themes/apokyn/content/resources/apokyn_pi.pdf). Entacapone (Comtan®) PI, 2020 (https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=b1aceb59-9be8-43b8-83d6-81e05e4b51e4) (www.accessdata.fda.gov/drugsatfda_docs/label/2010/020796s15lbl.pdf). Istradefylline (Nourianz®) PI, 2020 (www.nourianzhcp.com/assets/pdf/nourianz-full-prescribing-information.pdf). Amantadine extended-release (Gocovri®) PI (www.gocovrihcp.com/pdf/Gocovri_Prescribing_Information.pdf). URLs accessed 8/12/2021.

Delayed ON, Morning OFF, and Dose Failures

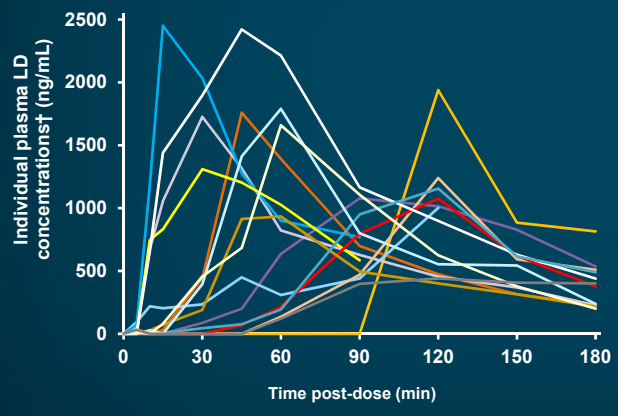
- Variability of intestinal levodopa absorption can be addressed with non-GI, on-demand formulations of levodopa and apomorphine
- GI (all affected by GI dysmotility)
  - Oral CD/LD
  - Orally disintegrating CD/LD tablet
  - Liquid CD/LD
- Non-GI (avoids GI variability)
  - Apomorphine sublingual
  - Apomorphine subcutaneous injection
  - Inhaled LD

Pfeiffer RF, et al. *Parkinsonism Relat Disord*. 2020;76:63-71.

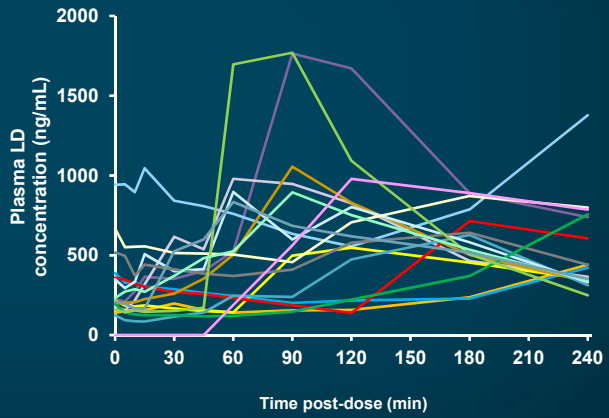
Plasma Levodopa Concentrations Variable After Oral CD/LD in PD

Oral CD/LD 25/100

Fasted: no food at least 1 hour before and 1 hour after dose[1]

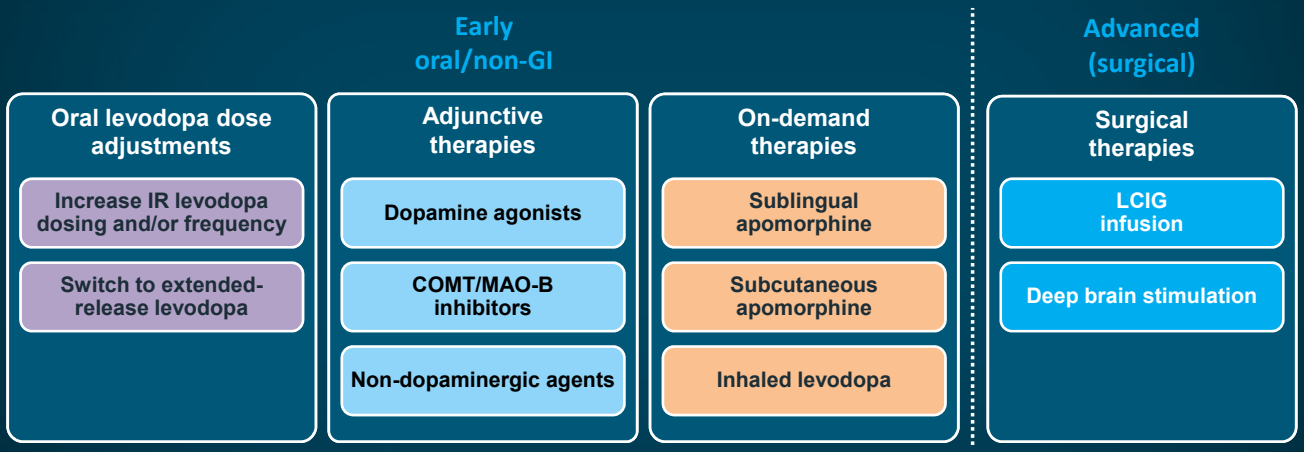


After meal: 4–5 hours after morning CD/LD, patients ate meal then dose[2]



1. Lipp MM, et al. *Sci Transl Med*. 2016;8:360ra136. 2. Safirstein BE, et al. *Clin Ther.* 2020;42:1034-1046.

Once OFF Episodes Emerge, Shared Clinical Decision-Making Can Help Guide Adjustment to Levodopa Regimen and/or Addition of Adjunctive Therapy



Vijiaratnam N, Foltynie T. *Drugs*. 2020;80:775-796. Tanner CM. *Am J Manag Care*. 2020;26(12 suppl):S255-S264.

Please click here for whiteboard animation

Mechanism of Action of Therapies for Off Episodes

On-Demand Therapies Are Efficacious and Generally Well Tolerated for Management of "OFF" Episodes

Drug	Efficacy	Most common adverse events
Sublingual apomorphine	• **Significant improvement in UPDRS-III scores vs PBO (LSM treatment difference: −7.6 at 30 min after dosing at week 12)** • 35% of apomorphine patients turned ON 30 min post dose vs 16% on PBO	• Nausea (treat with antiemetic beginning 3 days prior to 1st dose) • Oral/pharyngeal soft tissue swelling • Oral/pharyngeal soft tissue pain and paresthesia • Dizziness • Somnolence
Subcutaneous apomorphine	• **Significant improvement in UPDRS-III scores vs placebo (-23.9 vs -0.1)** • Significant efficacy as recorded by Columbia Parkinson's disease score	• Nausea and/or vomiting • Dyskinesia • Dizziness/ postural hypotension • Rhinorrhea • Somnolence/drowsiness • Yawning • Hallucination/confusion • Edema/swelling of extremities
Inhaled levodopa	• **Significant improvement in UPDRS-III scores vs PBO (LSM treatment difference: −3.07 at 30 min after dosing at week 12 (84 mg))** • 58% of inhaled levodopa 84 mg patients turned ON by 60 min post dose vs 36% on PBO	• Cough • Upper respiratory tract infection • Sputum discolored

LSM = least squares mean.

Hauser RA, et al. *Postgrad Med.* 2021;Jun 30: Epub ahead of print.

Levodopa Inhalation Powder

- Levodopa inhalation powder is a self-administered, LD inhalation powder for treatment of OFF periods in people with PD as an adjunct to oral CD/LD regimen[1]
- Drug/device combination consists of an LD powder formulation in capsules that are placed in a breath-actuated inhaler that delivers dose
  - Absorbed in lower lung, thereby bypassing GI system and avoiding first-pass metabolism[1–3]
- 84-mg dose consists of two 42 mg capsules; may be taken a maximum 5 times/day[3]

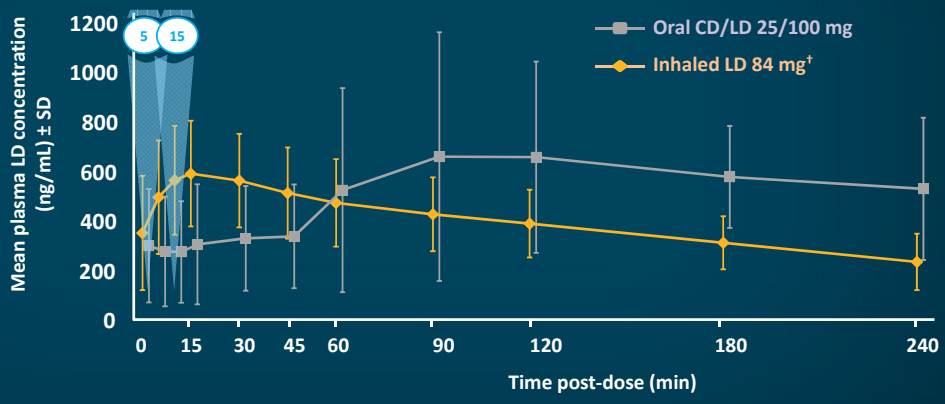
1. LeWitt PA, et al. *Mov Disord*. 2016;31:1356-1365. 2. Lipp MM, et al. *Sci Transl Med*. 2016;8:360ra136. 3. LD inhalation powder (Inbrija) PI, 2020 (www.inbrija.com/prescribing-information.pdf). Accessed 8/12/2021.

Inhaled Levodopa Reaches Mean Peak Plasma Concentrations Faster Than Oral Carbidopa/Levodopa

Single-dose PK study in 23 PD patients following high-fat, high-protein meal*

Increase in mean plasma LD levels within 5 minutes after inhalation

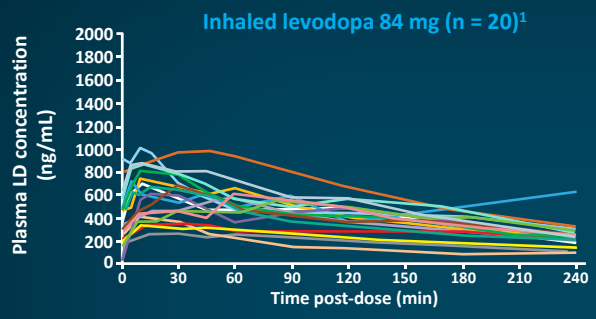
Median T_{max} 15 minutes as compared to 120 minutes for oral CD/LD

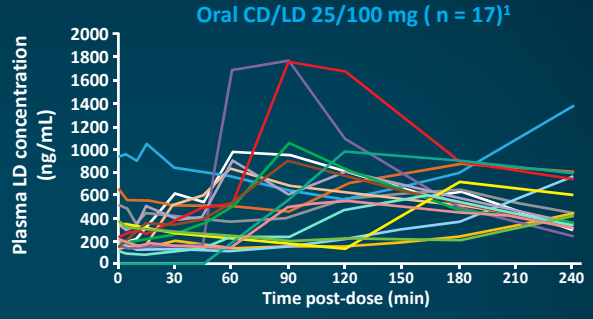


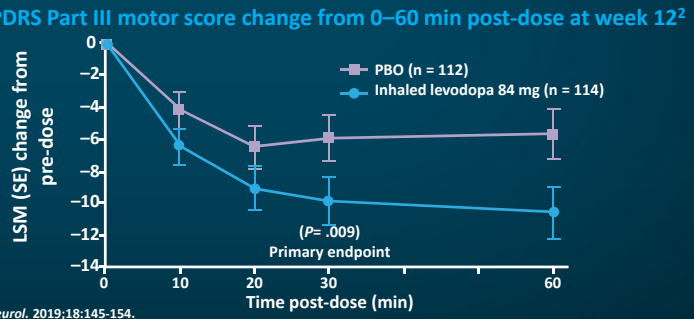
*4–5 hours after morning CD/LD, patients ate meal, then received study drug; †Inhaled LD 84 mg co-administered with 25 mg oral CD for true PK comparison of LD.
PK = pharmacokinetic; SD = standard deviation.

Modified from Safirstein BE, et al. *Clin Ther*. 2020;42:1034-1046.

Orally Inhaled Levodopa





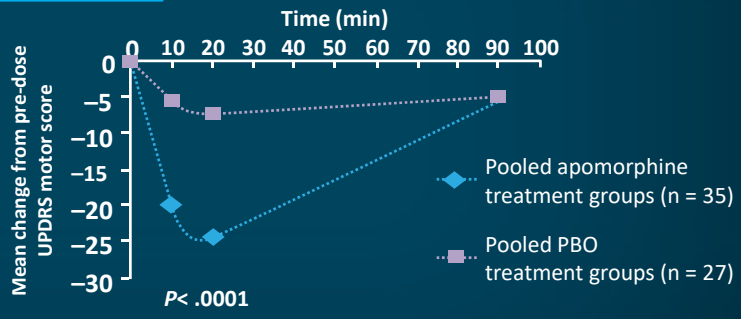


1. Safirstein BE, et al. *Clin Ther*. 2020;42:1034-1046. 2. Modified from LeWitt PA, et al. *Lancet Neurol*. 2019;18:145-154.

Apomorphine Subcutaneous Injection

- Apomorphine, "old" drug, used since 1869 as emetic
- Potent dopamine agonist at both D1 and D2 dopamine-receptor sites
- Administered subcutaneously with ~100% bioavailability
  - Fast-acting (T_{max} = 10–60 min)
  - Short duration (half life = 30–60 min)
- Consistent efficacy similar to levodopa

Rapid, reliable improvement after apomorphine injection (APO302 study)



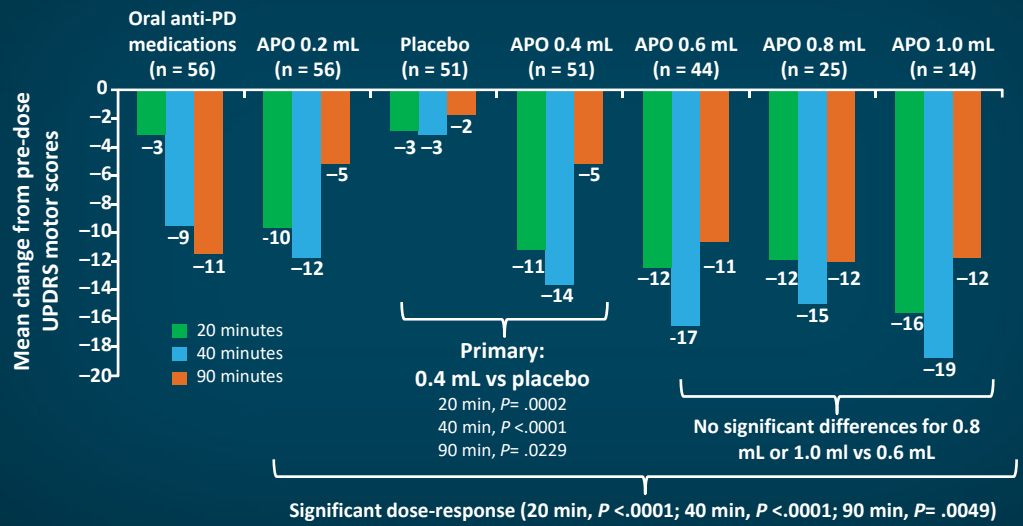
Mean change in UPDRS motor scores did not differ between APO vs APO+2 treatment groups

APO = apomorphine; APO+2 = APO at typically effective dose + 0.2 mL; T_{max} = time to maximum plasma concentration, min = minute(s).

Apomorphine subcutaneous injection (Akpkyn) PI, 2020 (www.apokynhcp.com/sites/all/themes/apokyn/content/resources/apokyn_pi.pdf). Accessed 8/12/2021. Pfeiffer RF, et al. *Parkinsonism Relat Disord.* 2007;13:93-100.

Study APO-303: Robust, Rapid, Reliable

Change in UPDRS motor score with SC APO



Pahwa R, et al. *J Neurol Sci.* 2007;258:137-143.

Delayed-ON of Initial Morning Dose (Morning OFF)

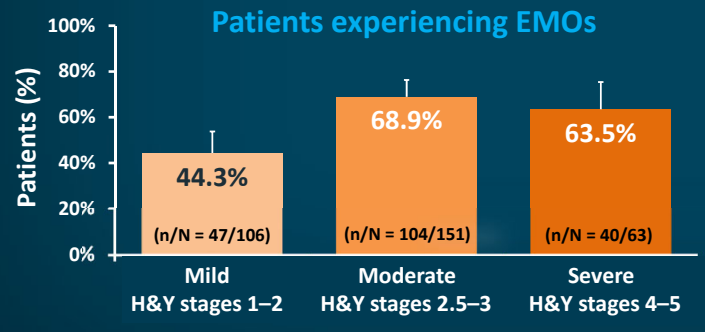
- Common in PD
  - EUROPAR study: 59.7% of patients[1]
  - Japanese study: patient-reported prevalence of 79.8%, with 37.8% reporting EMO every day[2]
- Cause of impaired mobility until onset of effect
- Significantly reduces patients' quality of life[2,3]
- Significantly increases caregiver burden[2]

EMO = early morning OFF.

1. Rizos A, et al. *Parkinsonism Relat Disord.* 2014;20:1231-1235. 2. Onozawa R, et al. *J Neurol Sci.* 2016;364:1-5. 3. Chapuis S, et al. *Mov Disord.* 2005;20:224-230.

Early Morning OFF (EMO) Periods Prevalent Throughout Course of PD

- EMO periods experienced by 59.7% of PD patients
- EMO prevalent across all stages of the disease with a higher proportion in moderate disease ($P < .01$)



EUROPAR study

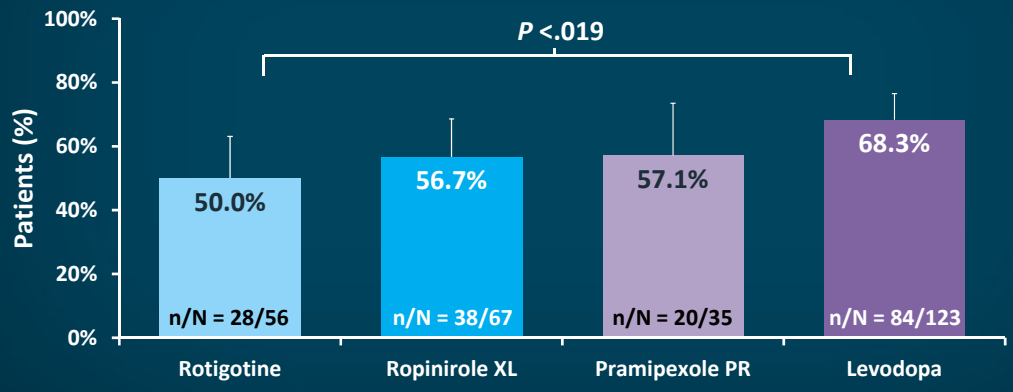
- European observational study
- 320 Parkinson's patients receiving dopaminergic treatment
- EMO periods identified by structured questionnaires (UPDRS-35 and PDSS-14)

PDSS = PD sleep scale; H&Y = Hoehn and Yahr (scale).

Rizos A, et al. *Parkinsonism Relat Disord.* 2014;20:1231-1235.

At least 50% of PD Patients Experienced EMOs Despite Rotigotine Patch or Prolonged-Release DAs

Patients experiencing EMOs despite treatment (EUROPAR study)

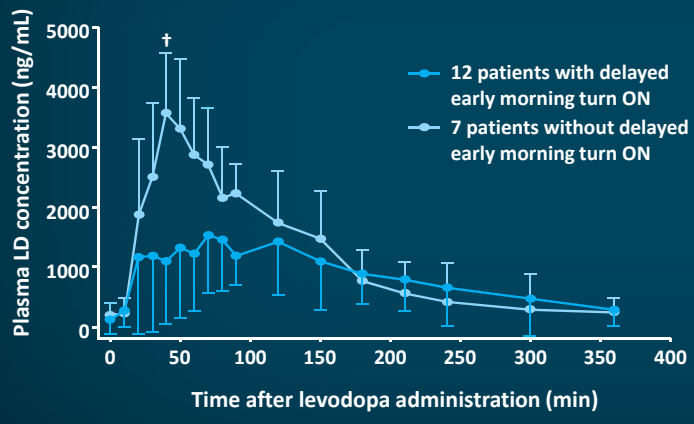


DA = dopamine agonist.

Modified from Rizos A, et al. *Parkinsonism Relat Disord.* 2014;20:1231-1235.

First Oral Levodopa Dose Is Delayed In Morning Akinesia, Probably Due to Gastroparesis

Pharmacokinetic curve after single dose of levodopa*



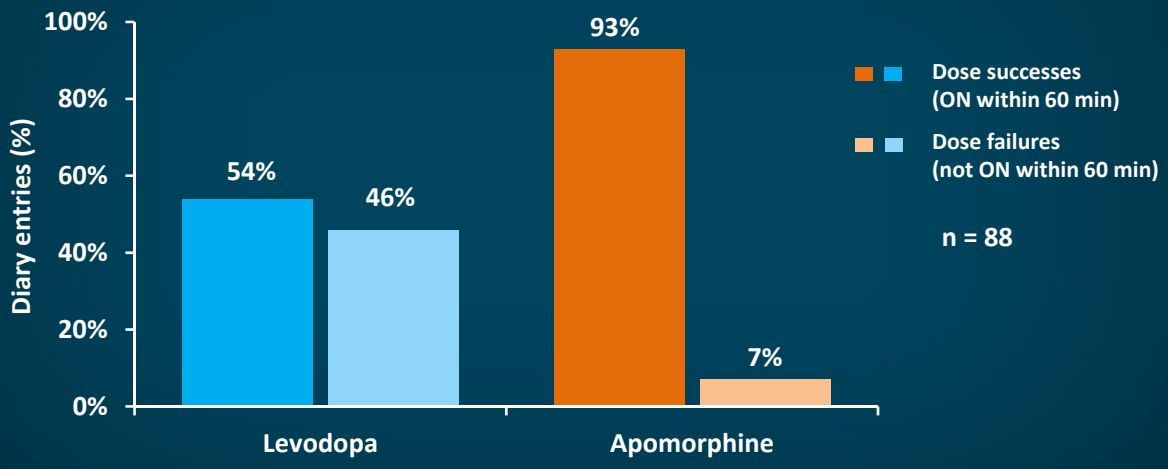
- Pharmacokinetics of levodopa assessed in 19 patients with advanced PD with and without delayed onset of first levodopa dose in morning
- Difference in plasma concentrations in two groups likely due to delayed gastric emptying

*Data are shown as mean (SD); †*P* <.05.

Chaná P, et al. *J Neurol Neurosurg Psychiatry.* 2004;75:1782-1783.

AM-IMPAKT

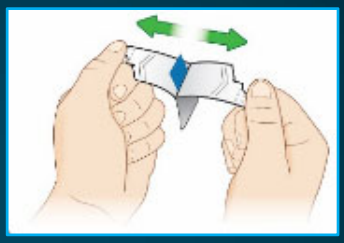
Apomorphine produced more reliable ON than levodopa

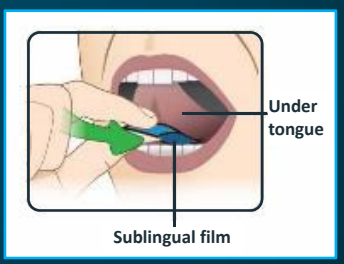


Modified from Isaacson S, et al. *Mov Disord Clin Pract*. 2017;4:78-83.

Sublingual Apomorphine

- A sublingual formulation of apomorphine was approved in May 2020, for use as rescue medication in overcoming OFF periods
- Thin-film strip containing apomorphine in bilayer (to avoid oral irritation)
- Patients are instructed to keep film under their tongue for drug to be absorbed through oral cavity
- Initial study showed OFF reversal within 30 minutes
  - ON mean duration of 50 minutes
  - No major AEs, including oral mucosal irritation
  - Rapid delivery

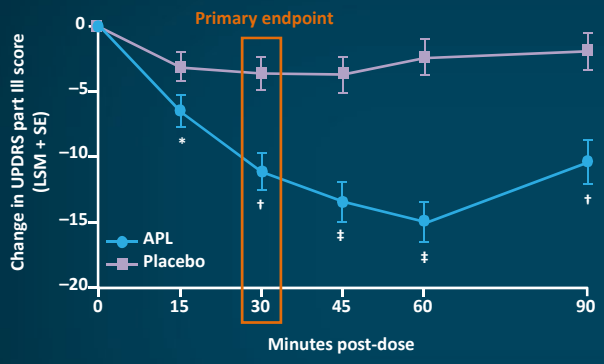




Apomorphine sublingual film (Kynmobi™) PI, 2020 (www.kynmobi.com/Kynmobi-Prescribing-Information.pdf). Accessed 8/12/2021. Hauser RA, et al. *Mov Disord*. 2016;31:1366-1372.

Sublingual Apomorphine Efficacy

Change from pre-dose in UPDRS Part III motor examination score at week 12 (mITT population)

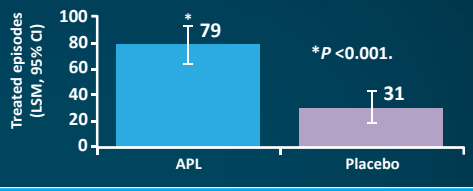


Change from pre-dose to 30 min post-dose for UPDRS part III score at 12 weeks was –11.1 (SE 1.5) and –3.5 (SE 1.3) for APL and PBO groups, respectively (mean difference = –7.6; *P*= .0002).

**P* <.05; †*P* <.001; ‡*P* <.0001.

APL = apomorphine sublingual film; mITT = modified intent-to-treat.

Full ON response at week 12 (treated episodes at 30 min post-dose based on home-dosing diary in mITT population)



AEs in ≥5% of patients treated with APL during maintenance phase of study 1 and with greater incidence than placebo

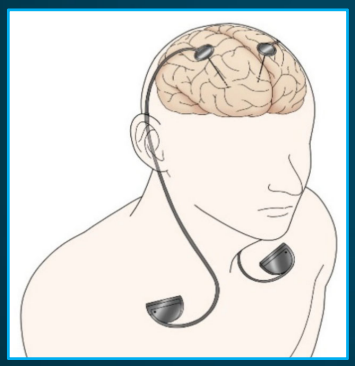
	Titration %	Maintenance %	
	APL (n = 141)	APL (n = 54)	PBO (n = 55)
Gastrointestinal disorders			
Nausea	21	28	4
Oral/pharyngeal soft tissue swelling	1	15	0
Oral/pharyngeal soft tissue pain and paresthesia	2	13	2
Oral ulceration and stomatitis	2	7	0
Oral mucosal erythema	4	7	4
Vomiting	4	7	0
Dry mouth	1	6	0
Nervous system disorders			
Somnolence	11	13	2
Dizziness	11	9	0
Headache	8	6	0

Olanow CW, et al. *Lancet Neurol*. 2020;19:135-144. Apomorphine sublingual film (Kynmobi™) PI, 2020 (www.kynmobi.com/Kynmobi-Prescribing-Information.pdf).

Advanced Surgical Therapies

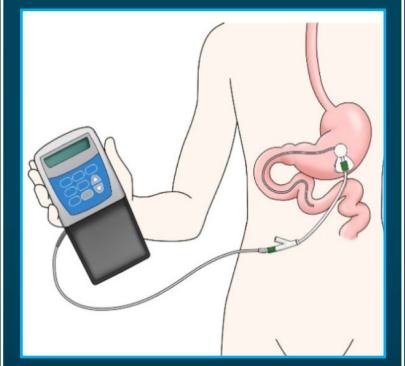
Deep-brain stimulation

Stimulation of globus pallidus interna or subthalamic nucleus



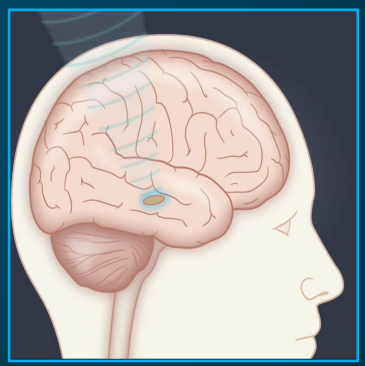
Intestinal levodopa infusion

Continuous infusion of levodopa directly into the jejunum



Focused ultrasound

Thalamic ablation for tremor



Mishima T, et al. *J Pers Med*. 2021;11:650. Martinez-Fernandez R, et al. *N Engl J Med*. 2020;383:2501-2513.

Identifying Candidates for Surgical Therapies

Candidates for surgical therapies

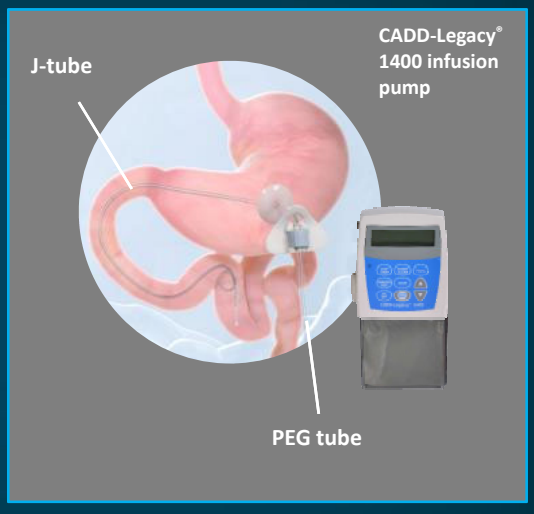
- **Medication-resistant motor fluctuations**
- **Medication-resistant dyskinesia**
- **Medication-resistant tremor**

✓ **Levodopa-responsive Parkinson's disease**

Rizek P, et al. *CMAJ*. 2016;188:1157-1165.

Levodopa-Carbidopa Intestinal Gel (LCIG)

- Developed in Sweden in 1990s, LCIG was approved in European Union in 2004 and in US in 2015
- Available in >40 countries worldwide for treatment of advanced levodopa-responsive PD with severe motor fluctuations
- LCIG bypasses stomach and is intended to avoid effects of slowed or delayed gastric emptying
- LCIG is administered directly into small intestine via PEG-J

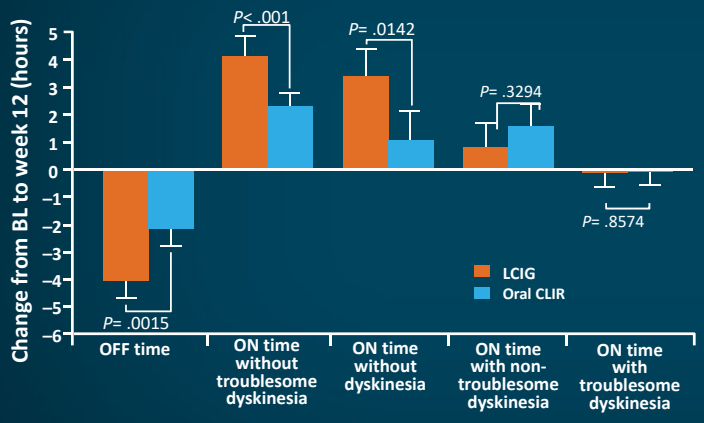


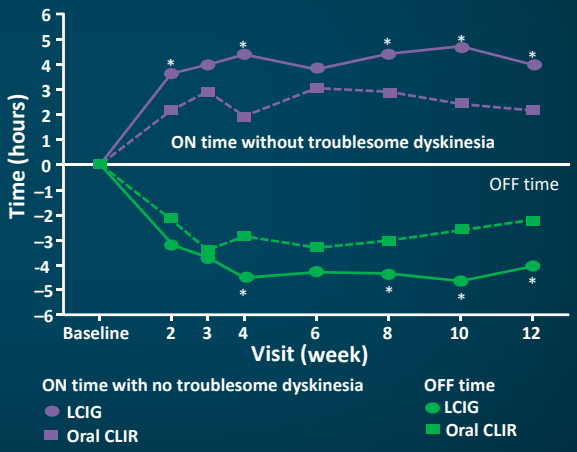
PEG-J = percutaneous endoscopic gastrostomy with a jejunal extension tube.

Carbidopa-levodopa enteral suspension (Duopa®) PI, 2020 (www.rxabbvie.com/pdf/duopa_pi.pdf). Accessed 8/12/2021. Wirdefeldt K, et al. *CNS Drugs*. 2016;30:381-404.

LCIG: Pivotal Study

Continuous intrajejunal infusion of LCIG for patients with advanced PD: randomized, controlled, double-blind, double-dummy study





*P< .05.

CLIR = carbidopa/levodopa immediate-release.

Modified from Olanow CW, et al. *Lancet Neurol*. 2014;13:141-149.

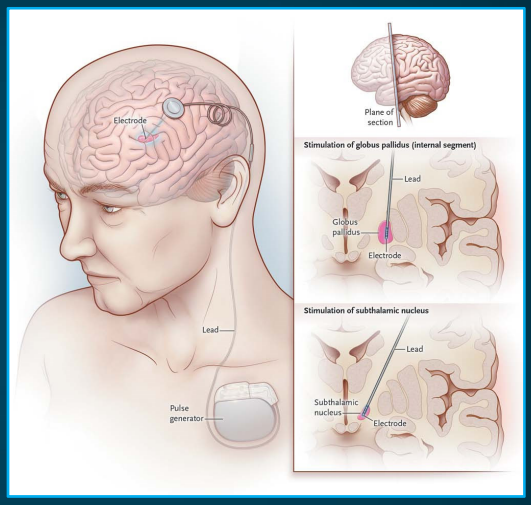
Deep-Brain Stimulation (DBS)

- Common targets: GPi, STN; rarely VIM thalamus for tremor
- Patient selection is critical
  - Advanced PD with wearing off and dyskinesias or prominent tremor
  - Dyskinesia that is bothersome
  - Younger patients with motor fluctuations within 2 years (onset in <50; may be candidates for earlier DBS)
  - Good levodopa response (exception: tremor dominant)
    - If gait/balance are primary problems, then DBS not likely to be helpful; could help some freezing
  - No significant cognitive impairment
    - May worsen after surgery
    - Neuropsychological testing performed to evaluate
- Management of expectations

GPi = globus pallidus internus; STN = subthalamic nucleus; VIM = ventral intermedius nucleus.

Okun MS. *N Engl J Med*. 2012;367:1529-1538.

Electrode implantation for DBS



Lead for deep-brain stimulation is implanted in either subthalamic nucleus or internal segment of globus pallidus, passing through burr hole in skull. Attached to lead is connecting wire, which is tunneled under skin of scalp and neck to anterior chest wall, where it is connected to impulse generator.

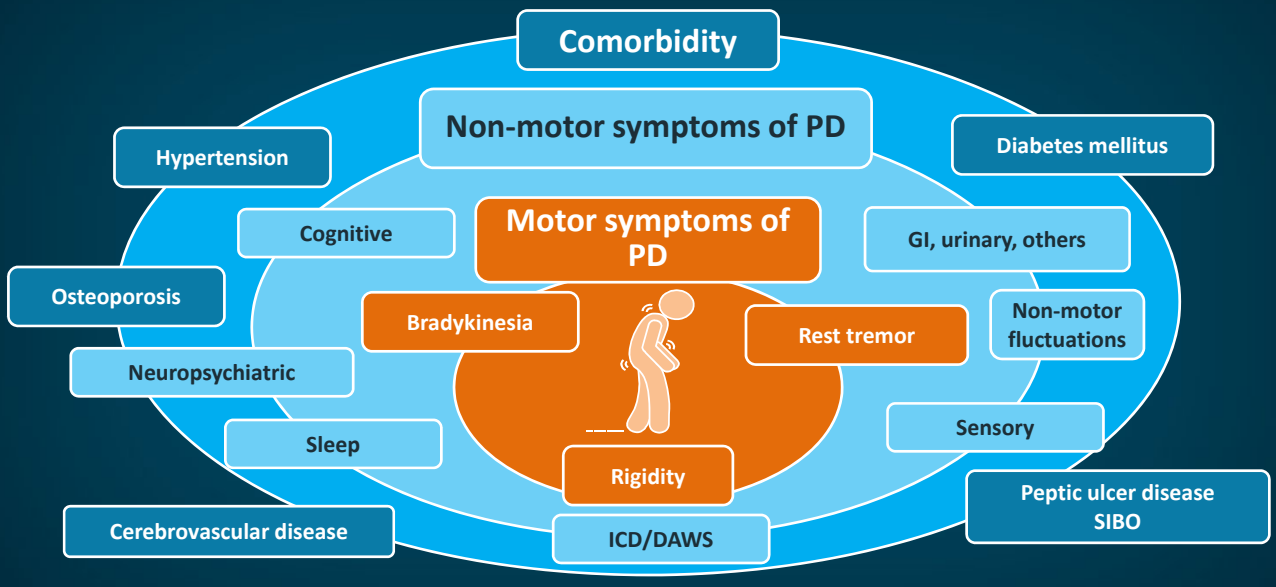
Subthalamic Nucleus (STN): DBS Outcomes

	DBSPD study group[1]	PROGRESS[2]	INTREPID[3]
# patients	94	234	160 (121 active/39 control)
Study duration	3 months	12 months	3 months
Study design	Prospective, double-blind crossover	Prospective crossover with double-blind primary endpoint	RCT—sham control (3:1)
Age	59.0 (9.6) yrs	61.7 (8.4) yrs	59.9 (8.0) yrs
Disease duration	14.4 yrs	10.2 (7.4) yrs	10.1 (3.6) yrs
ON without troublesome dyskinesia	4.5 hours	4.3 hours	3.74 hours difference from baseline
UPDRS motor meds OFF vs meds OFF/stimulation ON	49% improvement	43% improvement with directional stim at 6 mos	42% improvement with stim
Device	Constant voltage	Constant current	Multiple independent constant-current control
Lead	Non-segmented	Segmented	8-contact, non-segmented

DBSPD = Deep-brain stimulation for Parkinson's disease; meds = medications; stim = stimulation; RCT = randomized controlled trial.

1. Obeso JA, et al. *N Engl J Med.* 2001;345:956-963. 2. Schnitzler A, et al. *Neuromodulation.* 2021;May 27: Epub ahead of print. 3. Vitek J, et al. *Lancet Neurol.* 2020;19:491-501.

The Complete Picture of Parkinson's Disease



NMS = non-motor symptoms; DAWS = dopamine agonist withdrawal syndrome; ICD = impulse control disorders; SIBO = small intestinal bacteria overgrowth.

Todorova A, et al. *Pract Neurol.* 2014;14:310-322.

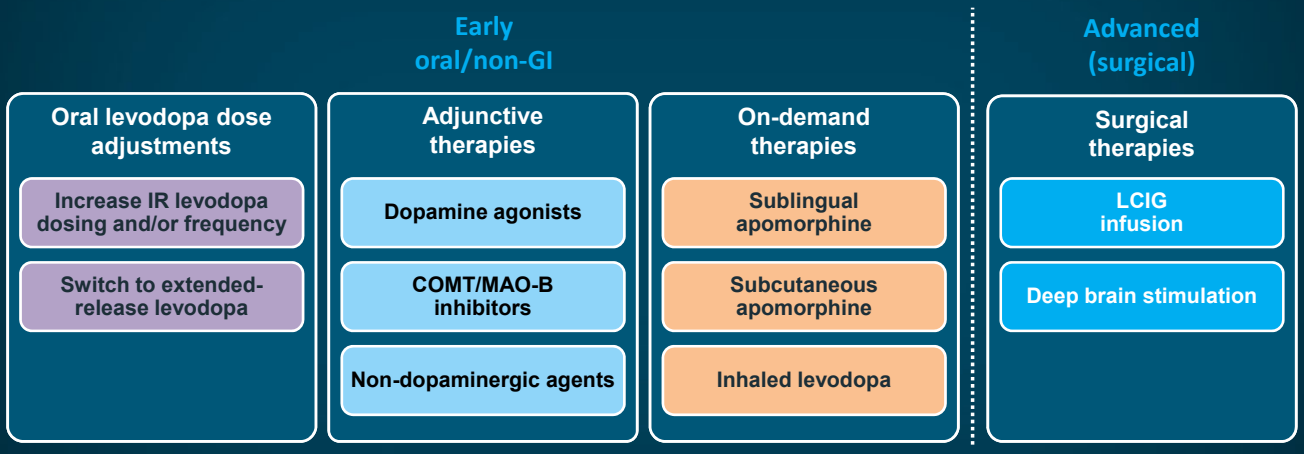
Multidisciplinary Team for Parkinson's Disease

Members of multidisciplinary team listed by European PD Standards of Care consensus statement and their role in care and management of people with PD[1,2]

Multidisciplinary team member	Role is to:
General practitioner	Provide day-to-day clinical management
Movement disorder specialist/neurologist	Plan and monitor treatment
Geriatrician	Provide general in- and outpatient management
PD nurse specialist	Manage care and coordinate with hospital and community services
Physiotherapist	Maximize functional ability
Speech and language therapist	Manage difficulties with speech, communication, eating, drinking, and swallowing
Occupational therapist	Advise on measures to retain independence
Nutritionist	Ensure optimal nutrition
Psychologist	Treat depression and other mental health problems
Pharmacists	Ensure supplies of specialty medications
Complementary therapists	Provide massage and relaxation therapies

1. Pedersen SW, et al. *J Multidiscip Healthc*. 2017;10:13-27. 2. EPDA (European Parkinson's Disease Association) standards of care consensus statement. 2012 (www.epda.eu.com/media/1181/epda-consensus-statement-en.pdf). Accessed 8/12/2021.

Once OFF Episodes Emerge, Shared Clinical Decision-Making Can Help Guide Adjustment to Levodopa Regimen and/or Addition of Adjunctive Therapy



Vijiaratnam N, Foltynie T. *Drugs*. 2020;80:775-796. Tanner CM. *Am J Manag Care*. 2020;26(12 suppl):S255-S264.

Goal of Treatment: Continuous "Best-ON"

- Maintain duration of ON
  - Use extended/continuous levodopa formulations and COMT inhibitors
  - Consider MAO-B inhibitors, dopamine agonists, NMDA, and A2A antagonists
- Reduce variability of ON
  - Use non-oral medications, extended release and continuous formulations, and adjunctive medications
  - Utilize on-demand, non-oral therapies for rapid, reliable, and robust response
- Address dose-limiting levodopa-induced dyskinesias, Parkinson's disease psychosis, neurogenic orthostatic hypotension, and drug-related adverse events
  - Treat when cannot avoid

MAOI = MAO inhibitor; PDP = Parkinson's disease psychosis; NOH = neurogenic orthostatic hypotension; D-AEs = drug adverse events

Managing OFF Episodes: Shared Decision-Making Should Consider Many Factors

OFF episodes can help guide treatment decision-making

- Type of OFF episodes
- Frequency and severity of OFF episodes
- Timing of OFF episodes
- Impact on daily life

Medication prescribing information should be considered

- Access
- Dosing and route
- Efficacy
- Tolerability and safety
- Clearance and drug-drug interactions

Patient factors can impact treatment decisions

- Comorbidities
- Concomitant medications
- Prior sensitivity to medication changes
- Presence (or absence) of dyskinesia, psychosis, orthostatic hypotension
- Non-motor symptoms

Stocchi F. *Expert Opin Pharmacother.* 2006;7:1399-1407. Olanow CW, et al. *Mov Disord.* 2020;35:1731-1744. Poewe W, Mahlknecht P. *Neurol Clin.* 2020;38:255-267. Pahwa R, Isaacson SH. *J Clin Psychiatry.* 2020;82:SU19004BR2C. Grimes D, et al. *CMAJ.* 2019;191:E989-E1004.

Case Study

Anita

History

- 56-year-old LH woman with PD for 6 years, beginning with left-hand tremor and overnight left foot dystonia
- Tennis pro at local country club
- Initial treatment with ropinirole XL
- CD/LD 25/100 TID was begun 5 years ago with robust response
- 4 years ago, 25/100 increased to 1.5/1.5/1 for slowness playing tennis and occasional tremor

Emergence of OFF Episodes

- 3 years ago, end-dose wearing off occurred 4 hours after each dose; rasagiline added
- 2 years ago, overnight and morning OFF, and CD/LD was adjusted to 2/1/1/1 at 7 am/ 11 am/3 pm/7pm
- Dose failures some afternoons led to increased CD/LD: 2/1.5/1.5/1

Current Evaluation

- Evaluation in clinic today, with OFF episode almost every morning, lasting over 60 minutes
- Onset of other doses sometimes delayed for 30–60 minutes: "I never know if the dose will work quickly or take forever or not work at all!"
- Exam in clinic today 3 hours after last CD/LD dose with OFF symptoms emerging
  - Mild anxiety and emergence of left-hand tremor with activation
  - L>R rigidity and bradykinesia
  - Arises from chair without use of arms, has mildly stooped posture, and gait with reduced left arm swing and stride
  - Postural reflexes normal, but takes 1–2 steps to maintain balance when pulled backwards

L>R = left greater than right.

How would you manage this patient?

Management

- Adjusting CD/LD timing to less than 4 hours was difficult for her to adhere to
- Increasing CD/LD did not improve OFF episodes and mild dyskinesia emerged
- Increasing ropinirole in past was limited by somnolence
- Discussed with patient adding MAO-B or COMT inhibitor, nondopaminergic medication, and/or use of on-demand therapy
- Patient was hesitant to begin new daily medication when she was mainly having symptoms in morning, when dose was delayed in onset, or when failed to work; most of day, she was feeling good
- She wanted a medication she could use to return to ON when OFF symptoms occurred and opted for sublingual apomorphine

Case Study

Samira

History

- 69-year-old RH woman with PD for 11 years, beginning with micrographia and slow walking
  - Retired CPA
- Initial treatment with rasagiline 1 mg, then rotigotine patch
- CD/LD 25/100 TID begun 8 years ago with robust response
- 6 years ago, 25/100 increased to 1/1/1/1 and then to 1.5/1/1.5/1 for reemerging slowness

CPA = certified public accountant.

Emergence of OFF Episodes

- Over past few years, 25/100 was adjusted for OFF episodes and now on 1.5/1.5/1.5/1/1 at 8 am/11 am/2 pm/5 pm/8 pm/11 pm
- Apomorphine subcutaneous injection was added for morning OFF but was stopped after amantadine ER qhs was added one year ago for dyskinesia and OFF episodes

Current Evaluation

- Evaluation in clinic today, with her reporting an OFF episode almost every morning, lasting for over 45 minutes
- Other doses sometimes work quickly, but some doses are delayed in onset for over 60 minutes: "I can't plan my day if I don't know when my meds will work!"
- Exam when ON with mild-to-moderate bradykinesia
  - Arises from chair with use of arms, and gait with reduced arm swing and stride
  - Postural reflexes normal, but she requires 2 steps to maintain balance when pulled backwards

How would you manage this patient?

Management

- Further adjusting CD/LD timing was difficult for her to adhere to
- Increasing 25/100 led to return of dyskinesia
- Increasing rotigotine in past was limited by irritation beneath patch
- Discussed with patient adding COMT inhibitor, another nondopaminergic, and/or use of on-demand treatment
- Patient considering DBS
- Patient opted to restart subcutaneous apomorphine

Project ECHO®

Personalizing Treatment for PARKINSON'S DISEASE:

What Can You Do to Manage OFF EPISODES *in Your Patients?*

WHITEBOARD ANIMATIONS

How Patients Experience the 4 Types of Off Episodes: https://youtu.be/ueRuYAMG0QY

Mechanism of Action of Therapies for OFF Episodes: https://youtu.be/5KHXj6jufGY

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This activity is supported by an educational grant from Sunovion.

Personalizing Treatment of Parkinson's Disease: What Can You Do to Manage Off Episodes in Your Patients?

TOOLKIT

Off Episodes in Parkinson's Disease

Resource	Web Address
Todorova A, et al. **Non-motor Parkinson's: integral to motor Parkinson's, yet often neglected.** *Pract Neurol*. 2014;14:310-322.	https://pubmed.ncbi.nlm.nih.gov/24699931/
Chapuis S, et al. **Impact of the motor complications of Parkinson's disease on the quality of life.** *Mov Disord.* 2005;20:224-230.	https://pubmed.ncbi.nlm.nih.gov/15384126/
Onozawa R, et al. **The impact of early morning off in Parkinson's disease on patient quality of life and caregiver burden.** *J Neurol Sci.* 2016;364:1-5.	https://pubmed.ncbi.nlm.nih.gov/27084204/
Rizos A, et al. **Characterizing motor and non-motor aspects of early-morning off periods in Parkinson's disease: An international multicenter study.** *Parkinsonism Relat Disord.* 2014;20:1231-1235.	https://pubmed.ncbi.nlm.nih.gov/25269446/
Pfeiffer RF, et al. **Clinical implications of gastric complications on levodopa treatment in Parkinson's disease.** *Parkinsonism Relat Disord.* 2020;76:63-71.	https://pubmed.ncbi.nlm.nih.gov/32461054/
van Kessel SP, et al. **Gut bacterial tyrosine decarboxylases restrict levels of levodopa in the treatment of Parkinson's disease.** *Nat Commun.* 2019;10:310.	https://pubmed.ncbi.nlm.nih.gov/30659181/
Hauser RA, et al. **Onset and duration of effect of extended-release carbidopa-levodopa in advanced Parkinson's disease.** *Neuropsychiatr Dis Treat.* 2018;14:839-842.	https://pubmed.ncbi.nlm.nih.gov/29606877/

On-Demand Therapies

Resource	Web Address
Olanow CW, et al. **On-demand therapy for OFF episodes in Parkinson's disease** [published online ahead of print, 2021 Aug 7]. *Mov Disord*. 2021;10.1002/mds.28726.	https://pubmed.ncbi.nlm.nih.gov/34363424/
Olanow CW, et al. **Apomorphine sublingual film for off episodes in Parkinson's disease: A randomised, double-blind, placebo-controlled phase 3 study.** *Lancet Neurol*. 2020;19:135-144.	https://pubmed.ncbi.nlm.nih.gov/31818699/

Hauser RA, et al. **Sublingual apomorphine (APL-130277) for the acute conversion of OFF to ON in Parkinson's disease**. *Mov Disord*. 2016;31:1366-1372.	https://pubmed.ncbi.nlm.nih.gov/27430123/
Lipp MM, et al. **Preclinical and clinical assessment of inhaled levodopa for OFF episodes in Parkinson's disease.** *Sci Transl Med*. 2016;8:360ra136.	https://pubmed.ncbi.nlm.nih.gov/27733560/
Safirstein BE, et al. **Pharmacokinetics of inhaled levodopa administered with oral carbidopa in the fed state in patients with Parkinson's disease.** *Clin Ther.* 2020;42:1034-1046.	https://pubmed.ncbi.nlm.nih.gov/32482490/
LeWitt PA, et al. **A randomized trial of inhaled levodopa (CVT-301) for motor fluctuations in Parkinson's disease.** *Mov Disord*. 2016;31:1356-1365.	https://pubmed.ncbi.nlm.nih.gov/27090868/
LeWitt PA, et al. **Safety and efficacy of CVT-301 (levodopa inhalation powder) on motor function during off periods in patients with Parkinson's disease: A randomised, double-blind, placebo-controlled phase 3 trial.** *Lancet Neurol.* 2019;18:145-154.	https://pubmed.ncbi.nlm.nih.gov/30663606/
Pfeiffer RF, et al. **Continued efficacy and safety of subcutaneous apomorphine in patients with advanced Parkinson's disease**. *Parkinsonism Relat Disord*. 2007;13:93-100.	https://pubmed.ncbi.nlm.nih.gov/17055329/
Pahwa R, et al. **Subcutaneous apomorphine in patients with advanced Parkinson's disease: A dose-escalation study with randomized, double-blind, placebo-controlled crossover evaluation of a single dose.** *J Neurol Sci*. 2007;258:137-143.	https://pubmed.ncbi.nlm.nih.gov/17466338/
Isaacson S, et al. **Apomorphine subcutaneous injection for the management of morning akinesia in Parkinson's disease**. *Mov Disord Clin Pract.* 2017;4:78-83.	https://pubmed.ncbi.nlm.nih.gov/28239615/

Adjunctive Therapies

Resource	Web Address
Kalia LV, et al. **Novel nondopaminergic targets for motor features of Parkinson's disease: Review of recent trials.** *Mov Disord.* 2013;28:131-144.	https://pubmed.ncbi.nlm.nih.gov/23225267/
Lees AJ, et al. **Opicapone as adjunct to levodopa therapy in patients with Parkinson disease and motor fluctuations: A randomized clinical trial.** *JAMA Neurol*. 2017;74:197-206.	https://pubmed.ncbi.nlm.nih.gov/28027332/

Poewe W, et al. **Extended-release pramipexole in early Parkinson disease: A 33-week randomized controlled trial.** *Neurology.* 2011;77:758-766.	https://pubmed.ncbi.nlm.nih.gov/21832218/
Pahwa R, et al. **Ropinirole 24-hour prolonged release: Randomized, controlled study in advanced Parkinson disease.** *Neurology.* 2007;68:1108-1115.	https://pubmed.ncbi.nlm.nih.gov/17404192/
Müller T. **Safinamide: An add-on treatment for managing Parkinson's disease.** *Clin Pharmacol*. 2018;10:31-41.	https://pubmed.ncbi.nlm.nih.gov/29670409/
Pahwa R, et al. **ADS-5102 (amantadine) extended-release capsules for levodopa-induced dyskinesia in Parkinson disease (EASE LID study): A randomized clinical trial.** *JAMA Neurol.* 2017;74:941-949.	https://pubmed.ncbi.nlm.nih.gov/28604926/