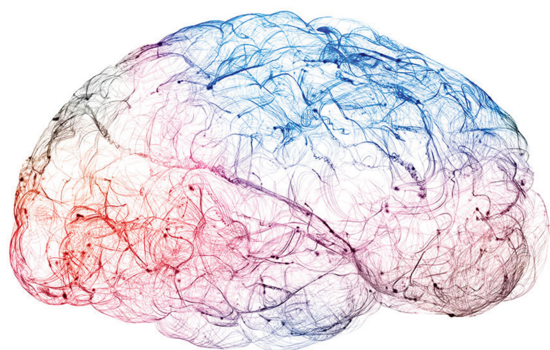

Novel Therapies to Manage Off Episodes in Patients with Parkinson's Disease

Clinical Compendium

- Motor fluctuations emerge in 50% of patients with PD within 5 years and 90% within 10 years.[1,2]
- A patient with PD is said to be "off" when medications are not providing good benefit for motor symptoms. An "off" period refers to a single period between when the medication benefit is lost and when the benefit from the next dose begins. Daily "off" time refers to the total amount of time spent in "off" throughout the day.[3]
- Factors in increased "off" time:
  - Early on in treatment, the benefits of levodopa can last several hours, likely due to levodopa being stored in the remaining dopamine-producing brain cells. But as time goes on and patients lose more dopaminergic neurons, the storage and release capacity for dopamine decreases which diminishes medication duration and leads to longer "off" periods.[1]
  - Oral carbidopa/levodopa is absorbed in the small bowel, presenting a challenge for PD patients with gastrointestinal dysmotility and/or gastroparesis. This variability can lead to delayed "on".[4,5]
  - Over time, the upregulation of adenosine A_{2A} receptors and an increase in NMDA glutamate activity worsen PD symptoms and increase "off" time.[6]

NEW ADJUNCTIVE AGENTS

Agent	Form	FDA Approval	Indication, Notes[7]
Apomorphine HCl (Kynmobi)	Sublingual film	May 2020	*Indication:* For the acute, intermittent treatment of "off" episodes in patients with PD. *Note:* Non-ergoline dopamine agonist absorbed through the mucosa beneath the tongue. Dose range is 10-30 mg per dose separated by at least 2 hours between doses. Maximum 5 doses per day.
Opicapone (Ongentys)	Oral (capsule)	April 2020	*Indication:* Add-on treatment to levodopa/carbidopa in patients with PD experiencing "off" episodes. *Note:* Once-daily COMT inhibitor. Recommended dose is 50 mg at bedtime ≥ 1 hour away from food.
Istradefylline (Nourianz)	Oral (tablet)	August 2019	*Indication:* Add-on treatment to levodopa/carbidopa in patients with PD experiencing "off" episodes. *Note:* Adenosine A_{2A} receptor antagonist; non-dopamine medication. Recommended dosage is 20 mg once daily, may be increased to 40 mg once daily.
Levodopa (Inbrija)	Inhaled powder	December 2018	*Indication:* For the intermittent treatment of "off" episodes in patients with PD treated with carbidopa/levodopa. *Note:* On-demand/as-needed therapy. Maximum dose per "off" period is 84 mg up to five times per day for a maxium daily dose of 420 mg.
Amantadine ER (Gocovri)	Oral (capsule)	February 2018	*Indication:* For the treatment of dyskinesia in patients with PD receiving levodopa-based therapy, with or without concomitant dopaminergic medications. *Note:* NMDA receptor antagonist. Initial dose is 137 mg daily, increased after one week to the recommended dose of 274 mg daily.
Safinamide (Xadago)	Oral (tablet)	March 2017	*Indication:* Add-on treatment for patients with Parkinson's disease who are currently taking levodopa/carbidopa and experiencing "off" episodes. *Note:* Inhibitor of MAO-B, an enzyme in the brain that breaks down dopamine. Recommended initial dose is 50 mg once daily; can be increased to 100 mg after 2 weeks.

RECENT LEVODOPA AGENTS

Agent	Form	FDA Approval	Indication, Notes[7]
Carbidopa/Levodopa Extended-Release (Rytary)	Oral (capsule)	January 2015	*Indication:* Treatment of patients with PD, postencephalitic parkinsonism and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication. *Note:* Contains carbidopa/levodopa beads that provide both immediate and extended-release pharmacokinetic properties.
Carbidopa/Levodopa Enteral Suspension (Duopa)	Infusion	January 2015	*Indication:* Treatment of motor fluctuations in patients with advanced PD. *Note:* Infused up to 16 hr/day via portable pump connected to a tube that goes through the abdominal wall, into the stomach and has the tip positioned in the small bowel.

1. Jankovic J. Mov Disord. 2005;20 (Suppl 11). **2.** Obeso JA, Rodriguez-Oroz MC, et al. Neurology. 2000;55(11 Suppl 4):S13-20; discussion S21-3. **3.** Parkinson's Foundation. *Managing PD Mid-Stride.* https://www.parkinson.org/sites/default/files/attachments/MidStride.pdf - accessed on 8/15/2020. **4.** Stocchi F. Expert Opin Pharmacother. 2006;7(10):1399-1407. **5.** Goetze O et al. Neurogastroenterol Motil. 2006;18(5):369-375. **6.** Mishina M, et al. PLoS One. 2011;6(2):e17338. **7.** Prescribing information.

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